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

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI - 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-I – PHARMACEUTICS

Submitted by

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TAMILNADU.

MAY – 2017

CERTIFICATES

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND EVALUATION OF NEBIVOLOL IMMEDIATE RELEASE TABLETS WITH IMPROVED DISSOLUTION USING SOLID DISPERSION TECHNIQUE",** submitted by the student bearing **Reg. No: 261510263** to "**The Tamil Nadu Dr. M.G.R. Medical University – Chennai**", in partial fulfilment for the award of Degree of **Master of Pharmacy** in **Pharmaceutics** was evaluated by us during the examination held on.....

Internal Examiner **External Examiner**

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DECLARATION

I do hereby declared that the dissertation **"FORMULATION AND EVALUATION OF NEBIVOLOL IMMEDIATE RELEASE TABLETS WITH IMPROVED DISSOLUTION USING SOLID DISPERSION TECHNIQUE"** submitted to "**The Tamil Nadu Dr.M.G.R Medical University - Chennai",** for the partial fulfilment of the degree of **Master of Pharmacy** in **Pharmaceutics,** is a bonafide research work has been carried out by me during the academic year 2016-2017, under the guidance and supervision of **Mrs. S.BHAMA M. Pharm.,** Associate Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

I further declare that this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

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Dedicated to Parents, Teachers & My Family

ACKNOWLEDGEMENT

ACKNOWLEDGEMENT

I am proud to dedicate my deep sense of gratitude to the founder, (Late) Thiru **J.K.K. Nattaraja Chettiar,** providing the historical institution to study.

My sincere thanks and respectful regards to our reverent Chairperson **Smt. N. Sendamaraai, B.Com.,** and Director **Mr.S.OmmSharravana, B.Com., LLB.,** J.K.K. Nattraja Education all institutions, Kumarapalayam for their blessings, encouragement and support at all times.

It is my most pleasant duty to thank our beloved Principal and Professor **Dr. R. Sambathkumar, M. Pharm., PhD.,** of J.K.K.Nattraja College of Pharmacy, Kumarapalayam for ensuring all the facilities were made available to me for the smooth running of this project.

It is most pleasant duty to thank my beloved guide **Mrs. S. BHAMA, M.Pharm.,** Associate Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam, for suggesting solution to problems faced by me and providing in dispensable guidance, tremendous encouragement at each and every step of this dissertation work. Without her critical advice and deep-rooted knowledge, this work would not have been a reality.

Our glorious acknowledgement to our administrative officer

Dr. K. Sengodan, M.B.B.S., for encouraging using kind and generous manner to complete this work.

My sincere thanks to, **Mr. R. Kanagasabai, B.Pharm, M.Tech.,** Assistant Professor, **Mr.K. Jaganathan, M.Pharm.,** Assistant Professor, **Ms. S. Manodhini Ilakiya, M.Pharm.,** Lecturer, **Mr. C. Kannan M.Pharm.,** Assistant Professor, **Mr. V. Kamalakannan M.Pharm.,** Assistant Professor, and **Ms. S. Sivashankari, M.Pharm.,** Lecturer, Department of pharmaceutics for the invaluable help during my project.

My sincere thanks to **Mr.N.Venkateswaramurthy, M.Pharm.,** Professor and Head, Department of Pharmacy Practice, **Mrs. K. KrishnaVeni, M.Pharm.,** Assistant Professor, **Mrs. P. Kavitha M.Pharm,** Assistant Professor, **Mr. R. Kameswaran M.Pharm,** Assistant Professor, **Dr.Taniya Jacob, Pharm.D.,** Lecturer, **Dr. V. Viji Queen, Pharm.D.,** Lecturer, **Mr. C. Sampushparaj,** Lecturer, Mr.**T.Thiyagarajan M.Pharm** Lecturer, and **Ms.C. Sahana, M.Pharm.,** Lecturer, Department of Pharmacy Practice, for their help during my project.

It is my privilege to express deepest sense of gratitude toward **Dr.M.Vijayabaskaran**, **M.Pharm.,** Professor & Head, Department of Pharmaceuticalchemistry, **Dr.S. P. Vinoth Kumar M.Pharm.,** Assistant professor, **Mrs. S. Gomathi M.Pharm.,** Lecturer, **Mrs. B. Vasuki, M.Pharm.,** Lecturer and **Mrs. P. Devi, M.Pharm.,**

Lecturer, for their valuable suggestions and inspiration.

My sincere thanks to **Dr.V.Sekar,M.Pharm.,Ph.D.,** Professor and Head, Department of Analysis, **Dr. I. Caolin Nimila, M.Pharm.,Ph.D.,** Assistant Professor, and **Ms. V. Devi, M.Pharm.,** Lecturer, Department of Pharmaceutical Analysis for their valuable suggestions.

My sincere thanks to **Dr. Senthilraja, M.Pharm., Ph.D.,** Associate Professor and Head, Department of Pharmacognosy, **Dr. M. Rajkumar, M.Pharm., Ph.D.,** Associate Professor, **Mrs. Meena Prabha M.Pharm.,** Lecturer, Department of Pharmacognosy and **Mrs. P. Seema, M.Pharm.,** Lecturer, Department of Pharmacognosy for their valuable suggestions during my project work.

My sincere thanks to **Dr. R. Shanmugasundaram, M.Pharm., Ph.D.,** Vice Principal &HOD, Department of Pharmacology, **Mr. V. Venkateswaran, M.Pharm.,** Assistant Professor, **Mrs. M.Sudha M.Pharm.,** Lecturer, **Mrs. R. Elavarasi, M.Pharm.,** Lecturer, **Mrs. M. Babykala, M.Pharm.,** Lecturer, Department of Pharmacology for their valuable suggestions during my project work.

I greatly acknowledge the help rendered by **Mrs.K. Rani,** Office Superintendent, **Mr.E. Vasanthakumar, MCA,** Assistant Professor, **Miss.M. Venkateswari, M.C.A.,** Typist**, Mrs.V.Gandhimathi, M.A.,**

M.L.I.S., Librarian, **Mrs.S. Jayakala B.A., B.L.I.S.,** and Asst. Librarian, **Mrs. Punitha, Lab Assistant** for their co-operation. I owe my thanks to all the technical and non-technical staff members of the institute for their precious assistance and help.

I thank to my friends **Ms. Keerthana, Senthil, Sedhu, Rajan, Muthu, Kalai** all are encouragement and help extended to my project work.

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CONTENTS

1. INTRODUCTION

Oral dosage forms can be grouped as solid, liquid, semi solid and gaseous dosage forms. The solid dosage forms are available mostly in unit dosage forms (consisting of doses which are taken by numbers) such as tablets, capsules, lozenges etc.[1]. When drugs are administered orally in dry state, tablets and capsules are most convenient dosage form.[2] Tablets may be defined as solid pharmaceutical dosage forms containing drug substance with or without suitable diluents and prepared either by compression or molding process[3]. For all practical purposes only compression tablets are almost universally used while molded tablets being a rare commodity. Drugs are more frequently taken by oral administration[4].

Although a few drugs taken orally are intended to be dissolved within the mouth, vast majority of drugs taken orally are swallowed.[5] 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.[6] It is considered most natural, uncomplicated, convenient, safe means of administering drugs.[7] Some of it's advantages are greater flexibility in dosage design, ease of production, low cost etc.[8] Some of the undesirable effects of conventional solid dosage forms can be overcome by the use of immediate release tablets.[9] Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription which result in high incidence of noncompliance and ineffective the therapy. Other disadvantages related to conventional oral solid dosage forms are chocking, low bioavailability especially drugs which undergo first pass effect (eg. Nitroglycerin) delayed absorption etc.[10]

Recent advances in Immediate Release Drug Delivery Systems aim to enhance the safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance.[11] (Nearly 35-50% of general population, especially elderly and children suffer from dysphagia or difficulty in swallowing ,which results in high incidence of non-compliance and ineffective their Swallowing problems are very common in young individuals because of their poorly developed muscular and nervous systems[12]. Other groups who may experience the problems in swallowing conventional dosage forms are the patients with tremor of extremities, mentally ill, developmentally disabled, non co-operative 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 motion sickness, sudden episodes of allergic attack or coughing and due to the lack of water. To overcome these problems scientist have developed an innovative drug delivery system known as immediate release tablets These are the novel solid oral dosage forms which dissolves rapidly in saliva without need for drinking water .The tablet disintegrates disintegrates instantaneously or disperse in saliva then swallowed and absorbed in normal way. Some drugs are absorbed from mouth, pharynx and oesophagus as the saliva passes down in to stomach and produce rapid on set of action. (.In such cases bioavailability of drug is significantly greater than those observed from conventional tablet dosage forms[13]. Immediate release tablets with good taste and flavor increase the acceptability of bitter drugs by various groups of population[14].

Immediate release Tablets are also known as fast disintegrating Tablet, melt in mouth tablet, rapimet, porous tablet, immediate release tablet, Rapidly Disintegrating Tablet, orally disintegrating tablet, quick disintegrating tablet, mouth dissolving tablet, fast disintegrating tablet[15] (United States Pharmacopoeia (USP) approved the dosage forms as immediate release tablet .Recently, European Pharmacopoeia has used the term immediate release tablet for tablet that disperses readily and within 3 minutes in mouth before swallowing. . The disintegration time of ODTs generally ranges from several seconds to about a minute[16].

United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually with a matter of seconds when placed up on the tongue[17]. The US Food and Drug Administration centre for Drug Evaluation and Research (CDER) defines in the Orange Book an ODT as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue". The European Pharmacopoeia defines the immediate release, as a tablet that can be placed in the mouth where it disperses rapidly, before swallowing[18].

Immediate release tablets are most widely used dosage form because of it's convenience in terms of self administration, compactness and ease in manufacturing. (IRTS rapidly gaining acceptance as an important new drug technology[19]. These dosage forms dissolve or disintegrate in oral cavity within a minute even without the need of water or chewing.

SIGNIFICANCE OF IMMEDIATE RELEASE TABLETS [20,21]

- They provide good stability, accurate dosing, easy manufacturing small packaging size and easy to handle by patients.
- No risk of obstruction of dosage form, which is beneficial for travelling patients who do not have access to water.
- Easy to administer for pediatric, geriatric and institutionalized patients (especially for mentally retarded and psychiatric patients)
- Rapid disintegration of the tablet results in quick dissolution and rapid absorption which provide rapid onset of action.[22]

1.1 DESIRED CRITERIA FOR IMMEDIATE RELEASE DRUG DELIVERY SYSTEM[23,24]

- Requires no water for oral administration
- Be compatible with taste masking agent
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions like humidity and temperature.
- Allow high drug loading.

1.2 IMMEDIATE RELEASE TABLETS

1.2.1 Definition[25]

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.

1.2.2 Advantages of Immediate Release Tablets[26,27,28] ;

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[29].
6. Product identification is easy and marking done with the help of grooved punched and printing with edible ink,

1.2.3 Disadvantages of Immediate Release Tablets[30,31] ;

1. It is difficult to convert a high dose poorly compressible API into tablet of multiple size for human use[32].
2. Difficult to formulate a drug with poor wettability, slow dissolution in to tablet.
3. Slow onset 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.

1.3 FACTORS AFFECTING THE DRUG RELEASE: [33]

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, wettability etc.

Dosage form factors include manufacturing process and excipients incorporated in them.[34]

Several manufacturing process infilence 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[35].

The techniques used in the preparation of immediate release tablets are

1.4 CONVENTIONAL TECHNIQUES:[36,37,38,]

1. Tablet molding:

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

blended, 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 (lyophilization):

Lyophilization is a pharmaceutical manufacturing technology, which allows drying of heat-sensitive drugs and biologicals at low temperatures under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability[39].

3. Spray drying:

Spray drying is a process by which highly porous, fine powders can be produced. The composition contains a bulking agent (mannitol and lactose), a disintegrant (sodium starch glycolate and croscarmellose sodium), an acidic ingredient (citric acid) and/ or alkaline ingredients (sodium bicarbonate), which when compressed into tablets show fast disintegration and enhanced dissolution[40].

4. Sublimation:

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

5. Addition of disintegrants:

Addition of disintegrants in fast dissolving tablets, leads to quik

disintegration of tablets and hence improves dissolution. Microcrystalline cellulose, cross-linked carboxy methyl cellulose sodium, cross-linked polyvinyl pyrrolidone and partially substituted hydroxy propyl cellulose, absorb water and swell due to capillary action and are considered as effective disintegrants in the preparation of fast dissolving tablets[41].

6. Sugar based excipient:

Sorbitol, mannitol, dextrose, xylitol, fructose, maltose and polydextrose have been used as bulking agents. Because of their high aqueous solubility and sweetness, which impart a pleasing mouth feel and good taste masking, nearly all formulations for rapidly dissolving tablets contain sugar-based materials[42].

7. Mass Extrusion:

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

1.5 OTHER METHODS[43]

Other methods includes dry granulation, wet granulation and direct compression methods. The important component used in these methods is super disintegrant.

1.5.1 Dry Granulation

In this technique there is no use of liquids. The process involves the

formation of slugs. Then slugs are screened or milled to produce granules. The granules formed are then compressed to form tablets.

1.5.2 Wet Granulation

The process involves addition of liquid to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. These granules after drying are compressed to form tablets. This method have more operational manipulations and is more time consuming than other methods. This method is not suitable for drugs which as thermo labile or hydrolysable by presence of water in the liquid binder.

1.5.3 Direct Compression

The method involves direct compression of powder blends of active ingredient and suitable excipients, which will flow uniformly in the die cavity and forms a firm compact[44]. Direct compression methods are very popular because it reduces the number of steps involved and the materials required.

1.6 SUPER DISINTEGRANTS

Disintegrants have a major in the disintegration and dissolution process of orodispersible tablets made by direct compression [45]. 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[46] **.**

The understanding of disintegrant properties and their effect on formulation has advanced significantly during last few years practically regarding

superdisintegrants[47]..

Addition of super disintegrants 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 of fast dissolving tablets[48].

Table No-1 : List of Superdisintegrants[49]

Superdisintegrants Synthetic super disintegrants	**Example**	**Mechanism of action**
Croscarmellose®	Cross linked Cellulose	Swelling and wicking
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 ,wicking action
Natural super disintegrants		
Soy poly saccharides	-	-
Calcium silicate (20 – 40 %)		Wicking action

1.7 TECHNIQUES FOR SOLUBILITY ENHANCEMENT[50,51]

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are:

1.7.1 Physical Modifications

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

1.7.2. Chemical Modifications

Solid Dispersion Technology[52]:

The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state, prepared by the melting, solvent, fusion method, hot melt extrusion or supercritical fluid methods. The term co-precipitate has also been frequently used when solid dispersion is prepared by solvent method. During the past four decades, the solid dispersion technology was used to increase the dissolution rate and bioavailability of poorly water soluble drugs[13]. Some other techniques like salt formation, solubilization and particle size

reduction have been employed to increase dissolution rate and bioavailability but there are some practical limitations.

In 1961, Sekiguchi and Obi developed a solid dispersion method to increase bioavailability of poorly soluble drugs. This method involves formation of eutectic mixture of drug with water-soluble carriers by melting of their physical mixture. When the dispersion comes in contact with aqueous fluid, the carrier starts to dissolve followed by the release of drug in very fine colloidal particle form because of the formation of particles having the greatly enhanced surface area, the dissolution rate and solubility increases. Examples: Gris-PEG [Novartis] Nabilone in Povidone solid dispersion [Cesamet, Lilly] However, recently sustained release solid dispersions are developed using certain type of water insoluble carriers and water swellable carriers like, Methocel, Ethocel, Polyox, Carbopol, Klucel, Cellulose acetate phthalate, carboxymethyl cellulose. This approach consume less polymer in order to control the drug release rate, compared with physical mixture of drug and polymer. The solid dispersion can be prepared by fusion method, melting method, Solvent method, Hot melt extrusion and supercritical fluid method.

a. Fusion method:

The fusion method is sometime referred to as the melting method only 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 mixture is cooled with constant stirring in order to obtain homogeneously disperse matrix. The first dispersion of sulfathiazole and urea was prepared by fusion method, by melting at the eutectic composition followed by cooling step. The eutectic composition was choosen to obtain simultaneous crystallization of drug and

matrix during cooling. Polymers like Polyethylene glycols and Poly (vinyl pyrollidone) PVP are mostly used in this method.

Limitations:

- This method is suitable if the drug and polymer are compatible and can be mixed homogeneously at the heating temperature in order to prevent formation of two incompatible liquid phases or a suspension in heated mixture. This problem can be overcome by using surfactants.
- Sometime may be a 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 problem can be overcome by implementing faster cooling rate in order to form amorphous solid dispersion.
- 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 induced by the extruder. The twin-screw extruder or single-screw extruder is used in this method. This method offers the potential to shape the heated mixture in to implants, implants inserts, oral dosage forms. To predict the solid-state solubility and to select matrix suitable for melt extrusion, the solubility parameters are investigated. High 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 Hydroxypropyl cellulose, Hydroxypropyl cellulose phthalate, Eudragit, Cellulose 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

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 vaccume (sometime heat may be applicable with vaccume). When the solvent evaporates, super saturation may occur followed by simultaneous precipitation of the constituents resulting in a solid residue. During formulation, the formulation 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 coprecipitate takes longer time

Example[53]:

Ethanol: -5°C and reduced pressure followed by drying for 12 h in vacuum Methanol/Chloroform: 115°C for 1 hour or 125°C for 25 min 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.

Sometime solvent evaporation could be increased by using rotary evaporator followed by storing the residue in a vaccum desiccator to remove the residual solvent. Sometime vaccum drying at elevated temperature may cause phase separation because the mobility of drug and matrix decreases slowly. The freeze drying method can be used to evaporate the solvent hence the solvent should have high melting point and high vapor pressure.

For example: Dimethyl sulfoxide (DMSO) has high melting point (190' C) but it has very low vapor 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:[54]

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 technique does not involve use of any organic solvent termed as "Solvent free technique" and also known as Rapid Expansion of Supercritical Solution (RES). The application of this technique is very limited because most of the pharmaceutical compounds have very low solubility in carbon dioxide solution (less than 0.01 % wt).

Advantages of Solid Dispersion Technology:

- ✓ Single formulation can be used for multiple dose formulation
- ✓ Improves bioavailability of drug
- ✓ Improves dissolution of poorly water soluble drugs
- ✓ Controlled release formulations can be formulated Minimal use of excipients
- ✓ Less expensive machines needed during formulation
- ✓ Low cost and profitable production

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.

The development of technology to fill solid dispersion directly into hard gelation 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.

Law *et al*. demonstrated that by incorporating nifedipine with PEG based solid dispersion and 5%(w/w) phosphodityl choline may increase dissolution rate more than two folds.

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

Cardiovascular diseases are one of the life threatening diseases of mankind and hypertension is the most common cardiovascular disease, which requires constant monitoring. It is well known that hypertension is a major factor for congestive cardiac failure and coronary artery disease.[55]

Hypertension or high blood pressure is a condition in which the blood pressure in the arteries is chronically elevated. With every heart beat, the heart pumps blood through the arteries to the rest of the body. Blood pressure is the force of blood that is pushing up against the walls of the blood vessels. If the pressure is too high, the heart has to work harder to pump, and this could lead to organ damage and several illnesses such as heart attack, stroke, heart failure, aneurysm, or renal failure.

The current definition (WHO,2004) of hypertension is level of systolic blood pressure of 140 mm Hg or above, a level of diastolic pressure of 90 mm Hg or above, by repeated measurement over periods of several weeks. It may be systolic or diastolic, diastolic hypertension when diastolic BP is found to be 90 mm Hg or more on two consecutive visits.

1.8.1 Classification of hypertension:[56]

Hypertension is classified as either primary (essential) hypertension or secondary hypertension. About 90-95% of cases are categorized as “primary hypertension” which means high blood pressure with no obvious medical cause[14].

The remaining 5-10 % of cases (secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart or endrocrine system.

Persistent hypertension is a major risk factor for stroke, myocardial infarction (heart attacks), heart failure and aneurysms of the arteries (e.g. aortic aneurysm), and is a cause of chronic kidney disease. Even moderate elevation of arterial blood pressure is associated with a shortened life expectancy. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of associated health complications, although drug treatment is often necessary in patients for whom lifestyle changes prove ineffective or insufficient.

Category	**Systolic (mm of Hg)**	**Diastolic (mm of Hg)**
Normal	>130	<85
High Normal	130-139	85-89
Hypertension		
Mild stage (stage 1)	140-159	90-99
Moderate (stage 2)	160-179	100-109
Severe (stage 3)	180-209	110-119
Very sever (stage 4)	>210	>120
Malignant hypertension	>200	>140

1.8.2 Etiology:

In the year 2006 it is estimated that nearly one billion people or ~26% of the adult population had hypertension worldwide. It was common in both developed (333 million) and undeveloped (639 million) countries. However rates vary markedly in different regions with rates as low as 3.4% (men) and 6.8% (women) in rural India and as high as 68.9% (men) and 72.5% (women) in Poland.

In 2001 it is estimated that 43 million people in the United States had hypertension or were taking antihypertensive medication, almost 24% of the adult

population[16]. The prevalence of hypertension in the United States is increasing and reached 29% in 2004.It is more common in blacks and native Americans and less in whites and Mexican Americans, rates increase with age, and is greater in the southeastern United States. Hypertension is more prevalent in men (though menopause tends to decrease this difference) and those of low socioeconomic status.

Over 90–95% of adult hypertension is essential hypertension. One of the most common causes of secondary hypertension is primary aldosteronism[17].

1.8.3 Antihypertensive agents[57]:

Antihypertensive agents are the drugs which lower the blood pressure in hypertensive patients. Proteins, peptides and recombinant drugs**:**

a. Classification of antihypertensives:

1. Diuretics

eg. Chlorthalidone, Clopamide, Indapamide

2. β Adrenergic blockers

eg.Acebutolol, Atenolol, Metoprolol, Propranolol, Timolol

3. α Adrenergic blockers

eg. Terazosin, Prazosin, Doxazosin

4. α + β Adrenergic blockers

eg. Labetalol, Carvedilol,nebivolol

5. Ace inhibitors

eg. Perindopril, Captopril, Enalapril, Lisinopril, Fosinopril, trandolapril, benazepril etc.

6. Calcium channel blockers

eg. Amlodipine, Felodipine Nifedipine, Nimodipine, Verapamil

7. Vasodilators

eg. Hydralazine, Minoxidil, Sodium nitroprusside

8. Angiotension-II receptor antagonists

eg. Candesartan, Losartan, Valsartan

9. Central sympatholytics

eg. Clonidine, Methyldopa

2. LITERATURE REVIEW

- **Calò *et al.*, (1998)**[58] were studied that the antihypertensive and metabolic effects of nebivolol in hypertensive patients with type 1 diabetes. Author shown that the drug normalizes blood pressure, and while no improvement in glucose control was observed, it reduced total cholesterol and increased HDL cholesterol as well as the HDL to total cholesterol ratio.

- **Shougo Kaneko *et al.*, (1999)** investigated the renal protective effect of nifedipine (2-nitrophenyl derivative BAY a 1040) in streptozotocin (STZ) - induced spontaneously hypertensive rats (SHRs, 8 weeks of age). Author suggested that nifedipine inhibits the development of albuminuria and glomerular enlargement in STZ-induced diabetic SHRs.

- **Istvan Edes *et al.*, (2005)** examined the effect of the beta1-selective beta-blocker nebivolol, administered as add-on therapy, on left ventricular function in 260 elderly patients (N65 years) with chronic heart failure (CHF).

- **Zahid Dhakam *et al.*, (2008)** reported that nebivolol and atenolol have similar effects on brachial blood pressure and aortic stiffness. However, nebivolol reduces aortic pulse pressure more than atenolol, which may be related to a less pronounced rise in AIx and bradycardia.

- **P. V. Swamy *et al.*, (2007),**[59] prepared rapidly disintegrating oral tablets of meloxicam by direct compression method using superdisintegrants such as sodium starch glycolate, Ac-Di-sol and low molecular weight hydroxy propyl methyl cellulose. Combinations of superdisintegrants were used along with

directly compressible mannitol to enhance mouth feel. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, wetting time water absorption ratio and in-vitro dispersion time.

- **USPTO Patent 20070086974, (2007)[60],**described about pharmaceutical compositions of substituted benzhydrylpiperazines or their pharmaceutically acceptable salts, and their methods. It involves formulation of stable and palatable taste masked pharmaceutical compositions of cetirizine in combination with resins and the process for preparing the same.

- **Keith J. Simons *et al.*, (2006),** formulated fast-disintegrating sublingual tablets 0f Epinephrine bitartrate. Four tablet formulations, A, B, C, and D, containing 0%, 6%, 12%, and 24% of Epinephrine bitartrate, respectively, and microcrystalline cellulose: low-substituted hydroxypropyl cellulose (9:1), were prepared by direct compression, at a range of compression forces. Tablet weight variation, content uniformity, hardness, disintegration time, wetting time, and friability were measured for each formulation at each compression force. All 4 tablet formulations at each compression force were within the USP limits for weight variation and content uniformity. At a mean ± SD hardness of ≤ 2.3 ± 0.2 kg, all tablet formulations passed the USP friability test. At a mean ± SD hardness of ≥ 3.1 ± 0.2 kg, all tablet formulations resulted in disintegration and wetting times of <10 seconds and <30 seconds, respectively.

- **Istvan Edes *et al.*, (2005)[61]** examined the effect of the beta1-selective beta-blocker nebivolol, administered as add-on therapy, on left ventricular function in 260 elderly patients (N65 years) with chronic heart failure (CHF).

- **Zahid Dhakam *et al.,* (2008)** reported that nebivolol and have similar effects on brachial blood pressure and aortic stiffness. However, nebivolol reduces aortic pulse pressure more than atenolol, which may be related to a less pronounced rise in AIx and bradycardia.

- **Sarah E. Capes *et al.,* (2000)[62]** reported that clinical proteinuria patients with left ventricular (LV) dysfunction are unknown. Clinical proteinuria is an independent predictor of hospitalization for CHF and mortality in diabetic and nondiabetic patients with LV dysfunction. Enalapril significantly reduces the risk of clinical proteinuria in diabetic patients with LV dysfunction.

- **Anna K. Trauernicht *et al.,* (2003)** were studied that effects of chronic treatment with enalapril on cerebrovascular dysfunction and endothelial nitric oxide synthase (eNOS) protein in diabetic rats. These results suggested that enalapril prevents cerebrovascular dysfunction in diabetic rats. Author conclude that the protective role of enalapril may be independent of an alteration in eNOS protein in cerebral microvessels.

- **Jeevana Jyothi *et al.,* (2010)** developed fast dissolving tablets of nebivolol using crospovidone and it's kneading Mixture.

- **K. Danjo *et al.,* (2002)[63]** provides information regarding preparation evaluation and optimization of rapidly disintegrating tablets.

- **M M Patel *et al.,* (2006)** prepared rapid disintegrating tablets of nebivolol by using various superdisintegrants following direct compression technique.

- **Martin *et al.*, (2004)** reviewed the nebivolol and their uses. It provides information regarding the history preparation, complex formation of nebivolol and industrial applications.

- **Pisal *et al.*, (2004)**[64] formulated and evaluated tasteless complexes of Ciprofloxacin with Indione 234. Studies showed that solid dispersion affected by pH, but temperature not affected. Volunteers rated the complex as tasteless.

- **Rao *et al.*, (2000)** formulated taste masked oral suspension of Quinine sulfate. For taste masking solid dispersion was done with ion exchange resin (Indione – 234). The products were evaluated for bitterness, drug content, particle size, viscosity, sedimentation time, volume, redispersibility and drug release.

- **Ronchi M *et al.*, (2003)** provides the information regarding the use of disintegrants in solid dosage forms. Described the mechanism of disintegrants in disintegration process of tablets.

- **S.K Seth *et al.*, (2010)** al provides methods to mask the bitter taste of drugs – by solid dispersion with beta nebivolol, also described the methods of preparation and evaluation of immediate release tablets.

3. AIM AND OBJECTIVE

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

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

According to BCS classification nebivolol coming under class 2 category which has low solubility and high permeability. Nebivolol is a white powder, relatively insoluble in water. Solubility and dissolution was improved by formulating solid dispersion. Keeping in view the advantages of this delivery system, in the present study, attempts were made to formulate immediate dissolving tablet nebivolol, which is useful to reduce blood pressure level in the treatment of antihypertensive agents.

The direct compression was used to compress the tablets as it is the easiest 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 in hardness and have less friability.

Super disintegrants are the major components of immediate release tablets.Based on their origin they can be grouped in to two category, synthetic super disintegrants (micro crystalline cellulose, cross povidone, cros carmellose sodium, starch glycolate) and natural super disintegrants.

Natural origin is preferred over semi synthetic and synthetic substances because they are comparatively cheper, abundantly, non irritating non toxic in nature.

The formulation of immediate release using natural super disintegrants is an excellent example for the application of natural agents in the formulative field. And this proved that the natural agents have almost equivalent properties to synthetic agents, which can be widely used for formulation of dosage forms.

Nebivolol used to improve the solubility, stability of drug and also to mask its bitter taste.

4. PLAN OF THE WORK

- LITERATURE SURVEY
- SELECTION OF DRUG AND EXCIPIENTS
- PREFORMULATION STUDIES
    - Evaluation of Physical Parameters of Nebivolol
    - Drug Excipients Compatibility study
    - Construction of standard curve
- PREPARATION OF SOLID DISPERSION AND PHYSICHAL MIXTURE
- CHARACTERISATION OF SOLID DISPERSION AND PHYSICAL MIXTURE
- PREPARATION AND EVALUATION OF NATURAL SUPERDISINTEGARANTS
- PRECOMPRESSION PARAMETERS
- FORMULATION OF IMMEDIATE RELEASE TABLETS WITH DIFFERENT DISINTEGRANTS
- EVALUATION OF IMMEDIATE TABLETS BY
    - Weight variation
    - Friability
    - Thickness
    - Hardness
    - *In-vitro* disintegration

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

❖ STABILITY STUDY OF OPTIMISED FORMULAITON AS PER ICH GUIDELINES

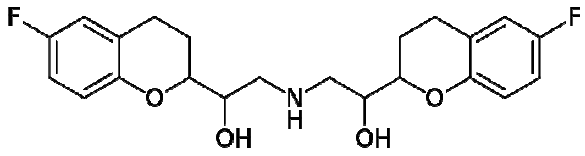
5. PROFILES

5.1 DRUG PROFILE:

5.1.1 NEBIVOLOL[65,66]

Nebivolol is a highly cardio selective vasodilator beta1 receptor blocker used in treatment of hypertension.

Chemical Structure:



Chemical Name:

1,1'-(bis(6-fluoro-3,4-dihydro-2h-1-benzopyran-2-yl)-2,2'-iminodiethanol.

Molecular Formula: C_{22} H_{25} F_2 NO_4

Molecular Weight: 405.4

Category: selective beta-1 receptor antagonist.

Description: white to almost –white powder.

Solubility:

The solubility of drug was determined in various solvents and it was found that the drug is freely soluble in N, N-dimethyl formamide, methanol, and dimethyl sulfoxide; sparingly soluble in polypropylene glycol and ethanol and insoluble in water.

Storage:

Store below 30^{o}c, protect from moisture. Store in tight light resistant container.

Mechanism of action:

Nebivolol is a selective , $\beta_{1,}$ - receptors antagonist. activation of receptors by epinephrine increase the heart rate and blood pressure, and the heart consumes more oxygen. nebivolol blocks these receptor which reverse effect of epinephrine, lowering the heart rate and blood pressure. in addition, beta blockers prevent the release of resin, which is a hormone produced by the kidneys which leads to construction of blood pressure. A enough concentration, this drug may also bind bete2 receptors.

Pharmacodynamics:

Nebivolol is a competitive and highly selective beta-1 receptor antagonist with mild vasodilating properties, its due to an interaction with the L-arginine\nitric acid pathway. In preclinical studies, nebivolol has been show induse endothelium-dependent arterial relaxation in a dose dependent manner, by stimulation of the release endothelial nitric oxide. Nictric acid acts to relax vascular smooth muscle cells and inhibits platelets aggregation adhesion.

Renal effects:

Plasma concentrations of nebivolol have been reported to be increased in patients with renal impairment. Based on mean AUC data, approximately 40% to 50% higher plasma concentrations of nebivolol were observed in hypertensive

patients with moderate to severe renal impairment compared to a control group of hypertensive patients with normal renal function.

Pharmacokinetics:

Absorption

Nebivolol is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability.

Distribution

The drug is highly lipophilic and is highly protein bound. The stereo selective tissue distribution of nebivolol enantiomers results from an enantiomeric difference in plasma protein binding rather than in tissue binding.

Metabolism

Nebivolol is metabolized primarily by aromatic ring oxidation and glucuronidation.The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. Demethylation and hydroxylation at the phenol ring produce 3 active metabolites with β-receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than nebivolol for β-blockade. Compared to nebivolol, the 3 active metabolites exhibit weak vasodilating activity. Plasma concentrations of the active

metabolites are about one-tenth of those observed for nebivolol and have pharmacokinetics similar to the parent.

Elimination

The metabolites of nebivolol are excreted primarily via the bile into the feces. The elimination half-life of nebivolol generally ranges from 7 to 10 hours.

Contraindications

- Bronchial asthma or related bronchospastic conditions.
- Second- or third-degree AV block
- Sick sinus syndrome
- Severe bradycardia (unless a permanent pacemaker is in place)
- Patients with cardiogenic shock or who have decompensated heart failure requiring the use of intravenous inotropic therapy.
- Patients with severe hepatic impairment
- Patients with a history of a serious hypersensitivity reaction (e.g., Stevens-Johnson syndrome, anaphylactic reaction, angioedema).

Therapeutic indications: Nebivolol can be used in the following indications:

- Hypertension
- Congestive heart failure
- Myocardial infarction

Marketed dosage forms:

Bystolic controlled release tablets of nebivolol in doses 2.5mg, 5mg, 10mg, 20mg.

5.2 EXCIPIENT PROFILE:

CROS POVIDONE[67]

Synonyms : Crosslinked povidone ;EI 202;Kollidon CL;Kollidon CL-M;polyplasdon XL 10 ; Polyvinyl poly pyrrolidone ;PVPP; 1-vinyl -2-pyrrolidone homopolymer.

Description : Crospovidone is a white to creamy white finely devided, free flowing practically tasteless, odourless or nearly odourless hygroscopic powder.

Chemical name : 1-ethenyl -2 –pyrrolidone homopolymer.

Molecular weight : >1000000

Functional category: Tablet disintegrant ***(Raymond C.Rowe et al, 2001)***

Applications in Pharmaceutical Formulation

Cropovidone 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[68]

Synonyms : Primojel; Starch carboxy Methyl ether, sodium salt, Tablo;

Description : Tasteless, free flowing powder. The Ph Eur 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 [69]

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 condact 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[70]

Synonyms : Fumeric acid, Otadecyl ester sodium salt; Pruv ; Sodium monosrearyl fumerate.

Description : Sodium stearyl fumerate 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 stearyl fumerate 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 [71]

Synonyms : Atalc ; E 55 3 b; hydrous magnesium calcium silicate ; hydrous magnesium Silicate; magnesium hydrogen metasilicate ; Magsil osmanthus; 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; tablet and capsule lubricant.

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[72]

Synonyms:

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

Chemical Name and CAS registry number:

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

Molecular weight:

5000 – 7000 (average molecular weight)

Description:

Polyethylene glycol 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.

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[73]

Nonproprietary Names:

- BP: Microcrystalline cellulose
- JP: Microcrystalline cellulose

- PhEur: Cellulosum microcristallinum
- USPNF: Microcrystalline cellulose

Synonyms:

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

Chemical Name and CAS Registry Number:

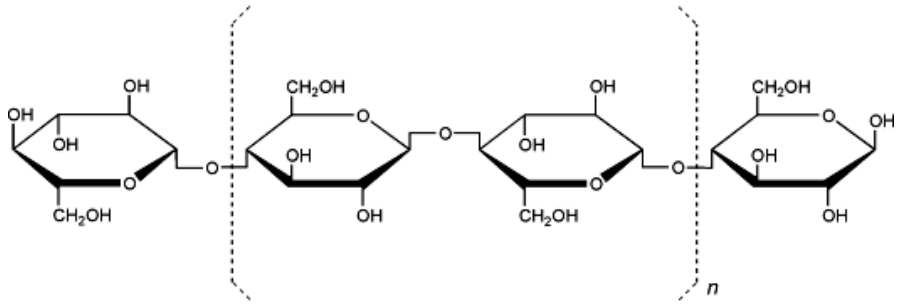
Cellulose [9004-34-6]

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[74]

Table No 3: Materials used and their suppliers

MATERIALS	SUPPLIERS
Nebivolol	Zydus pharma,Hosur
Ispagol	Gujarath International, Gujarath.
PEG 6000	Micro lab, Mumbai.
Microcrystalline cellulose	Loba chemi, Mumbai
Sodium starch glycolate	Research lab fine chem., Mumbai
Cros povidone	Reasearch lab fine chem., Mumbai
Sodium alginate	Loba chemi, Mumbai.
Talc	Lobachemi, Mumbai.
Aspartame	Bangalore antibiotics & Biological, Salam.
Aerosil	Lobachemi, Mumbai.
Methanol	Himedia lab, Mumbai.
Hcl	Micro Lab, Mumbai.

METHODS

Table No. 4. Process equipments and their suppliers

EQUIPMENTS	SUPPLIERS
Electronic balance	Shimadzu weighing balance
Magnetic stirrer	Remi equipments
Hot air oven	In lab equipments , Chennai.
Orbit shaker	Lab India.
Proton mini press tablet punching machine	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	Brukle alpha
Disintegration apparatus	Rolex

6.1 PRE-FORMULATION STUDIES:[75]

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 nebivolol powder was taken in a butter paper and viewed in well illuminated place.

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

6.1.2 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:

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

Where, W_1 = Weight of empty weighing bottle

W_2 = Weight of weighing bottle + sample

W_3 = Weight of weighing bottle + dried sample

6.1.3 Angle of repose:

Angle of repose is the maximum angle of a stable slope determined by friction, cohesion and the shapes of the particles. The internal angle between the surface of the pile and horizontal surface is known as the angle of repose and is related to the density, surface area and co-efficient of friction of the raw material.

Method: Angle of repose was determined by using funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed blend is allowed to pass through the funnel freely on the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.

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

Where, h = height of heap, r = radius of heap, Θ = angle of repose.

Table-5: Limits:

Angle of repose	Flow property
$<25^{o}$	Excellent
25-30 ^{o}	Good
30-40 ^{o}	Passable
$>40^{o}$	Very poor

6.1.4 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.

Method: A quantity of 5 gm of powder weighed and transferred to a measuring cylinder and observed the volume occupied by the sample. The initial volume was calculated. Bulk density was calculated using the formula.

Bulk Density = Bulk Mass / Bulk Volume

Tapped density: Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume changes is observed the mechanical tapping is achieved by raising the cylinder and allowing it to drop under its own weigh a specific distance. Device that rotates device during tapping may be preferred to minimize any possible separation of the mass during tapping down.

The powder in the measuring cylinder were tapped for specific times at a height of 2.5 cm at a interval of 2 seconds. The powder in the graduated cylinder were tapped for specific times at a height of 2.5 cm at an interval of 2 seconds. The final volume occupied by the sample was noted and tapped density was calculated by using the formula:

$$\textbf{Tapped Density} = \frac{m}{Vf}$$

Where, m = initial weight of material in gm, Vf = volume of material after tapping. Generally replicate determinations are desirable for the determination of this property.

6.1.5 Measurement of Powder Compressibility:

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

$$\textbf{Compressibilityindex:} = 100\,\frac{(V_0 - Vf)}{V_0}$$

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

Table – 6 : Limits:

S. No.	Compressiility 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

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

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

Table - 7: Limits:

S.No	Hausner' ratio	Flow
1	1-1.2	Free flowing
2	1.2-1.6	Cohesive powder

6.1.6 Solubility analysis:

Solubility is important pre-formulation parameter because it affects the dissolution of drug, bio availability of drug.

Method: solubility of nebivolol was determined in methanol, ethanol, dimethyl fluoride methylchloride,0.1NHCl.solubility studies were performed by taking excess amount of nebivolol in different beakers containing the solvent. The mixture was shaken for 10hrs at regular intervals .the solution was filtered by using whatmann filter paper. The filtered solution were analysed spectrophotometrically.

61.7. P^H

Weighed and transferred accurately about 1.0 g of sample in 20 ml clean and dried volumetric flask dissolved in carbon dioxide 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 nebivolol sample and added to 100 ml volumetric flask. Added 1ml of methanol mixed for 10 minutes added 70ml of 0.1 N

Hydrochloric acid and dissolved it.Make 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 282nm.

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 recording using Brukle alpha spectrometer. KBr powder was to prepare used to prepare pellet for sampling. The scanning range was 4000-400cm.

6.3 PREPARATION OF STANDARD CURVE

The calibration curve is based on the spectrophotometry. The maximum absorption was observed at 282nm. It obeyed Beer's law in the concentration range of 10-50 µg/mL.

Preparation of stock and standard solution:

The standard solution of nebivolol hydrochloride was prepared by accurately weighing 10 mg of the drug. It was diluted in a 100 mL volumetric flask with methanol to give a range of solutions with final concentrations of 5–50 mg/mL. The absorbance of each solution was determined at 282 nm.

Preparation of various concentrations:

10 ml stock solution was taken from stock solution-2 and volume made up to 100 ml by using 0.1 N HCl to get 100 µg/ml concentrations. From this solution 10-50 µg/ml concentrations were prepared.

6.4. Preparation of solid dispersion and physical mixture[76];

6.4.1. Solid dispersions prepared by melting the carrier

Solid dispersions (SDs) preparations containing different weight ratios of nebivolol in PEG6000 (1:1, 1:2, 1:5) were prepared by the melting method. Nebivolol 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 50#.

6.4.2. Physical Mixture

Physical mixture (PMs) having the same weight ratios were prepared by thoroughly mixing appropriate amounts of nebivolol and PEG 6000 in a mortar until a homogenous mixture was obtained. The resulting mixture were sieved through a 50# sieve and denoted as PM.

6.5. Characterization of solid dispersions of nebivolol with PEG 6000[77]

6.5.1. Drug content

The drug content in each solid dispersion and physical mixture was determined by the UV-spectroscopic method. An accurately weighed quantity of solid dispersion or physical mixture, equivalent to 40 mg of nebivolol, was transferred to a 100-mL volumetric flask containing 10ml of methanol and dissolved. The volume was made up to 100ml with 0.1 N HCL. The solution was filtered through 0.45-mm membrane filter paper. One ml of this solution was diluted 100 times with 0.1 N HCL to achieve 6 µmol L–1 and the absorbance was measured at 282 nm.

6.5.2. Phase-Solubility Study

Phase-solubility studies were carried out by adding excess of drug (20 mg) in screw-capped vials containing 20ml of aqueous solution of different PEG 6000 concentration. The suspensions were continuously stirred on electromagnetic stirrer at 25^0 and 37^0C and 300 rpm for three days (this duration was previously tested to be sufficient to reach equilibrium). The suspensions were filtered through 0.22µm membrane filter. The filtrate were suitably diluted and analyzed, spectrophotometrically, for the dissolved drug at 282nm.

6.5.3. Dissolution Studies:

Dissolution studies of nebivolol in powder form, SDs, and PMs were performed by using the USP type II paddle apparatus at the paddle rotation speed of 50 rpm in 900ml of 0.1 N HCl as a dissolution medium at 37±0.5 °C. The SDs or PMs equivalent to 10 mg of nebivolol were 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 nebivolol content by measuring the absorbance at 282 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 Alpha FTIR. The samples (nebivolol 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)[78]:

The powder of seeds and husk were prepared by an automatic grinder and sieved (#80). Then it stored in a desicator until use .For isolation of seed mucilage, the cleaned seeds of Plantago ovate 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 desicator 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 for 4 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 evaluvated for swelling factor, bulk density, tapped density, angle of repose. Angle of repose were 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 NEBIVOLOL.[79]

Different Nebivolol 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 Nebivolol Solid dispersion, and weighed the amount equivalent to 10 mg Nebivolol, was mixed with other excipents and compressed proton miniplus tablet punching machine. The tablet weight was adjusted to 430 mg. All formulation prepared according to the following formulation table.

Table No. 8 - FORMULATION OF IMMEDIATE RELEASE TABLET

INGREDIENTS	**Quantity in mg per tablets**											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
1:5 Solid dispersion equivalent to 40 mg Nebivolol	240	240	240	240	240	240	240	240	240	240	240	240
MCC	93.0	93.0	93.0	93.0	93.0	93.0	93.0	93.0	93.0	93.0	93.0	93.0
Mannitol	79.0	76.0	79.0	76.0	79.0	76.0	79.0	76.0	79.0	76.0	79.0	76.0
Isphagol mucilage	9.0	12.0	-	-	-	-	-	-	-	-	-	-
Isphagol powder			9.0	12.0								
Isphagol husk Powder	-	-	-	-	9.0	12.0	-	-	-	-	-	-
Cross povidone	-	-	-	-	-	-	9.0	12.0				
SSG	-	-	-	-	-	-	-	-	9.0	12.0		
Calcium CMC	-	-	-	-	-	-	-	-	-	--	9.0	12.0
SSF	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Talc	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Aerosil	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Aspartame	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Orange flavor	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Total weight (mg)	430	430	430	430	430	430	430	430	430	430	430	430

6.8 Evaluation of Immediate Release Tablet:

6.8.1. PHYSICAL APPEARANCE

Prepared Oral Disintegrating 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 weight between 80 – 250 mg, percentage deviation should not more than ± 7.5 % 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

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 25 rpm, dropping the tablets at a distance of 6 inches in each revolution. Pre weighed tablets were placed in friabilator, which was then operated for 100 revolutions. The tablets were dusted and reweighed.

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

W0 = initial weight, W =final weight.

6.8.4. THICKNESS

The thickness 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

Disintegration time of 6 tablets from each formulation was determined by using USP disintegration apparatus. Disintegration test was carried out in 900 ml buffer pH 6.8 at 37 ± 2 ^{0}C and 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 tables from each batch were separately kept in 100 ml water and gently tirred for 2 minutes. The dispersion was passed through 22 mesh. The tablet 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.

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

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

STANDARD PREPARATION

Weighed accurately 50 mg of Nebivolol and added to 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 ml from that solution and diluted to 10 ml with 0.1 N hydrochloric acid.

SAMPLE PREPARATION

Crushed 15 tablets and weighed quantity equivalent to 50 mg Nebivolol , dissolved in minimum quantity of methanol 0.1 N hydrochloric acid 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 282 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

Dissolution studies were carried out using USP type II (paddle apparatus) at 50 rpm 0.1 N Hydrochloric acid 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 absorbance were measured at 282 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. 9.

Table No. 9: Organoleptic Properties

Test	Specification/Limits	Observations
Color	White or almost 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 result were illustrated in table no. 10.

Table No.10 : Loss on Drying

Test	Specification/Limits	Observations
Loss on drying	Not more than 0.5%	0.087%

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. 11.

Table No.11: Flow properties

Material	Angle of repose
Nebivolol	$28^{o}.80$”

*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. 12.

Table No.12: Density

Material	Bulk Density (gm/ml)	Tapped density (gm/ml)
Nebivolol	0.21	0.31

*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. 13.

Table No.13: Powder Compressibility

Materials	Compressibility index	Hausner ratio
Nebivolol	15.23%	1.34%

*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. 14.

Table No.14: Solubility

Test	Specification	Result
Solubility in water, Methanol, Methylene chloride, alcohol.	Practically insoluble in water, freely soluble in methylene chloride, slightly soluble in ethanol.	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. 15.

Table No.15: pH

Test	Specification	Observation
pH	2.5	2.4

7.1.8. Assay

It was determined as per procedure given in 6.1.8. The results were illustrated in table no. 16.

Table No.16: Assay

Test	Specification	Observation
Assay	90 - 110.0 %	98.81%

7.2. DRUG EXCIPIENTS COMPATABILITY STUDY BY FTIR;

Compatability 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.

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

Table No. 17: FT-IR Peak Of Various Components.

Characteristic bands	Pure drug	Physical mixture
N-H	2905.89cm-1	3000.14cm-1
C=O	1710.74cm-1	1735.04cm-1
C-F	1350.08cm-1	1375.65cm-1

Fig. No. 1: IR spectrum of nebivolol

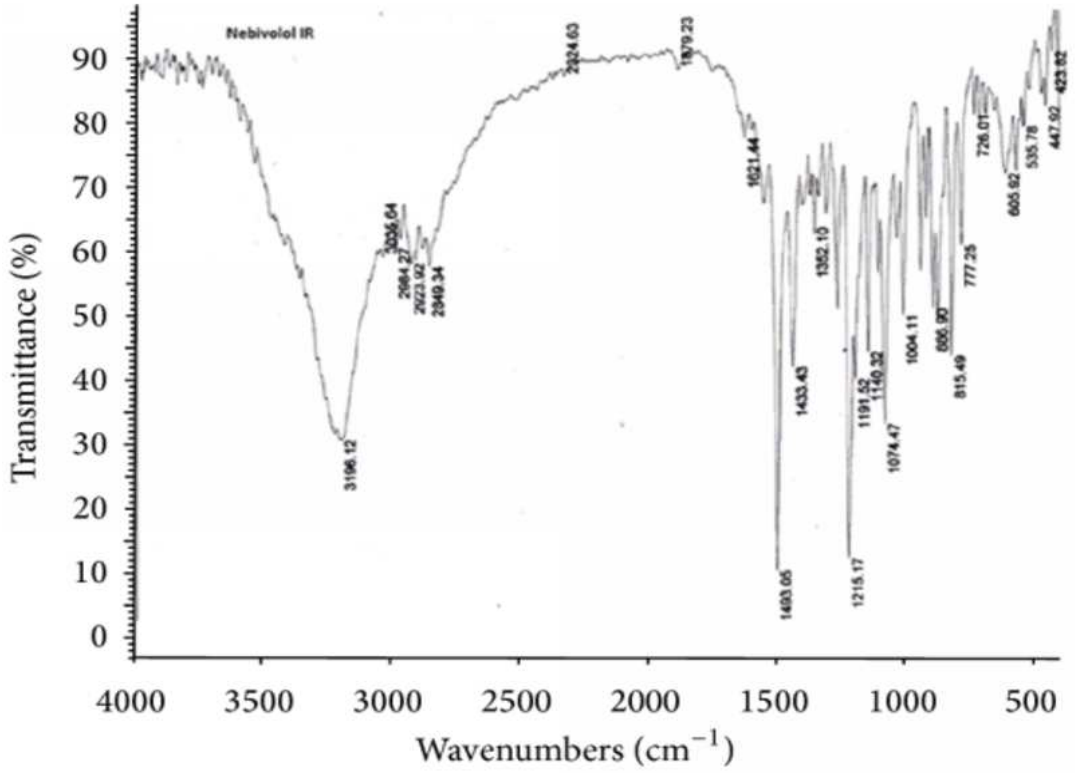


Fig. No. 2: Ispagol Mucilage

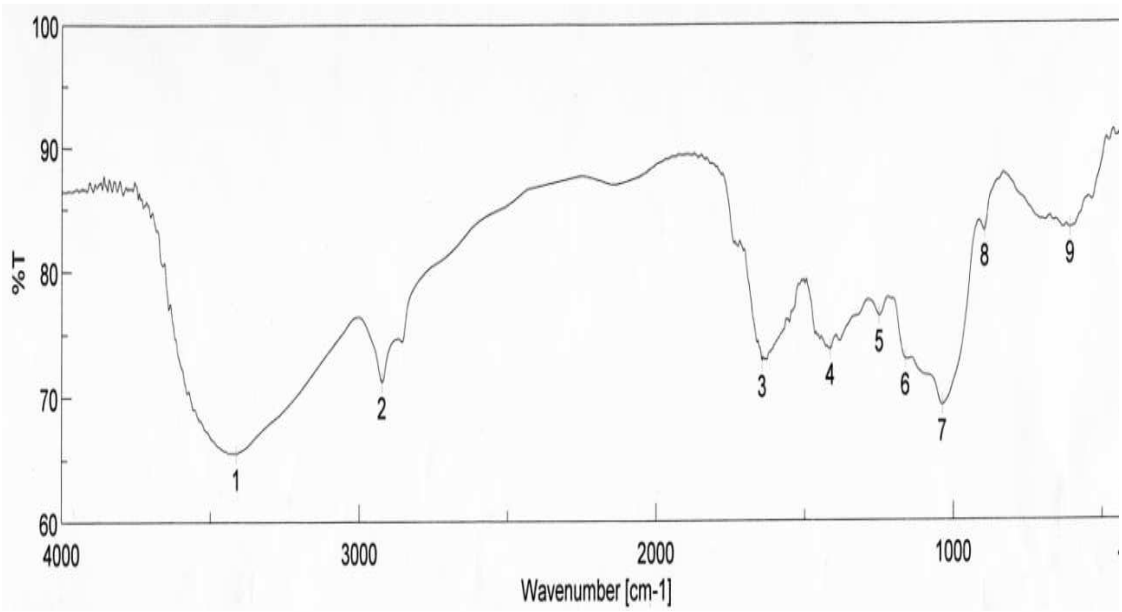


Fig. No. 3: Ispagol Seed Powder

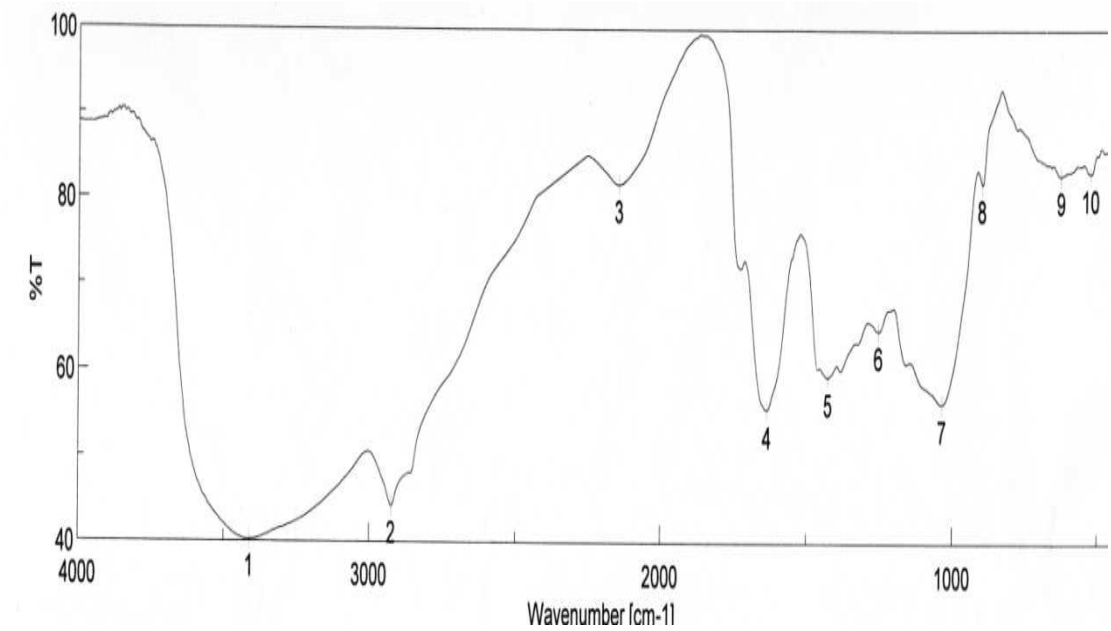


Fig. No. 4: Ispagol Husk Powder

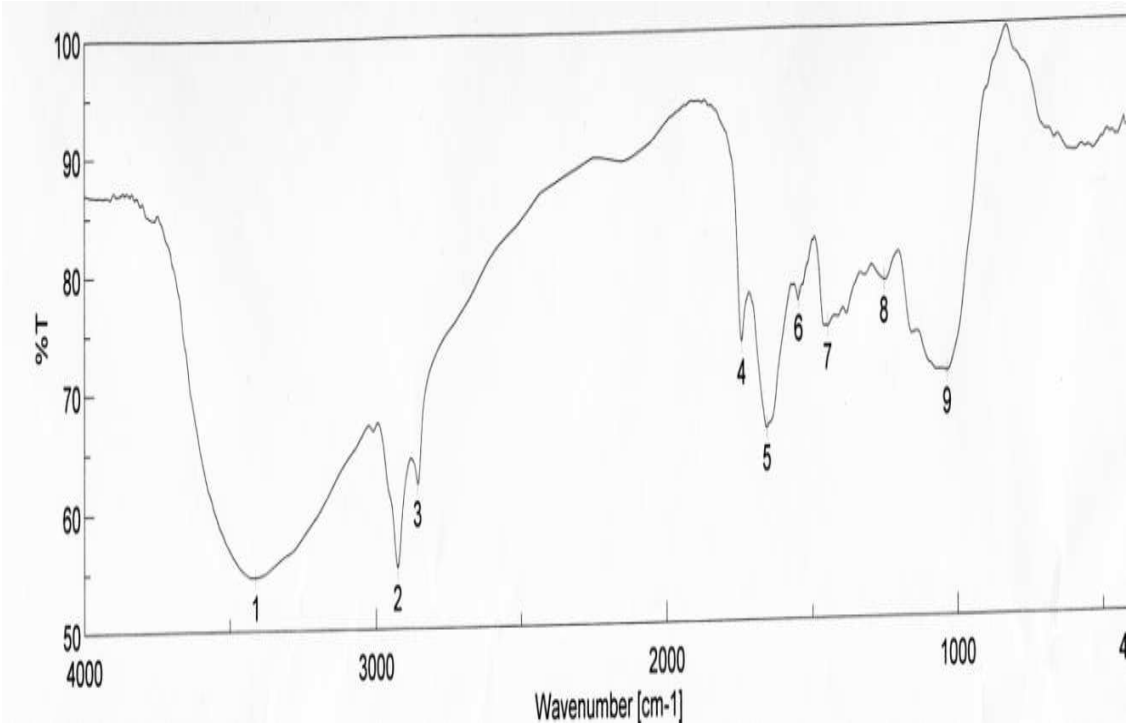


Fig. No. 5: IR Spectra of Microcrystalline Cellulose

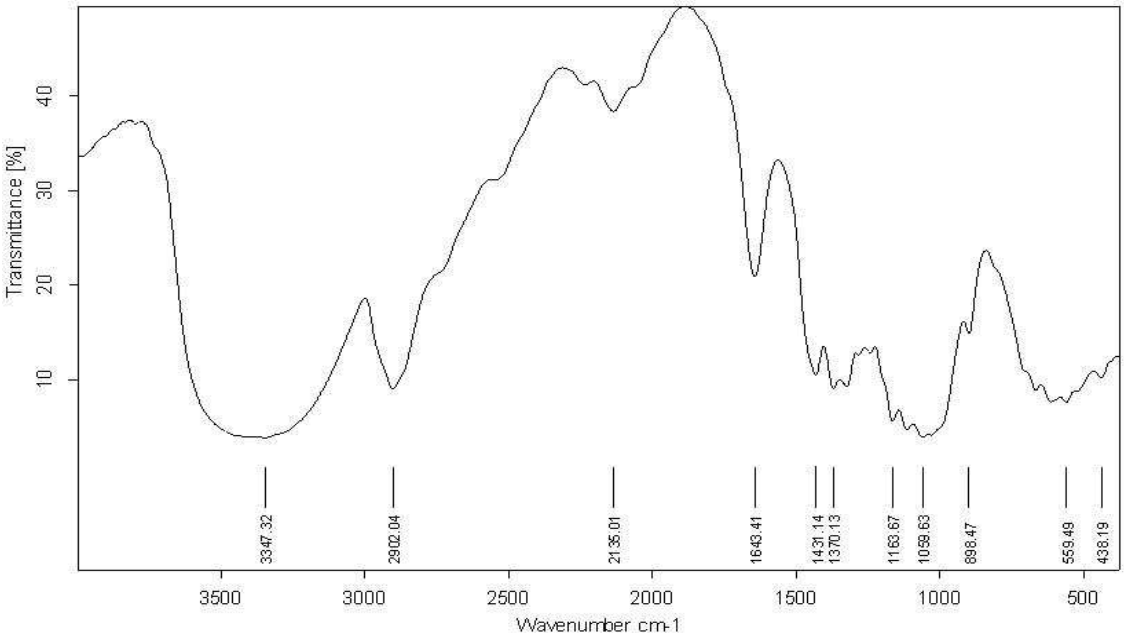


Fig. No. 6: IR Spectra of Crospovidone

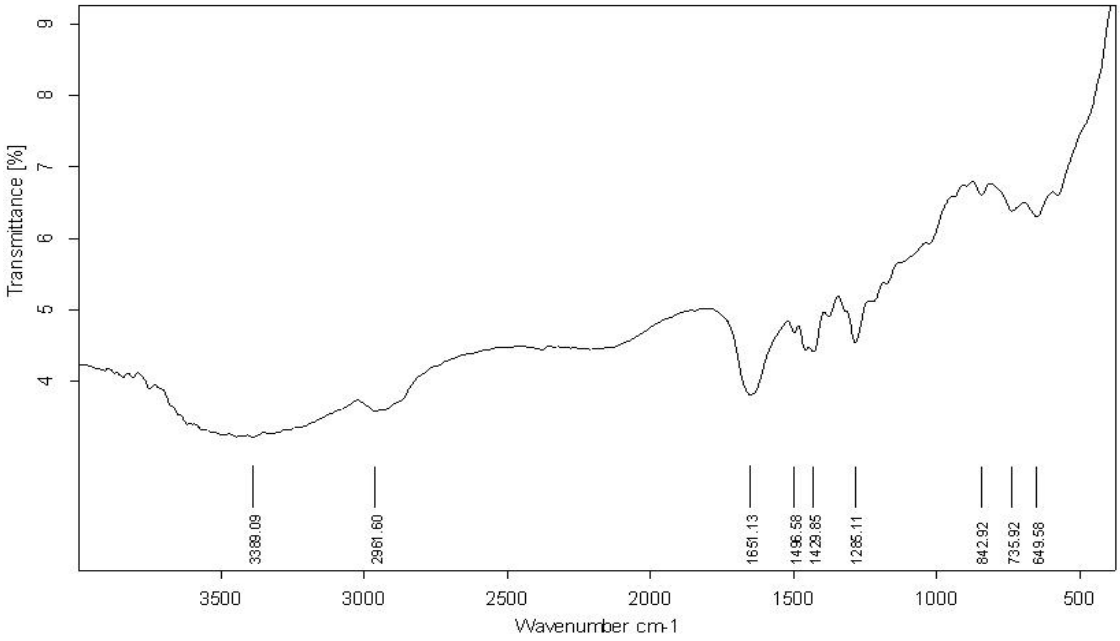


Fig. No. 7: IR Spectra of Croscarmellose Sodium

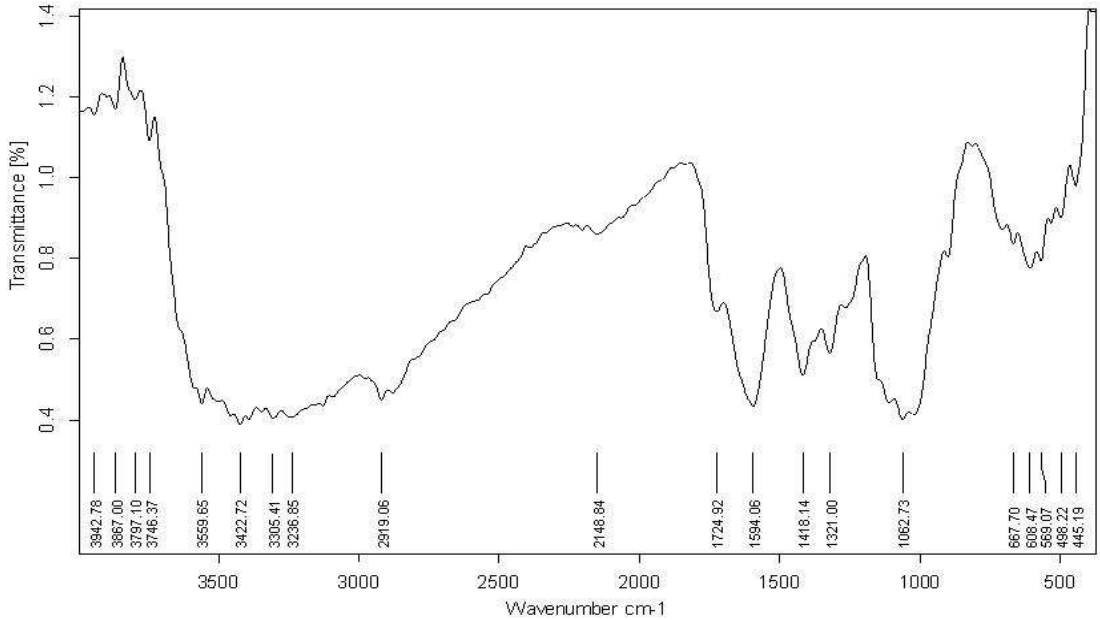


Fig. No. 8: IR Spectra of Sodium Starch Glycolate

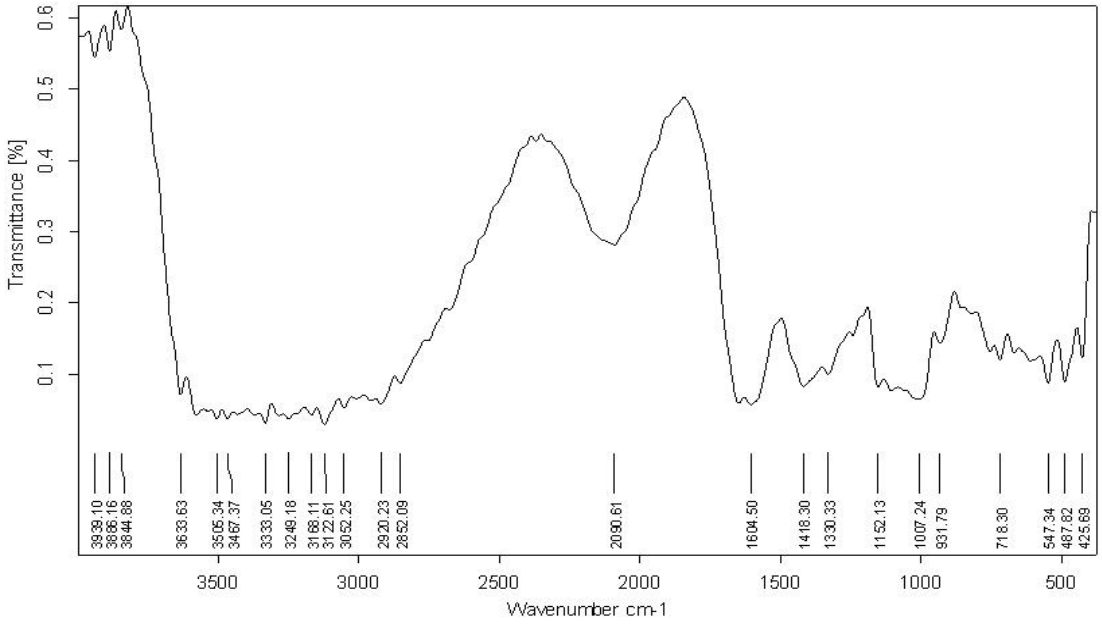


Fig. No. 9: IR Spectra of PEG 6000

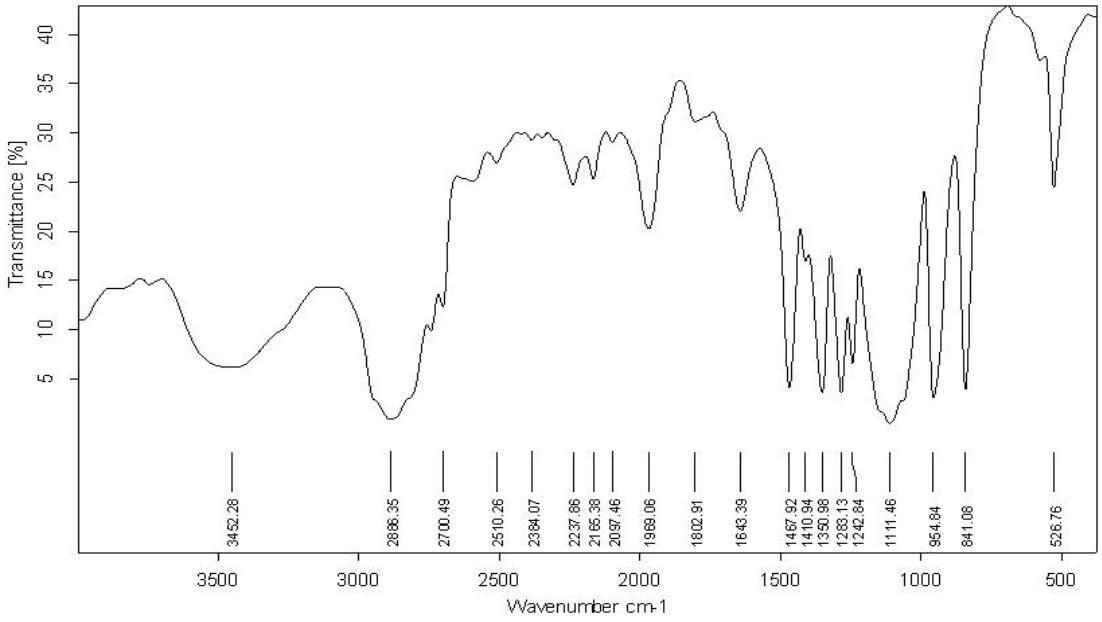
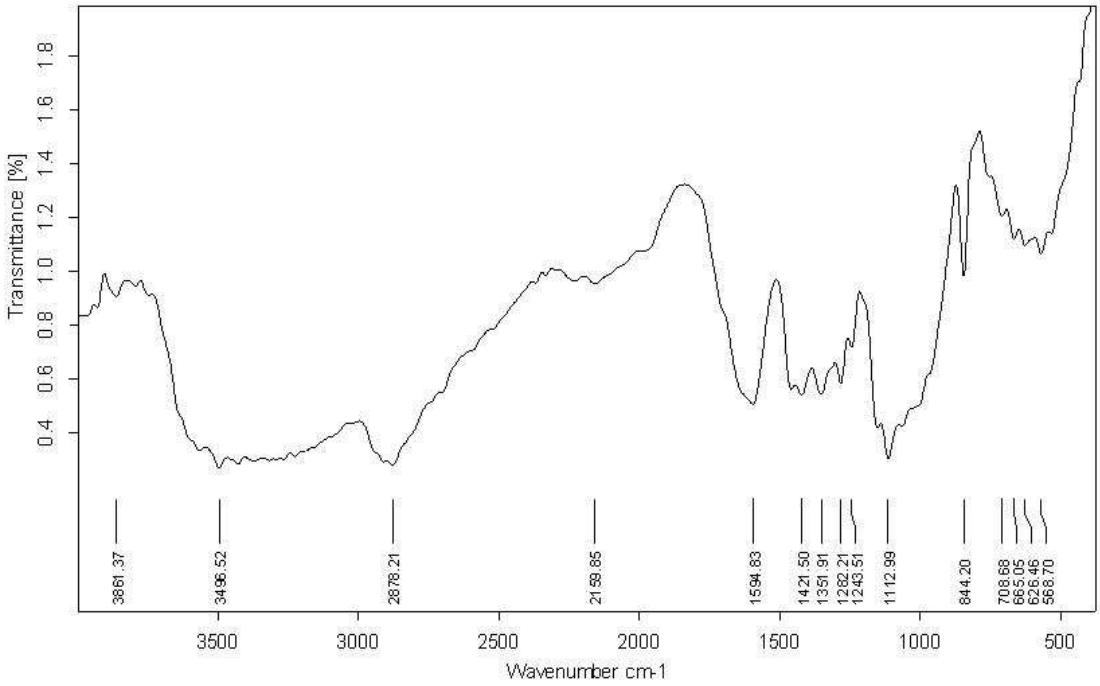


Fig. No. 10: IR Spectra of Nebivolol & Excipient Mixture



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 nebivolol 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 nebivolol tablet. Absorbance scans of drug in 0.1N HCL, showed maximum at 282 nm, which is selected as the analytical wavelength. Standard curve of nebivolol in 0.1N HCL. Calibration curve of nebivololl was determined by plotting absorbance (nm) versus concentration (µg/ml) at 282 nm. The results obtained are as follows.

Table – 18: Standard curve of nebivolol

Concentration	Absorbance
10	0.123
20	0.280
30	0.436
40	0.654
50	0.812

The linear regression analysis was done on absorbance data points. A straight line generated to facilitate the calculation of amount of drug, the equation is as follows:

$$Y = mx + c$$

Where Y=absorbance, m=slope, x=concentration

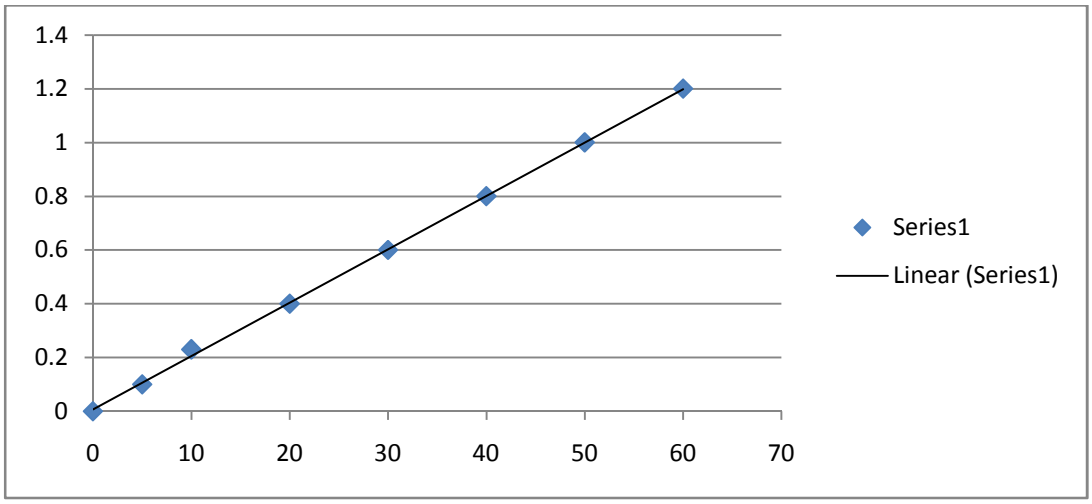


Fig. 11 : Standard plot for nevibolol in 0.1N HCL

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 Nebivolol 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. 19.

Table No. 19: 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	99.25	PM 1:1	96.61
SD 1:2	98.47	PM 1:2	97.98
SD 1:5	99.71	PM 1:5	99.11

7.5.2. Phase solubility Study

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

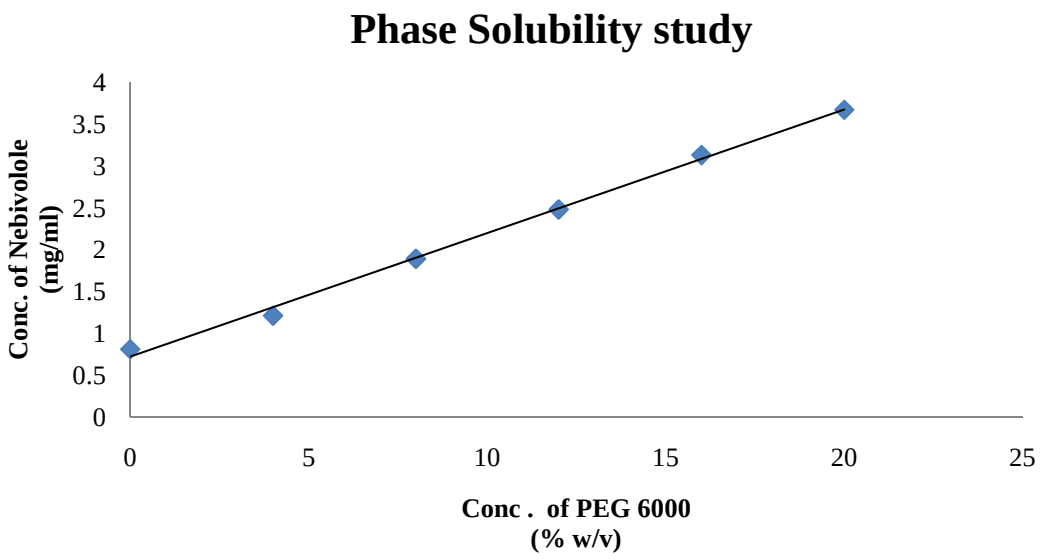


Fig. 12: Solubility diagram of Nebivolol in presence of PEG 6000

Fig no.12 represented the effect of different polymers concentration at different temperature on the solubility of Nebivolol. 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 Nebivolol increased with increasing temperature and carrier concentration.

Solubility of Nebivolol in pure water at 25^{o}C was 0.01 mg/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.

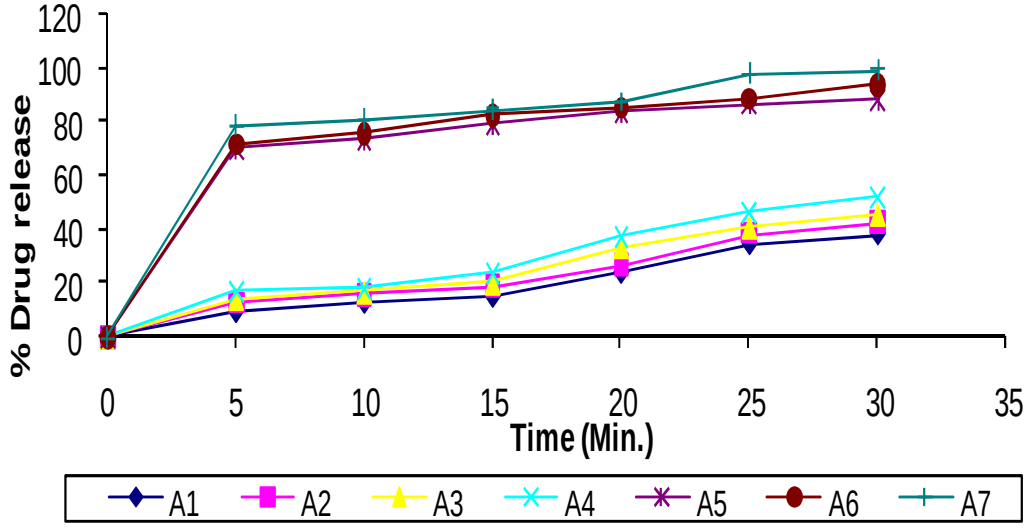
7.5.3. Dissolution studies

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 Nebivolol, Physical Mixture of Nebivolol and Solid Dispersion of Nebivolol in pH 1.2 Buffers.

Sr. No.	Formulations	Percentage drug released after 30 minutes (DR)
A1	Drug	38.23 ± 2.15 %
A2	PM 1:1	42.54 ± 2.78 %
A3	PM 1:2	45.86 ± 2.49%
A4	PM 1:5	52.12 ± 2.70%
A5	SD 1;1	88.89 ± 2.15 %
A6	SD 1:2	94.46 ± 2.45 %
A7	SD 1:5	99.35 ± 2.86 %

Fig. 13: Comparison of *in-vitro* dissolution profile of formulation A1-A7



The percentage release of Nebivolol 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 Nebivolol is very low, about 38.24% of drug being dissolved within 30 min. In the 30 minutes, physical mixtures of PEG 6000 (1:1, 1:2 and 1:5) showed 42.54, 45.86 and 52.12% drug release, and 88.89, 94.46, and 99.35 % drug release from solid dispersions (1:1, 1:2 and 1:5). SDs of Nebivolol with PEG 6000 considerably enhanced dissolution rates within 30 min compared to pure Nebivolol 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. 14: IR Spectra of Solid dispersion 1:1

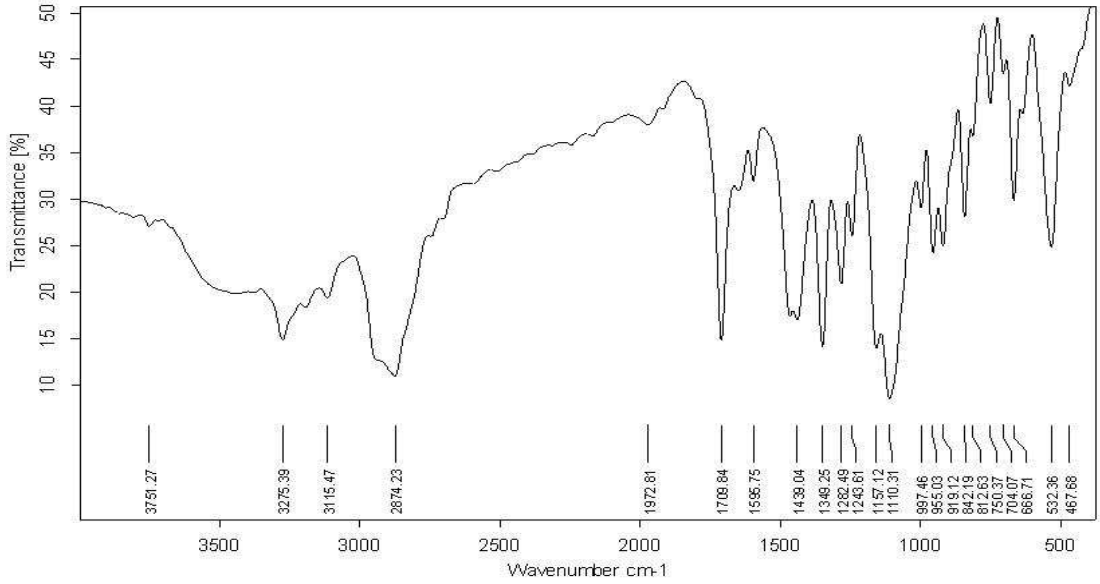


Fig. No. 15: IR Spectra of Physical mixture 1:1

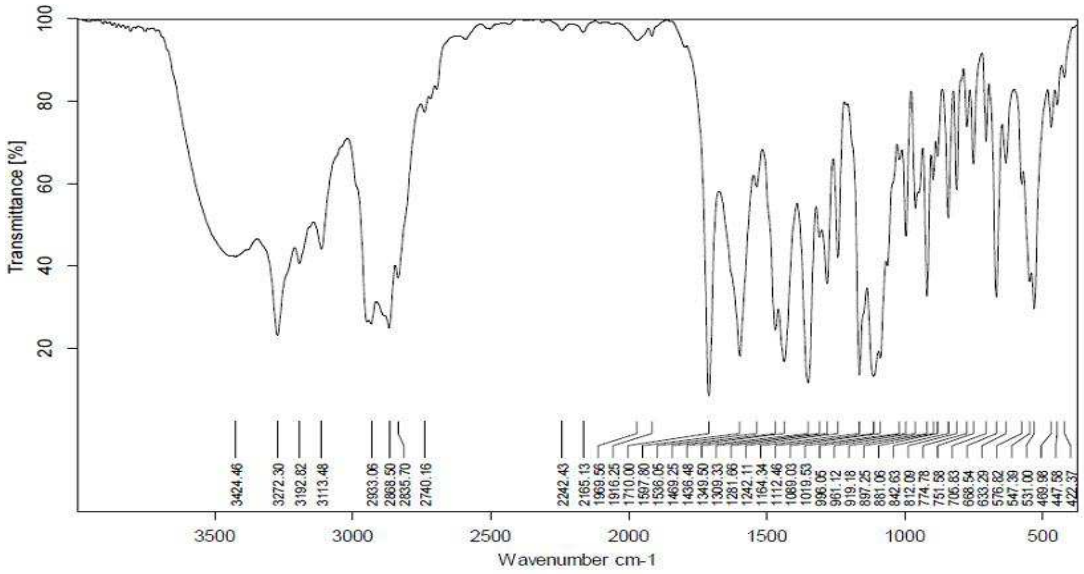


Fig. No. 16: IR Spectra of Solid dispersion 1:2

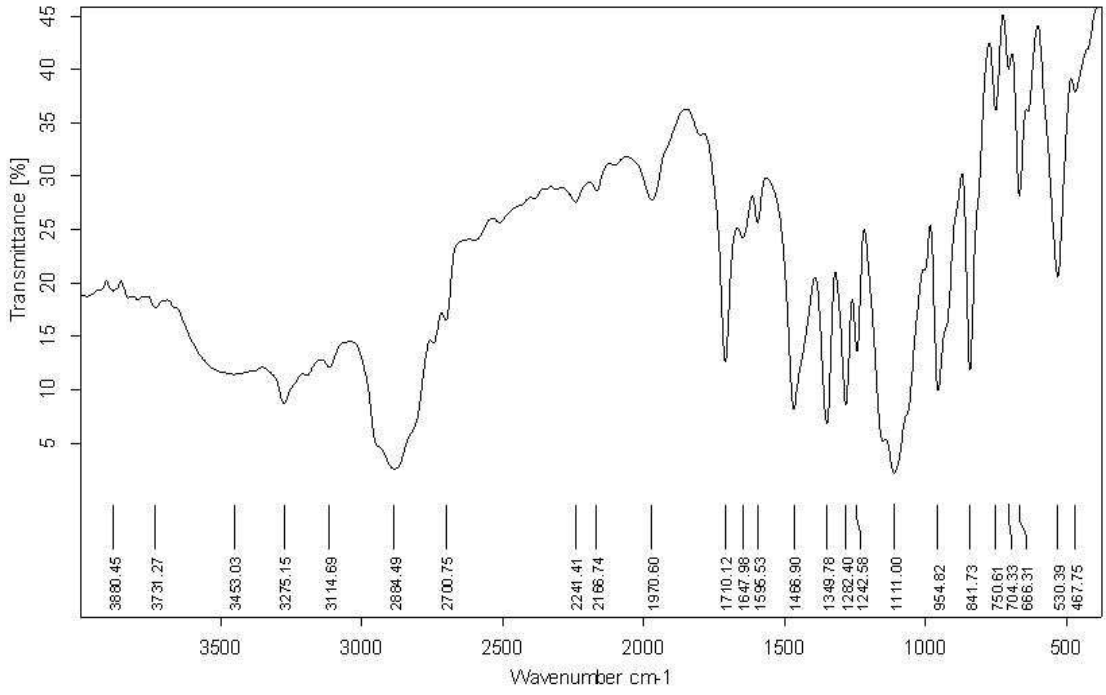


Fig. No. 17: IR Spectra of Physical mixture 1:2

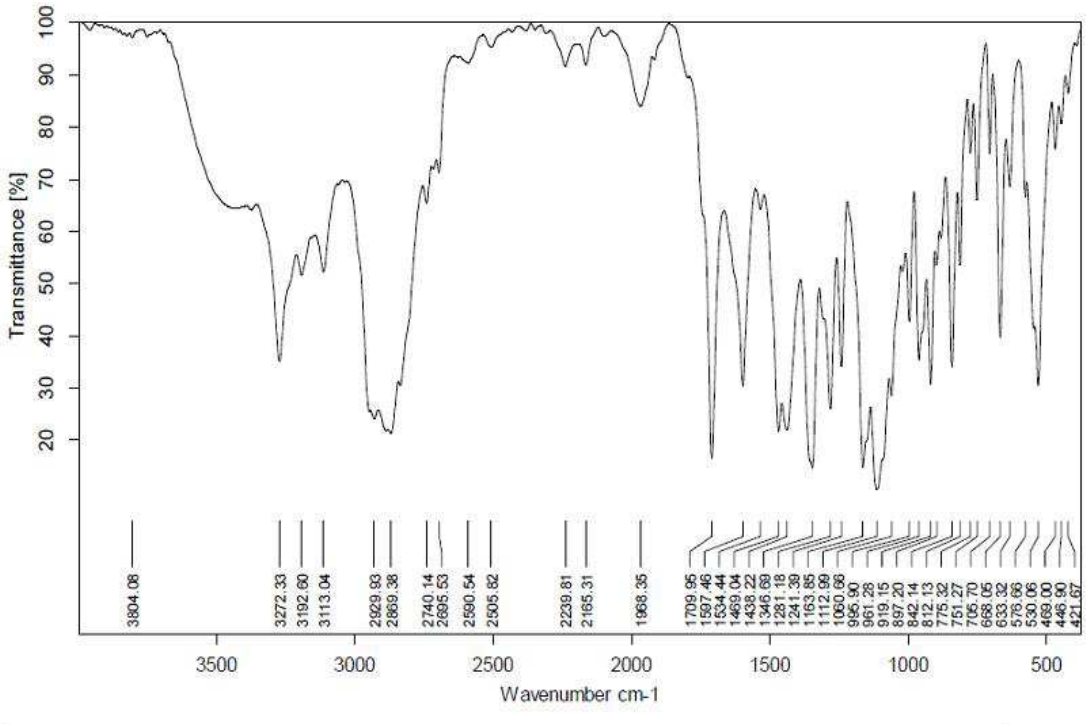


Fig. No. 18: IR Spectra of Solid dispersion 1:5

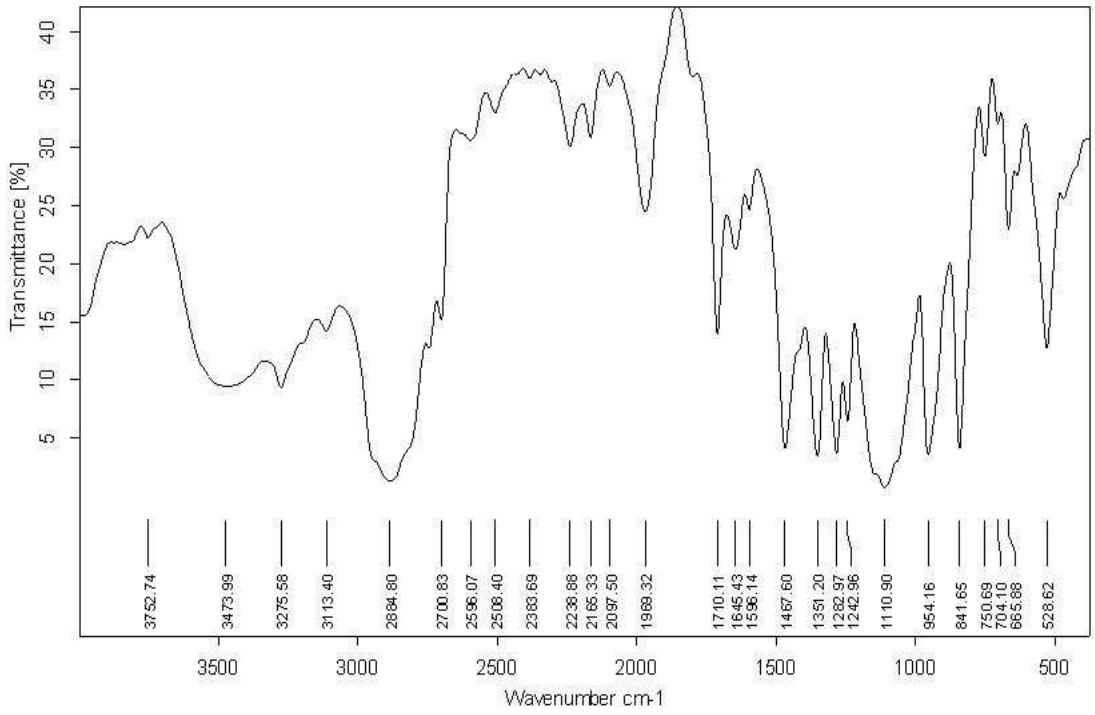
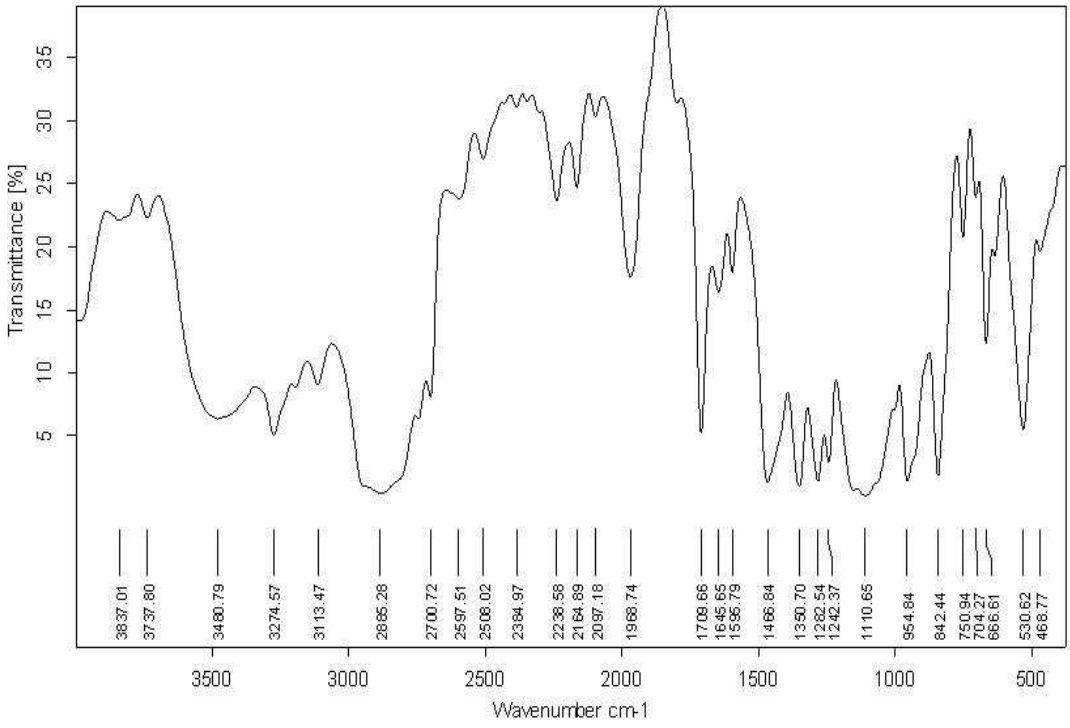


Fig. No. 19: IR Spectra of Physical mixture 1:5



The IR spectra of SDs and PMs were compared with the standard spectrum of Nebivolol. IR spectrum of Nebivolol was characterized by the absorption of carbonyl (C=O) sulphonyl urea group at 1,706 cm−1. In spectra of SDs and PMs, this band was shifted towards higher frequencies at 1,725 and 1,711 cm−1 respectively. Also the NH group which is located at 3,265 cm−1 from the IR spectrum of Nebivolol shifted to 3,365 cm−1 in SDs. The Flourine bands are located at 1,349 and 1,162 cm−1 in pure Nebivolol. In SDs, the asymmetric vibration peak of S=0 band was shifted from 1,349 to 1,341 cm−1 with decreased frequencies. It was concluded that there was no well defined chemical interaction between Nebivolol 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)	0.93	0.60	1.27
Tapped Density (gm/Cm^3)	1.02	0.81	1.45
Hausners Ratio	1.063	1.24	1.21
Compressibility index (%)	6.68	16.37	15.66
Angle of Repose (^{o})	26.20	41.36	34.15

7.7. FORMULATION OF NEBIVOLOL IMMEDIATE RELEASE TABLET

According to the formula given in table No. 8, Nebivolol 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	0.460	0.470	0.410	0.410	0.42	0.430	0.420	0.450	0.470	0.450	0.430	0.420
Tapped Density	0.550	0.540	0.530	0.520	0.53	0.540	0.510	0.540	0.54	0.55	0.53	0.51
% Compressibility	16.36	16.07	22.64	21.15	20.75	20.37	17.64	16.66	17.39	18.18	18.86	I7.64
Hausners Ratio	1.195	1.14	1.29	1.26	1.26	1.25	1.21	1.40	1.14	1.22	1.33	1.21
Angle of Repose	21.22	20.12	24.34	24.40	23.26	23.11	20.31	20.07	21.17	21.23	25.33	24.17

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 were tabulated in the Table No. 24.

7.8.4. THICKNESS

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

7.8.5. HARDNESS (KG/CM^2)

The Hardness test were carried out according to the procedure given in 6.8.5. The result were 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

Sr. No	Para meter	Formulation Code											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Weight Variation Test	428.61 ±0.26	429.62 ±0.21	428.66 ±0.36	431.12 ±0.46	430.14 ±0.26	429.63 ±0.45	431.15 ±0.36	429.11 ±0.31	431.52 ±0.26	428.71 ±0.28	428.26 ±0.26	431.63 ±0.26
3	% Friability	0.36	0.30	0.31	0.40	0.38	0.30	0.33	0.31	0.34	0.42	0.35	0.33
4	Thickness (mm)	2.78± 0.03	2.79± 0.02	2.65± 0.04	2.60± 0.03	2.71± 0.04	2.72± 0.03	2.72± 0.01	2.78± 0.05	2.74± 0.03	2.73± 0.04	2.71± 0.03	2.65± 0.04
5	Hardness (Kg / cm^2)	3.54 ±0.12	3.58 ±0.13	3.98 ±0.21	3.46 ±0.17	3.18 ±0.15	3.06 ±0.17	3.24 ±0.2	3.26 ±0.23	3.03 ±0.19	3.38 ±0.17	3.14 ±0.21	3.08 ±0.19
6	Disintegration Time(sec)	23.33 ±2.1	21.00 ±1.5	27.33 ±2.3	23.66 ±2.0	25.66 ±2.5	26.00 ±3.0	26.00 ±2.5	24.66 ±2.1	28.00 ±2.2	26.66 ±3.1	34.66 ±2.1	34.66 ±2.2
7	Wetting time (sec)	50.66 ±1.9	47.66 ±1.5	63.00 ±2.3	66.33 ±2.2	63.33 ±2.0	57.67 ±2.1	54.33 ±1.9	52.66 ±2.3	52.00 ±2.2	53.33 ±2.7	65.33 ±2.6	63.00 ±2.3
8	Uniformity of Dispersion	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
9	W.A.Ratio (%)	65.41	65.38	73.87	74.01	66.02	67.37	65.32	65.31	66.17	66.98	74.12	73.65
10	Assay(%)	99.2	99.8	98.6	98.4	98.2	98.7	98.6	99.7	99.8	99.9	99.9	98.4

7.8.11. *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	67.81
10	73.85
15	79.47
20	84.81
25	91.82
30	99.01

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

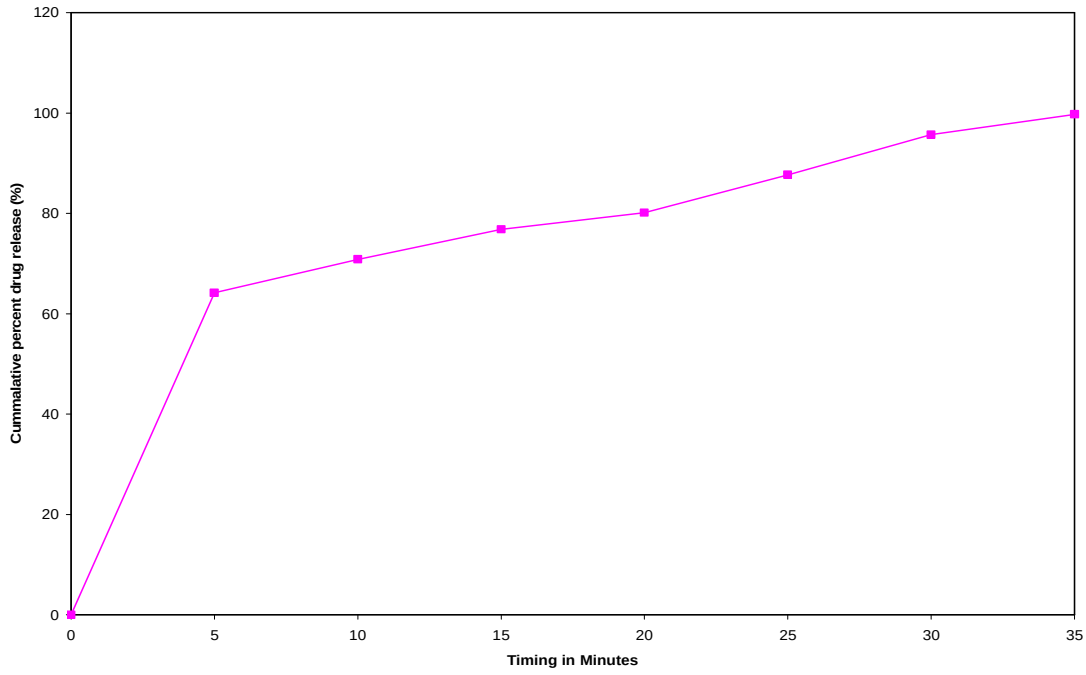


Table No.25: Dissolution profile of formulation F2

Time in minute	Cummulative Percent Drug Release(%)
0	0
5	68.30
10	74.06
15	79.03
20	85.16
25	92.18
30	99.93

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

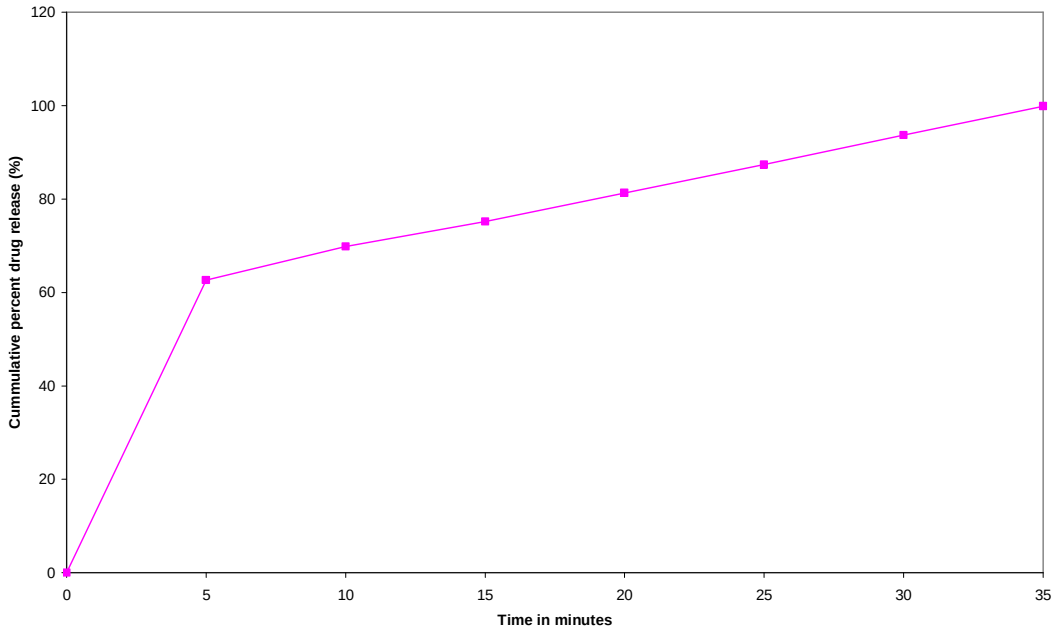


Table No.26: Dissolution profile of formulation F3

Time in minute	Percent Drug Release(%)
0	0
5	49.80
10	53.82
15	59.4
20	64.89
25	71.80
30	79.00

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

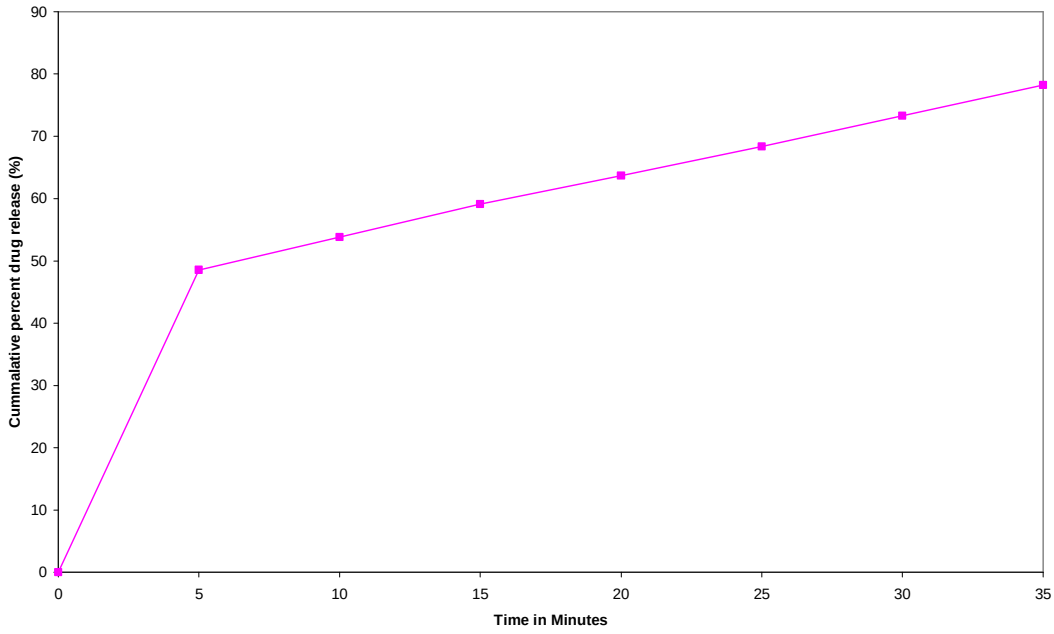


Table No.27: Dissolution profile of formulation F4

Time in minute	Cumulative Percent Drug Release(%)
0	0
5	50.5
10	54.27
15	60.06
20	71.85
25	74.97
30	80.21

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

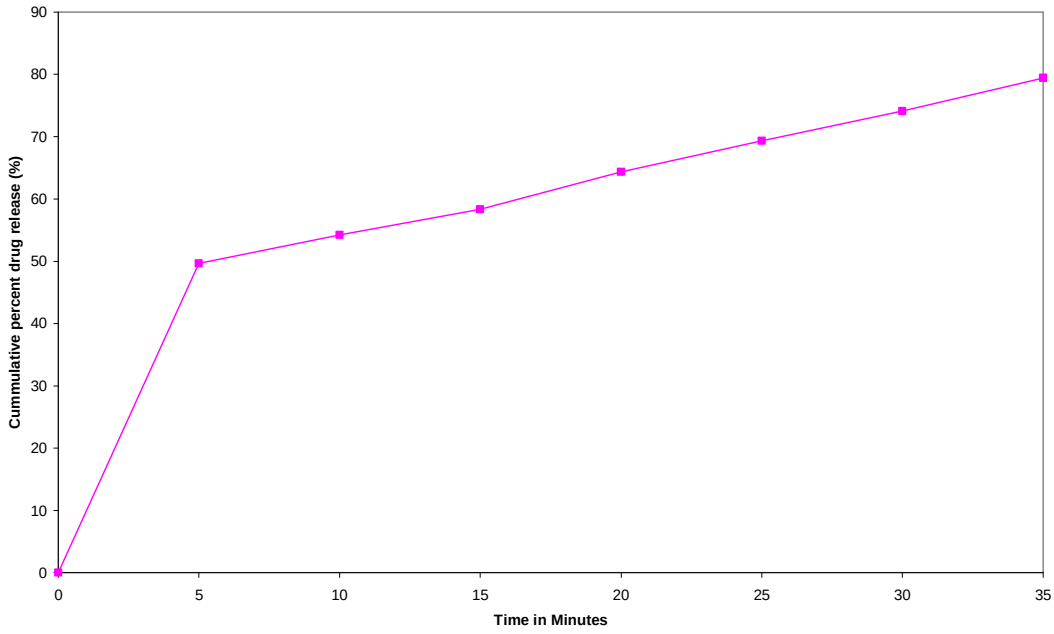


Table No.28: Dissolution profile of formulation F5

Time in minute	Cumulative Percent Drug Release (%)
0	0
5	67.11
10	73.45
15	78.82
20	83.14
25	91.50
30	98.12

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

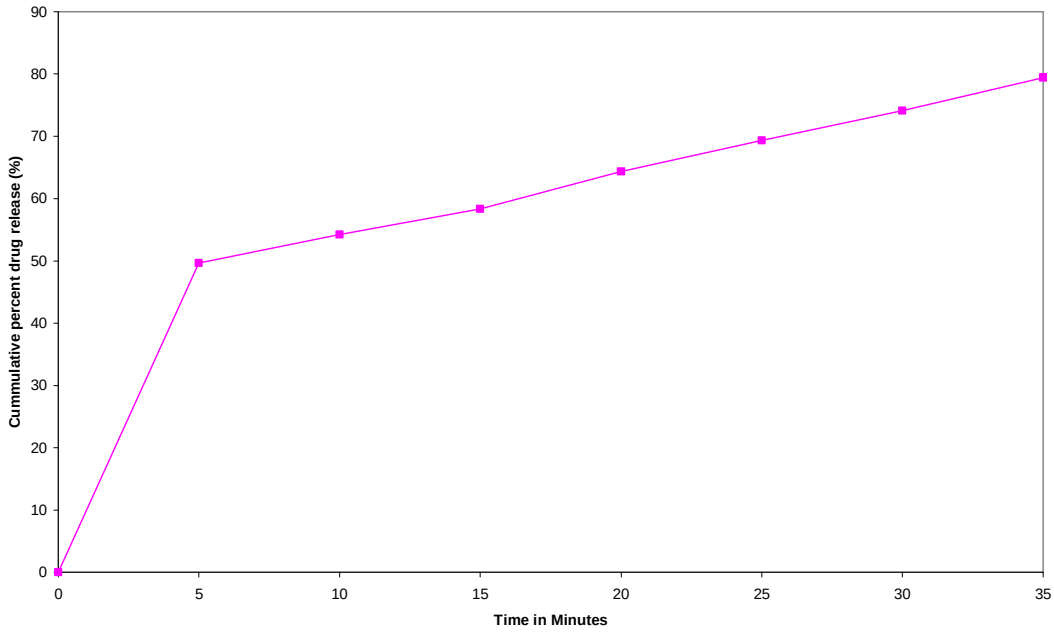


Table No.29: Dissolution profile of formulation F6

Time in minute	Cumulative Percent Drug Release(%)
0.0	0
5.0	67.14
10	73.50
15	78.87
20	83.15
25	91.50
30	99.15

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

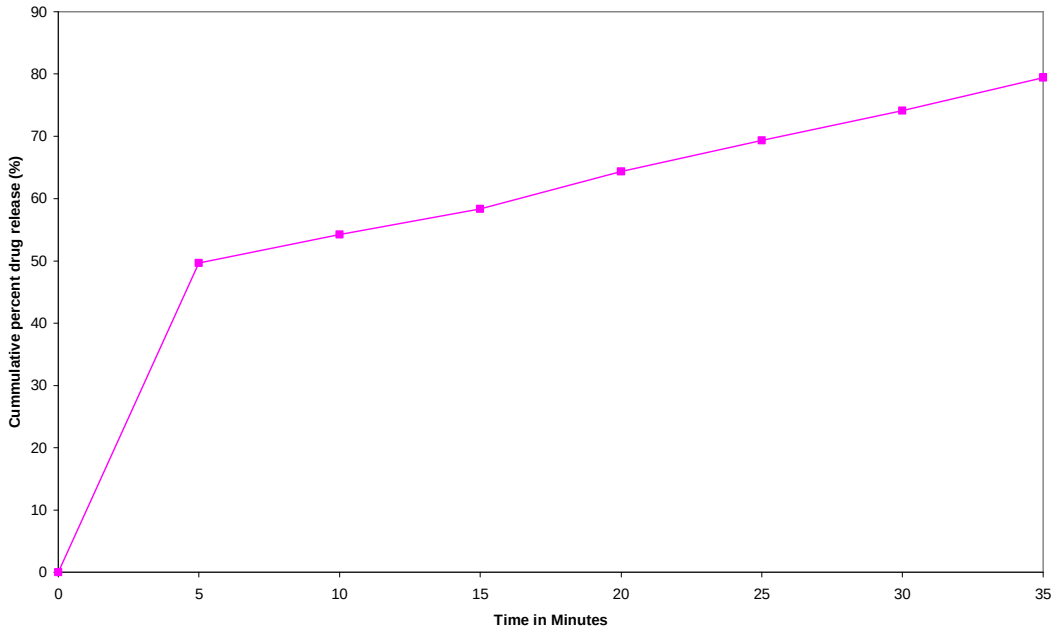


Table No.30: Dissolution profile of formulation F7

Time in minute	Cumulative Percent Drug Release(%)
0.0	0
5.0	67.61
10	73.74
15	79.12
20	84.36
25	92.01
30	99.50

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

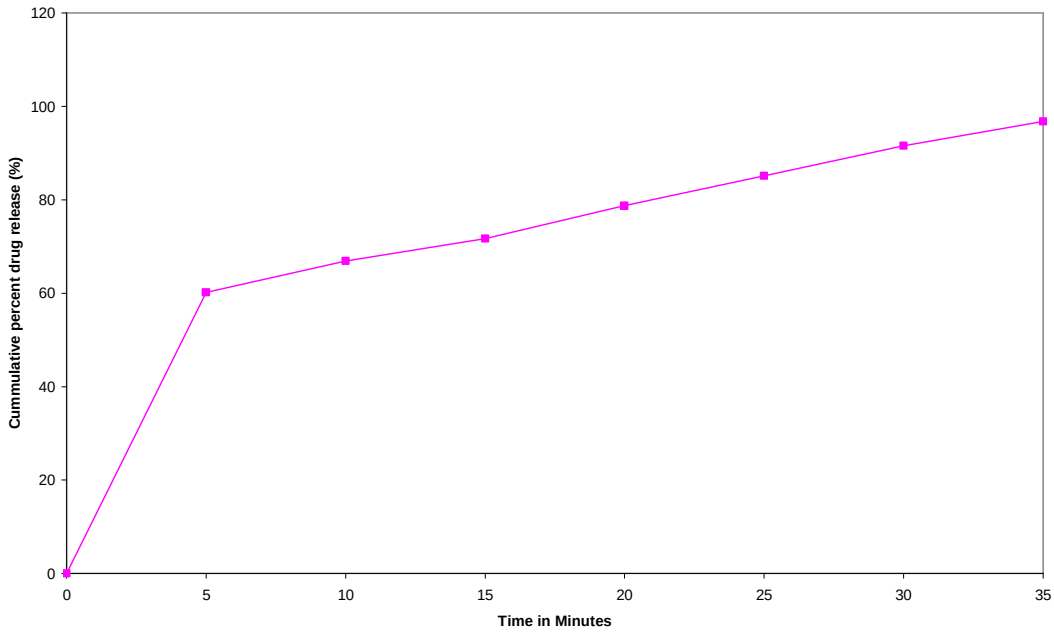


Table No.31: Dissolution profile of formulation F8

Time in minute	Cumulative Percent Drug Release(%)
0.0	0
5.0	67.80
10	74.04
15	79.75
20	84.96
25	92.80
30	99.86

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

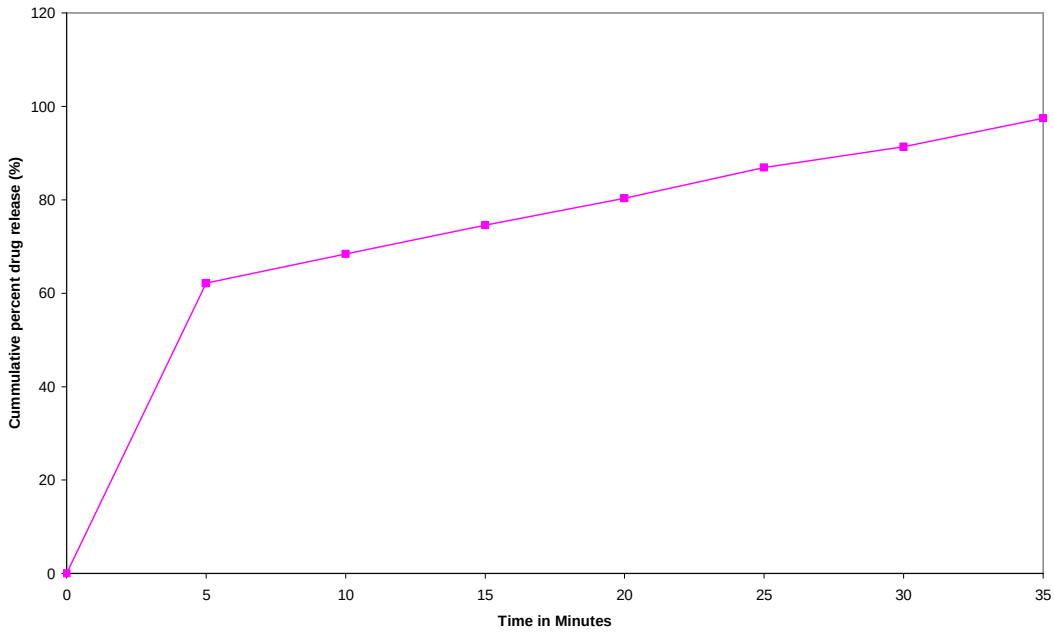


Table No.32: Dissolution profile of formulation F9

Time in minute	Percent Drug Release(%)
0.0	0
5.0	67.01
10	70.22
15	77.44
20	83.75
25	91.76
30	98.86

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

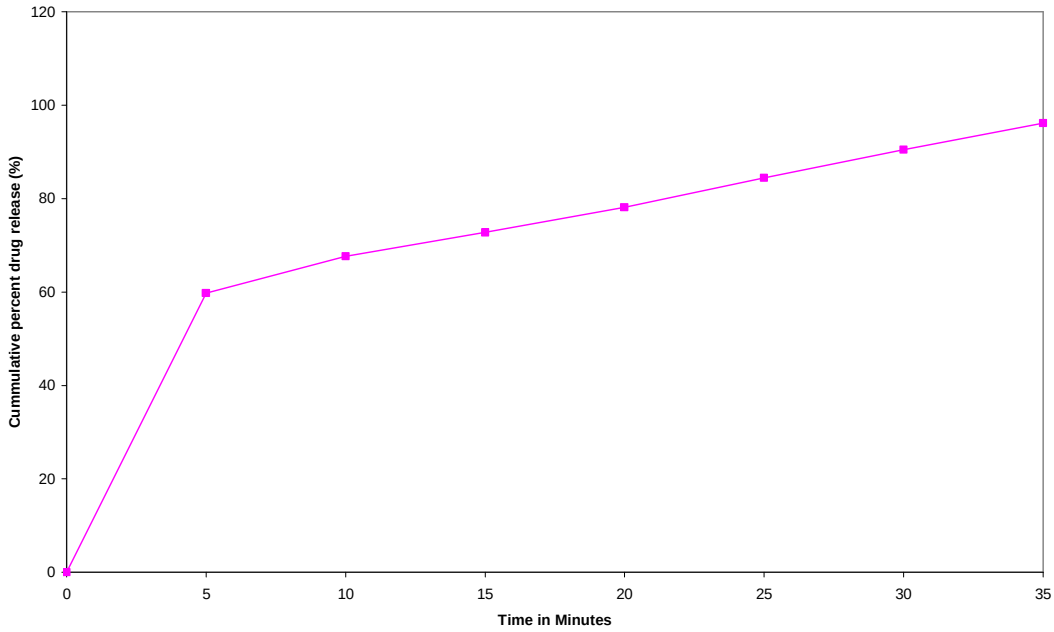


Table No.33: Dissolution profile of formulation F10

Time in minute	Cumulative Percent Drug Release(%)
0.0	0
5.0	67.73
10	70.91
15	77.91
20	84.01
25	92.14
30	99.06

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

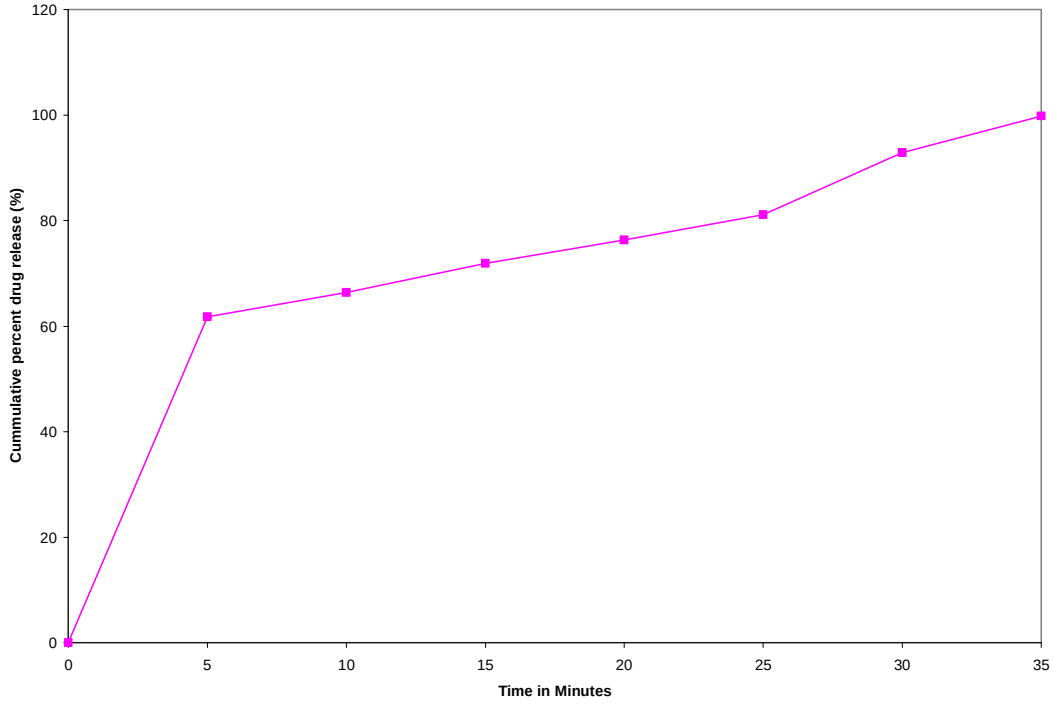


Table No.34: Dissolution profile of formulation F11

Time in minute	Cumulative Percent Drug Release(%)
0.0	0
5.0	66.11
10	73.19
15	78.78
20	84.07
25	91.23
30	97.49

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

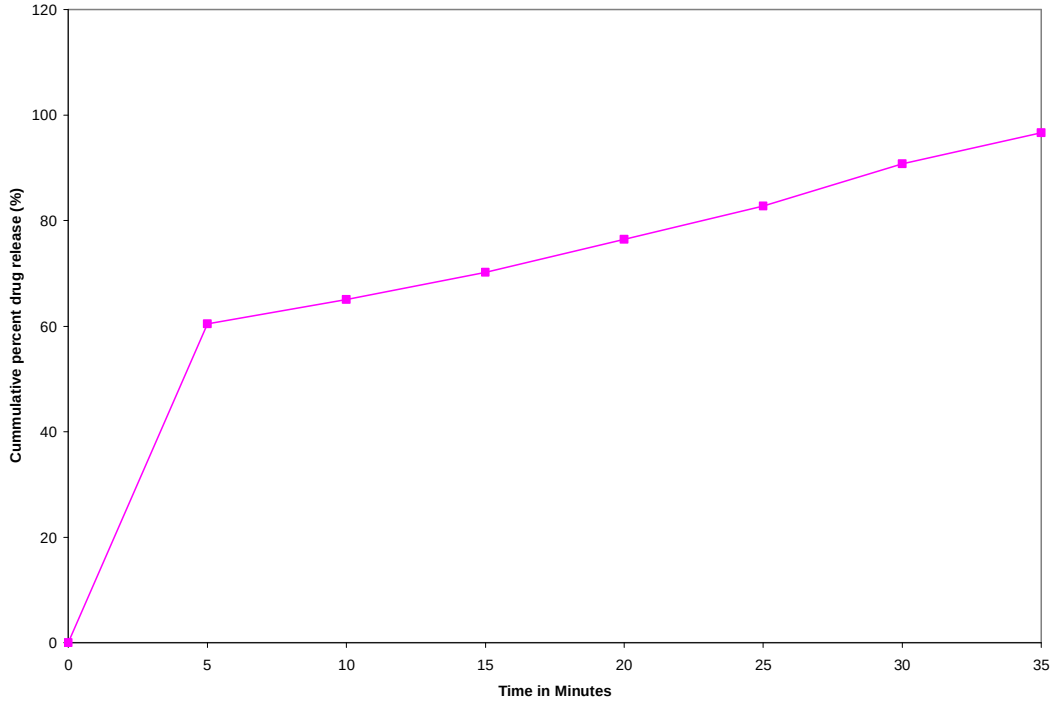


Table No.35: Dissolution profile of formulation F12

Time in minute	Cumulative Percent Drug Release(%)
0.0	0
5.0	66.75
10	73.85
15	79.11
20	84.50
25	91.73
30	98.01

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

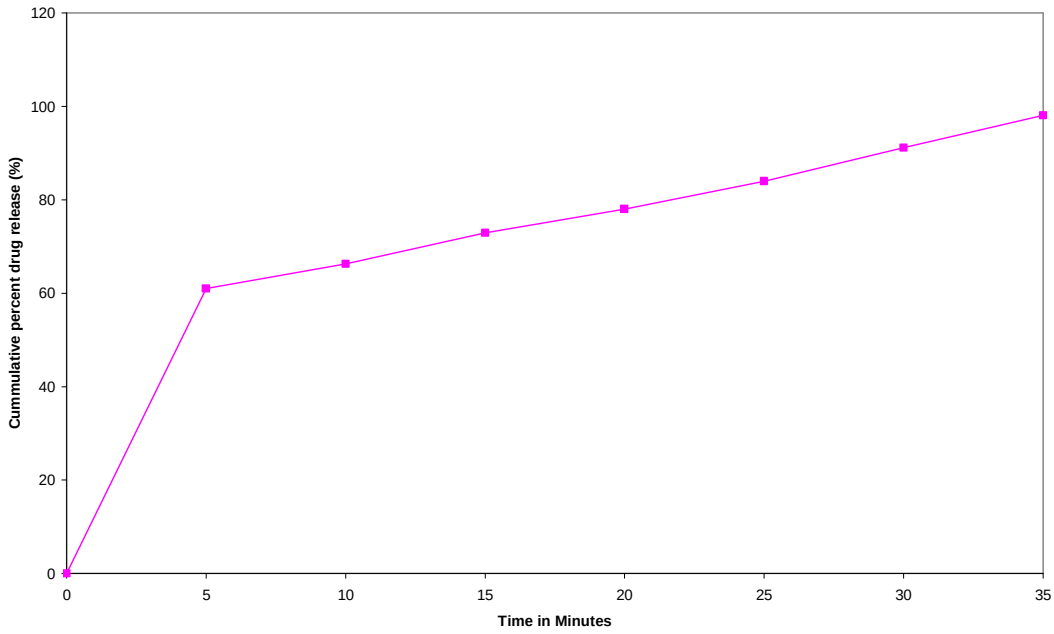
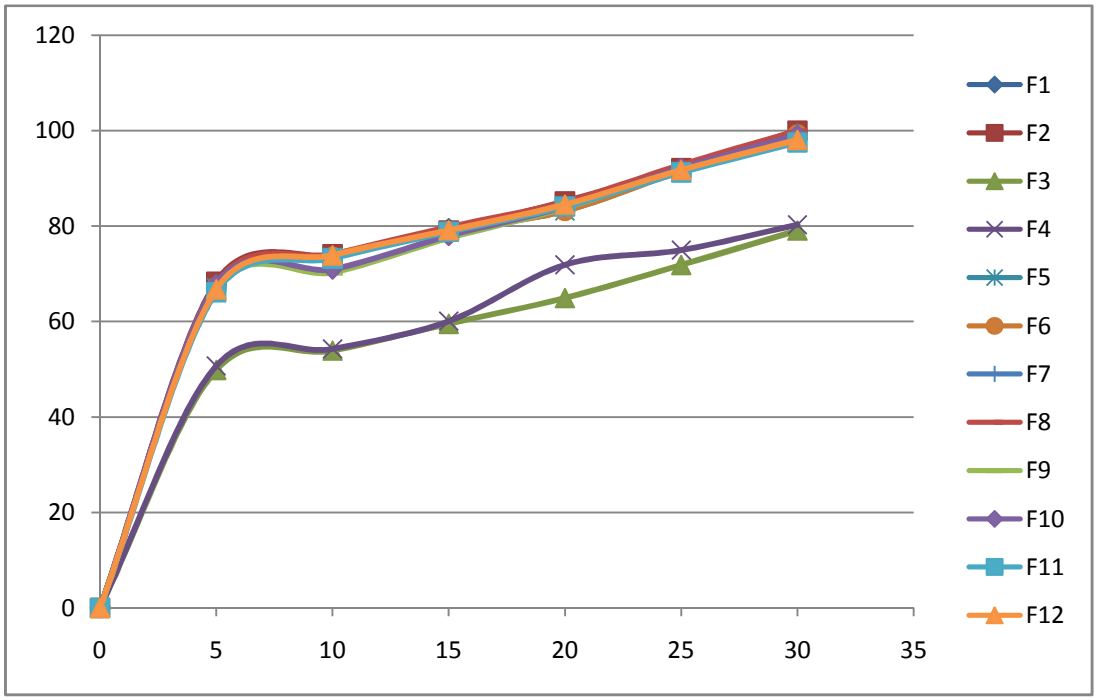


Table No :36 Comparative dissolution study F 1 – F 12 .

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	68.30	68.30	49.80	50.5	67.13	67.14	67.61	67.80	67.01	67.73	66.11	66.75
10	74.02	74.06	53.82	54.27	73.48	73.50	73.50	74.04	70.23	70.91	73.19	73.85
15	79.01	79.13	60.06	78.08	78.88	78.87	78.87	79.75	77.45	77.91	78.78	79.11
20	85.15	85.16	71.85	84.39	83.17	83.15	83.15	84.96	83.76	84.01	84.07	84.50
25	92.14	92.18	74.97	90.98	91.53	91.50	91.50	92.80	91.78	92.14	91.23	91.73
30	99.91	99.93	80.21	97.28	98.17	99.15	99.15	99.50	98.06	97.49	97.49	98.01

Fig. No. 32. Comparative dissolution study of F1 to 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

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
5	0.697	2.23675	62.61	1.7963	37.29	1.5715
10	1.0	3.16	69.84	1.8442	30.16	1.4794
15	1.176	3.872	75.22	1.8763	24.77	1.3939
20	1.301	4.471	81.31	1.9101	18.69	1.2716
25	1.396	5.00	87.34	1.9412	12.64	1.1022
30	1.477	5.477	93.73	1.9717	6.26	0.7965

Table No. 37 Kinetic data of Optimized Fomulation F2

Fig. No. 33 : ZERO ORDER

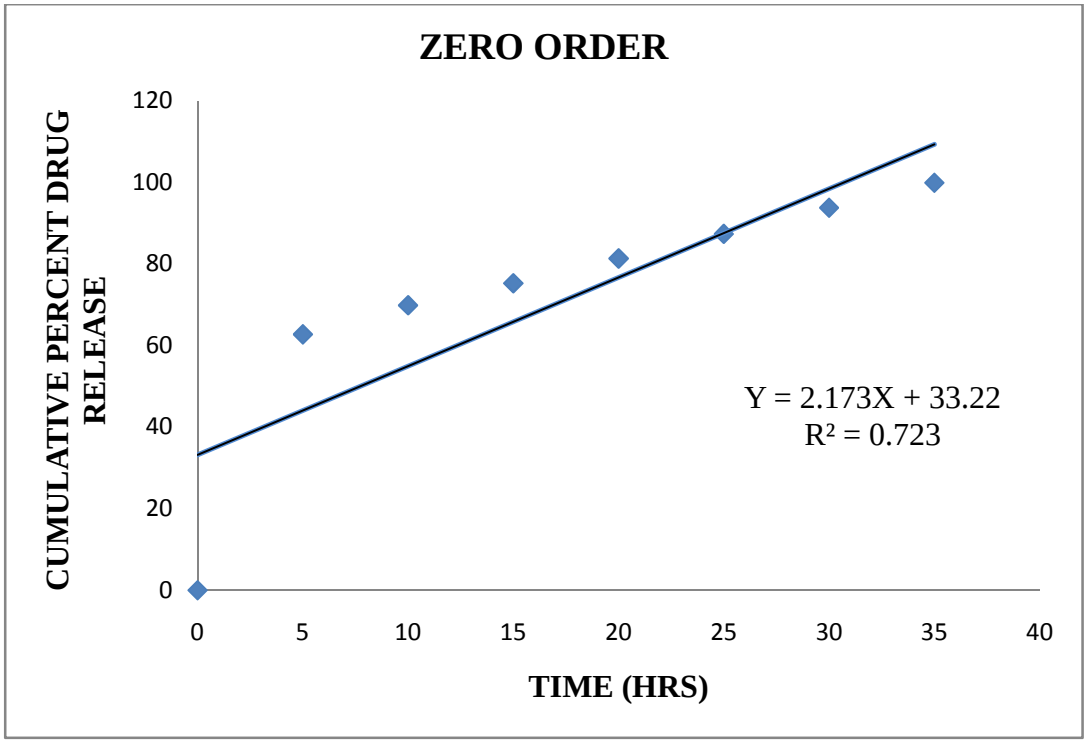


Fig. No. 34 : FIRST ORDER

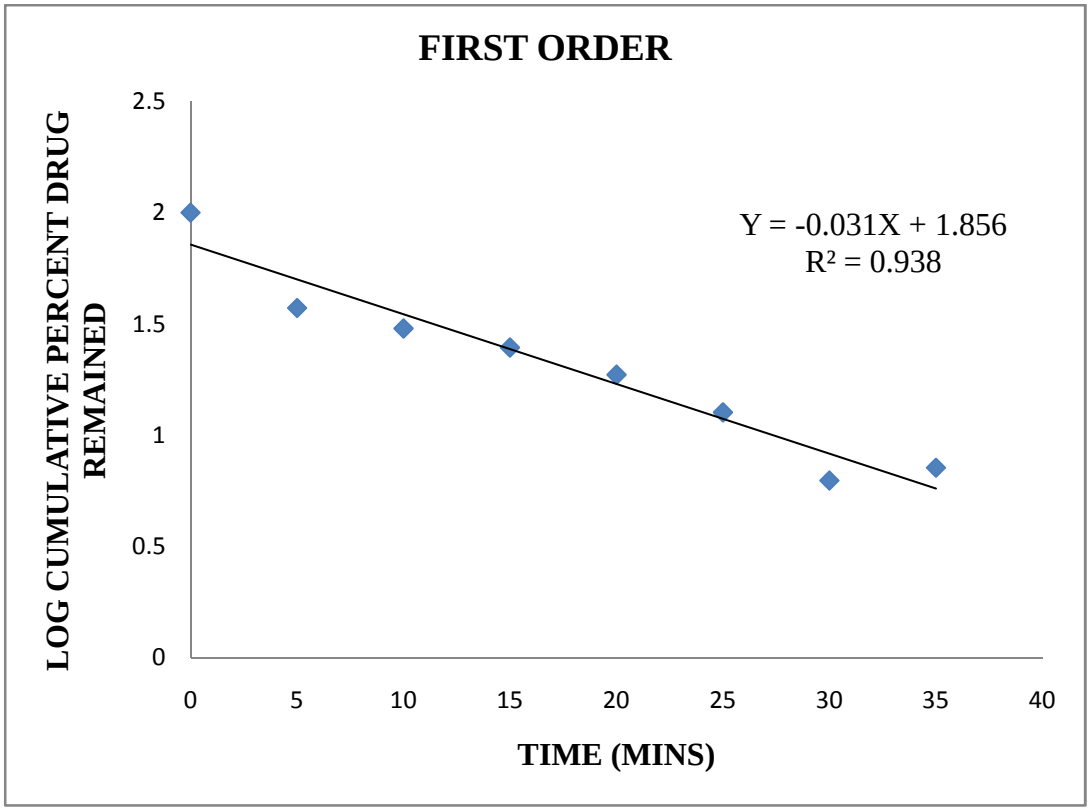


Fig. No. 35 : HIGUCHI

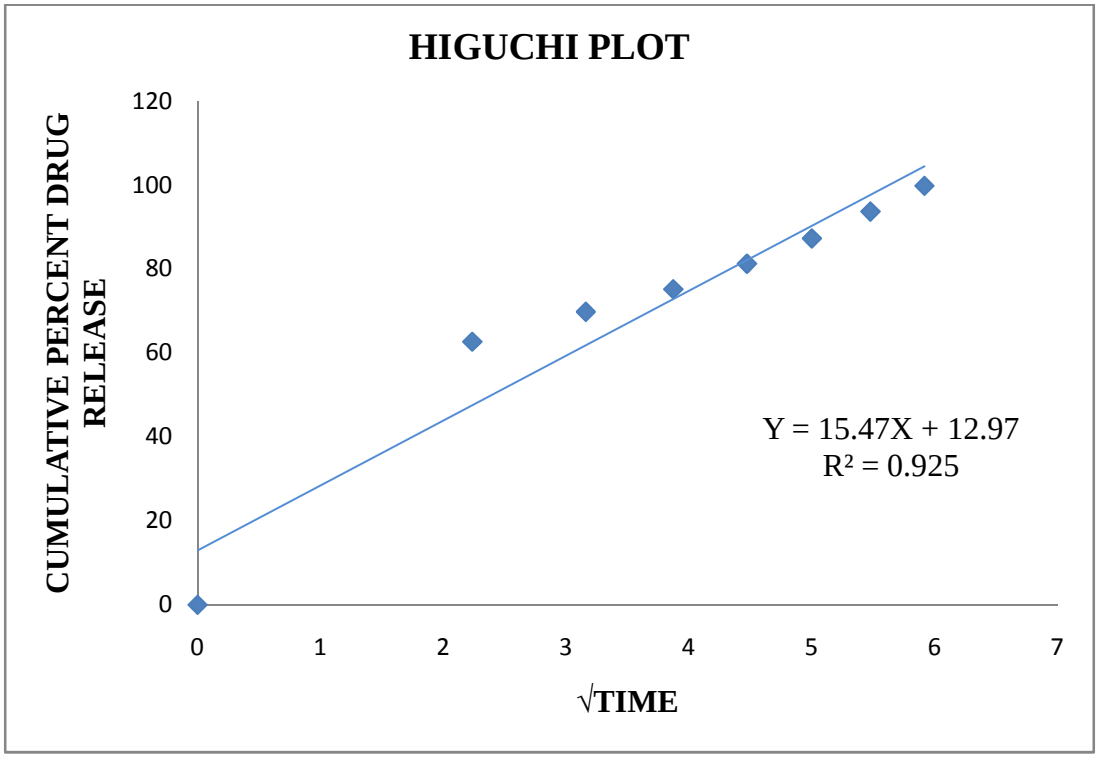
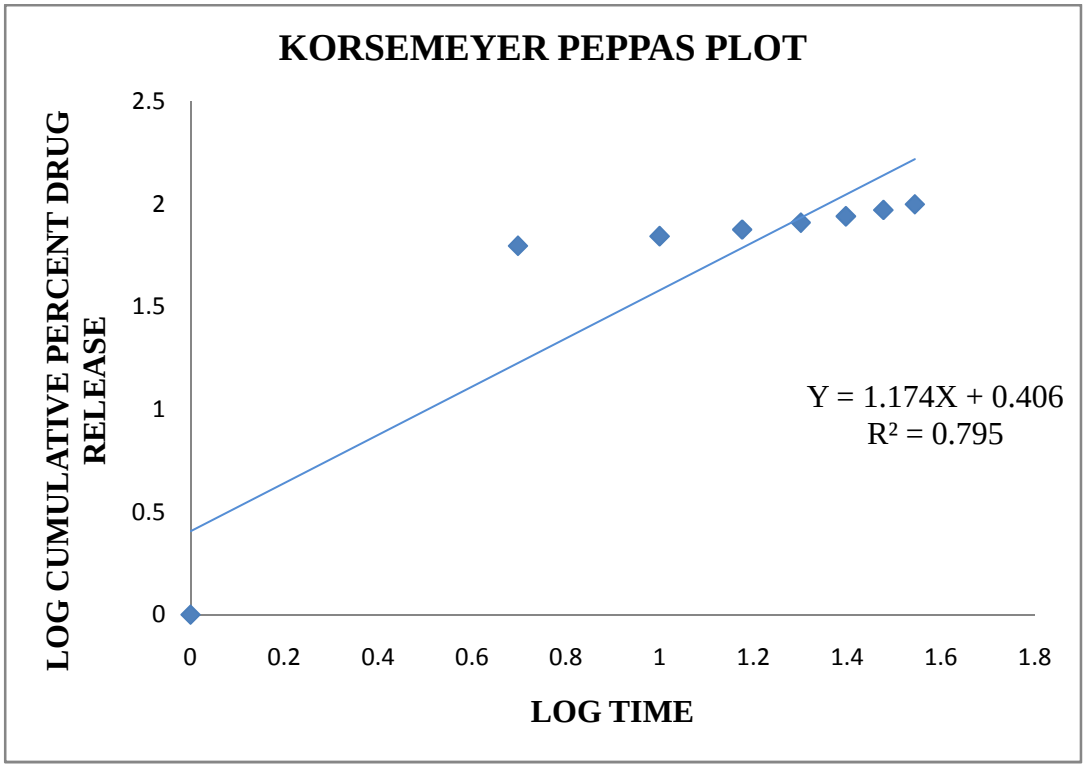


Fig. No. 36 : KORSEMEYER PEPPAS PLOT



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	0.274	0.271	0.270	0.273
2	Hardness (kg / cm^2)	3.0	2.7	3.1	3.2
3	Drug Content (%)	100.01	99.13	98.51	98.21
4	*In-Vitro Disin. Time(Sec)*	38	41	42.24	44.11

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°C + 2°C

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

Formulation (F2)	Percentage Drug Release After 30 minutes			
	Initial (0 Days)	30 Days	60 Days	90 Days
	99.83	99.24	98.84	98.40

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.

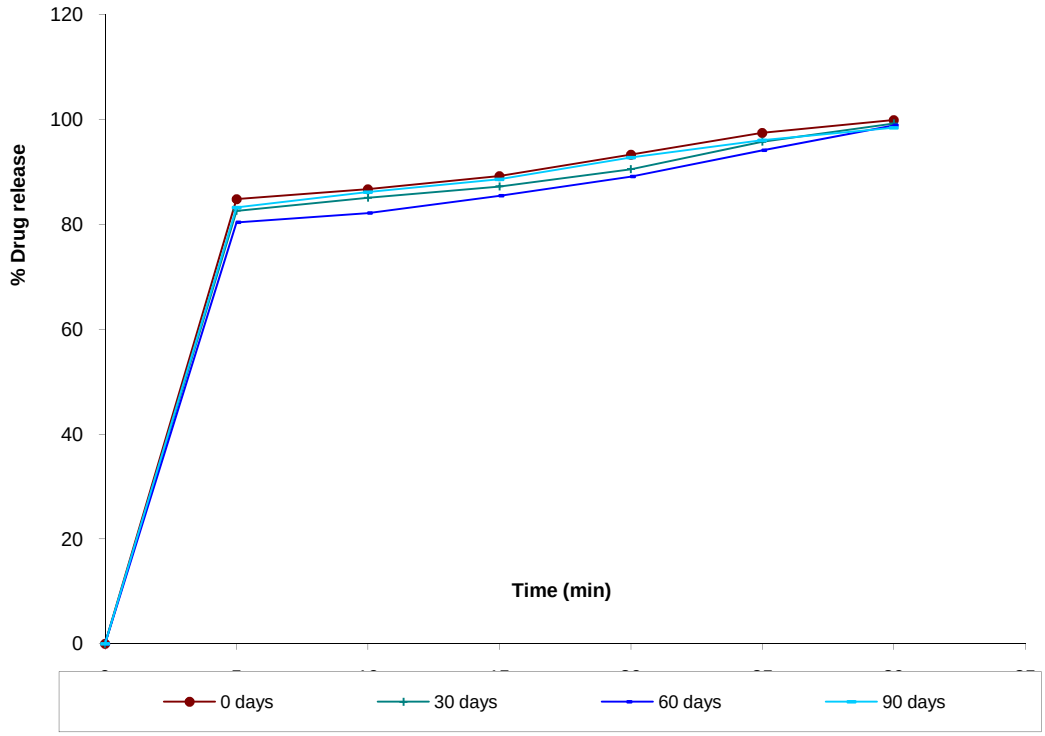


Fig. No. 37: *In-vitro* dissolution study F2 dissolution study

8. SUMMARY AND CONCLUSION

SUMMARY

In the present study immediate release drug delivery system of nebivolol 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 nebivolol 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 fast dispersion of the tablet, due to its high solubility in water.

For the nebivolol 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 nebivolol can be enhanced by formulating SDs of nebivolol with PEG 6000.The solubilization effect of PEG 6000, reduction of particle aggregation of the drug, formation of microcrystalline or amorphous drug, increased wettability and dispersibility, and alteration of the surface properties of the drug particles might be responsible for the enhanced solubility and dissolution rate of nebivolol from its SD and to some extent in PMs. No endothermic peak of nebivolol was present in of SDs with PEG 6000 suggesting the absence of crystalline nebivolol. From FTIR spectroscopy, it was concluded that there was no well defined chemical interaction between nebivolol 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 nebivolol immediate release tablet (F2) showed 68.30% drug release within first 5 min. and 99.93% 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.

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