FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF METOPROLOL TARTRATE

A Dissertation Submitted To
THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY
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In partial fulfillment of the requirements for the award of degree of
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IN
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Submitted by
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Under the guidance of
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Principal

CERTIFICATE

*This is to certify that the dissertation entitled **"FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF METOPROLOL TARTRATE"** submitted to The Tamilnadu Dr.M.G.R Medical University, Chennai, is a bonafide project work of **Ms. M.SUGANYA (Reg. No: 261711355),** carried out in the Department of Pharmaceutics, Jaya College Of Paramedical Sciences College Of Pharmacy Thiruninravur**,** in partial fulfillment for the degree of **MASTER OF PHARMACY** under the guidance of Prof **A. MAHESWARAN, M, Pharm., PGDBM.,MBA., (Ph.D.)** Principal, Department of Pharmacy, Jaya College Of Paramedical Sciences College Of Pharmacy Thiruninravur**,** Chennai-602024.*

Date: *Signature*

Place: Chennai.

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EVALUATION CERTIFICATE

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DECLARATION BY THE CANDIDATE

I hereby declare that the matter embodied in the dissertation entitled ***"FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF METOPROLOL TARTRATE"*** *is a bonafide and genuine research work carried out by me under the guidance of* ***PROF A. MAHESWARAN, M. PHARM, PGDBM, MBA (PH.D.),*** *Principal Department of Pharmacy, Jaya College Of Paramedical Sciences College Of Pharmacy. The work embodied in this thesis is original and has not been submitted the basis for the award of degree, diploma, associate ship (or) fellowship of any other university (or) institution.*

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Acknowledgement

The completion of this dissertation is not only fulfillment of my dreams but also the dreams of my ***Parents*** *who have taken lots of pain for me in completion of my higher studies.*

Lastly I thank 'God' the Almighty, to show the path to the ladder of success.

Thankful I ever remain……..

Date: *M.SUGANYA*

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LIST OF ABBREVIATIONS

FTIR	:	Fourier Transform Infrared spectroscopy
ICH	:	International Conference for Harmonization
mg	:	Milligram
ODT	:	Orodispersible tablet
Rpm	:	Revolution per minute
hrs	:	Hours
min	:	Minutes
sec	:	Seconds
w/v	:	Weight/Volume
µg/mcg	:	Micrograms
°C	:	Degree Centigrade
%	:	Percentage
% RH	:	Percentage relative humidity
MDDS	:	Mouth dissolving drug delivery system
Mannitol DC	:	Direct compressible mannitol
B. P	:	British Pharmacopoeia
I.P	:	Indian Pharmacopoeia
MCC	:	Microcrystalline cellulose
IND	:	Indion414
CCS	:	Croscarmellose sodium
CP	:	Crossvine
SSG	:	Sodium starch glycolate

Nm	:	Nano meter
TBD	:	Tapped bulk density
LBD	:	Loose bulk density
SD	:	Standard deviation
U. S	:	United States of Pharmacopoeia

FORMULATION CODE

DC	:	Direct compression method
DCI	:	Formulation containing Idion414
DCC	:	Formulation containing Croscarmellose Sodium
DCP	:	Formulation containing Crosspovidone
DCS	:	Formulation containing Sodium Starch Glycolate
SB	:	Sublimation method
SBI	:	Formulation containing Indion414
SBC	:	Formulation containing Croscarmellose Sodium
SBP	:	Formulation containing Crosspovidone
SBS	:	Formulation containing Sodium Starch Glycolate

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CHAPTER -1

INTRODUCTION

Solid dosage forms like tablet and capsule are most popular and preferred drug delivery system because they have high patient compliance, relatively easy to produce, easy to market, accurate dosing, and good physical and chemicalstability[1]

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily. In fact, the development of pharmaceutical products for oral delivery, irrespective of physical form involves varying extents of optimization of dosage form characteristics within the inherent constraints of GI physiology. Therefore, a fundamental understanding of various disciplines, including GI physiology, Pharmacokinetics, Pharmacodynamics and formulation design are essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. The more sophisticated a delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system. In any case, the scientific frame work required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects:

1. Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug,

2. The anatomic and physiologic characteristics of the GIT, and

3. Physicochemical characteristics and the drug delivery mode of the dosage form to be designed.[2].

Drinking water plays an important role in the swallowing of oral dosage forms. Often people experience inconvenience in swallowing conventional tablets and capsules. When water is not available, in the case of motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic conditions and bronchitis.[3] For these reasons, tablets which can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Rapidly dissolving or disintegrating tablets are not only indicated for people who have swallowing difficulties, but also are ideal for activepeople.[4]

Many patients find difficulty to swallow tablet and hard gelatin capsule, consequently they do not take medication as prescribed. It is estimated that 50% of the population is affected by this problem which result high incident of incompliance and ineffective therapy[5].

The difficulty is experienced by pediatric and geriatric patients, but it also applied to people who are ill in bed and those active working patients who are busy or traveling, especially those who have no access to water[6].

The growing importance of mouth dissolving tablet was underlined recently when European Pharmacopoeia adopted the term “Orodispersible Tablet” as a tablet that to be placed in the mouth where it disperses rapidly before swallowing[7].

To overcome this weakness, scientist have developed innovative drug delivery

system known as fast dissolving “melt in mouth” or mouth dissolve (MD) tablet. These are novel type of tablet that disintegrate dissolve / disperse insaliva[8].

There are two different types of dispersible tablet which must be distinguished, one dosage form disintegrates instantaneously in the mouth, to be swallowed without the need for drinking water, while other tablet formulation can readily be disperse in water, to form dispersion, easy to ingest by thepatient[9].

To develop drug products that are more convenient to use and to address potential issues of patient compliance for certain product indications and patient populations, recent developments in technologies have come out with mouth dissolving tablets (MDT) that can be ingested simply by placing them on the tongue. MDT is a solid dosage form that dissolves or disintegrates within a minute in the oral cavity without the need of water and has a pleasant taste. MDT is also known as orally disintegrating tablet, fast-dissolving tablet, fast-melting tablet, mouth melting tablet or fast-disintegrating tablet[2].

Orally disintegrating tablets are also called as orodispersible tablet, quick disintegrating tablets mouth dissolving tablets. Fast integrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelt. European pharmacopoeia has used the term orodispersible tablet for tablet that disperse readily and within 3 min in mouth beforeswallowing[10].

United State Food and Drug Administration (FDA) defined ODT as “a solid dosage form containing medicinal substance or active ingredients which disintegrate rapidly usually within a matter of second when placed upon the tongue[11]

1.1 Desired criteria for mouth disintegrating drug delivery system[12,13]:

Orodispersible or mouth dissolving tablets should:

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in a matter of seconds.
- Have a pleasing mouthfeel.
- Should be compatible with taste masking.
- Should be potable without fragility concern.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions such as humidity and temperature.
- Allow the manufacture of tablet using conventional processing and packaging equipment at low cost.

1.2 Salient features of mouth dissolving drug deliverysystem[14]:

- Ease of administration to patients who refuse to swallow a tablet such as, pediatric, geriatric patients and psychiatric patients.
- Convenience of administration and accurate dosing as compared to liquids.
- No need of water to swallow the dosage form, which is highly convenient especially for patients who are traveling and do not have immediate access to water.
- Good mouth feel property of MDDS helps to change the basic view of medication as “bitter pill”, particularly for pediatric patients.
- Rapid dissolution and absorption of drug, which may produce quick onset of

action.

- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passed own into the stomach in such cases bioavailability of drugs is increased.
- Ability to provide advantages of liquid medication in the form of solid form.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

To ensure the tablet's fast dissolving attribute, water must quickly egress into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet. Maximizing the porous structure of the tablet matrix and incorporating an appropriate disintegrating agent or highly water-soluble excipients in the tablet formulation are the basic approaches used in current fast dissolving tablet technologies. Basically, the disintegrants major function is to oppose the efficacy of the tablet binder and the physical forces that act under compression to form the tablet. The mechanism by which tablet is broken down into smaller particles and then produces a homogeneous suspension or solution is based on:

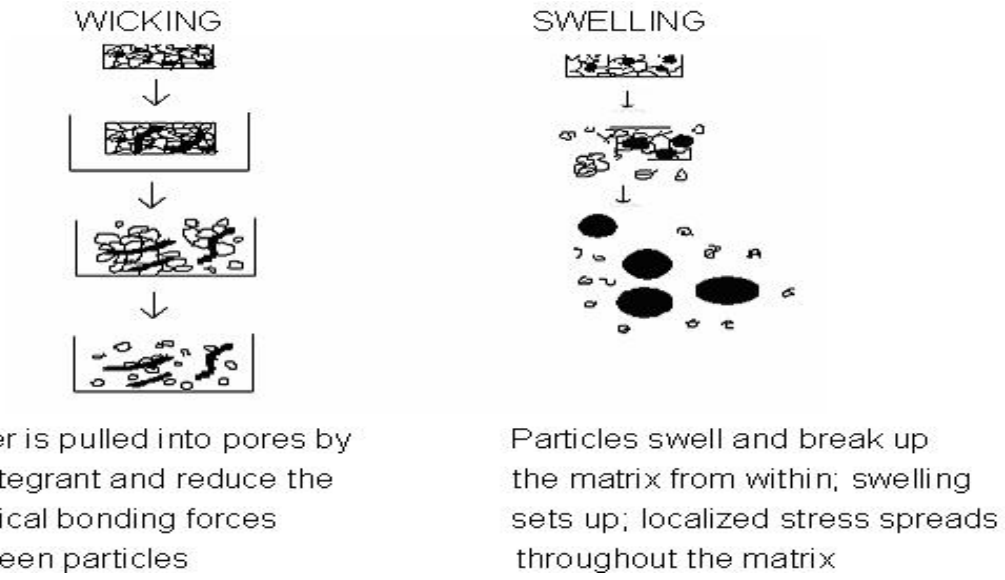
I) Capillary action II) swelling III)Air Expansion IV)Particle Repulsive force V)Particle Deformation VI) Release of Gases VII) Enzymatic reaction

I. By capillary action

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

II. By swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, enough swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.



Disintegration of tablet by wicking and swelling

III. Because of heat of wetting (air expansion)

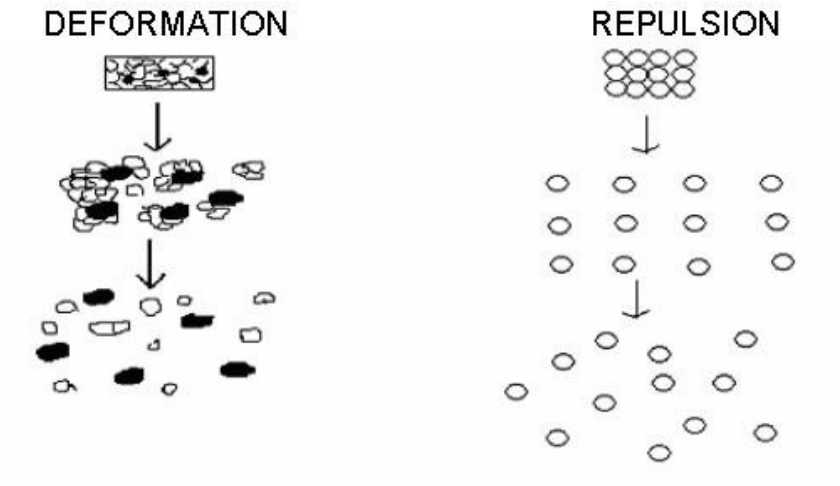
When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

IV. Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

V. Due to deformation.

Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they meet aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.



Disintegration by deformation and repulsion

VI. Due to release of gases

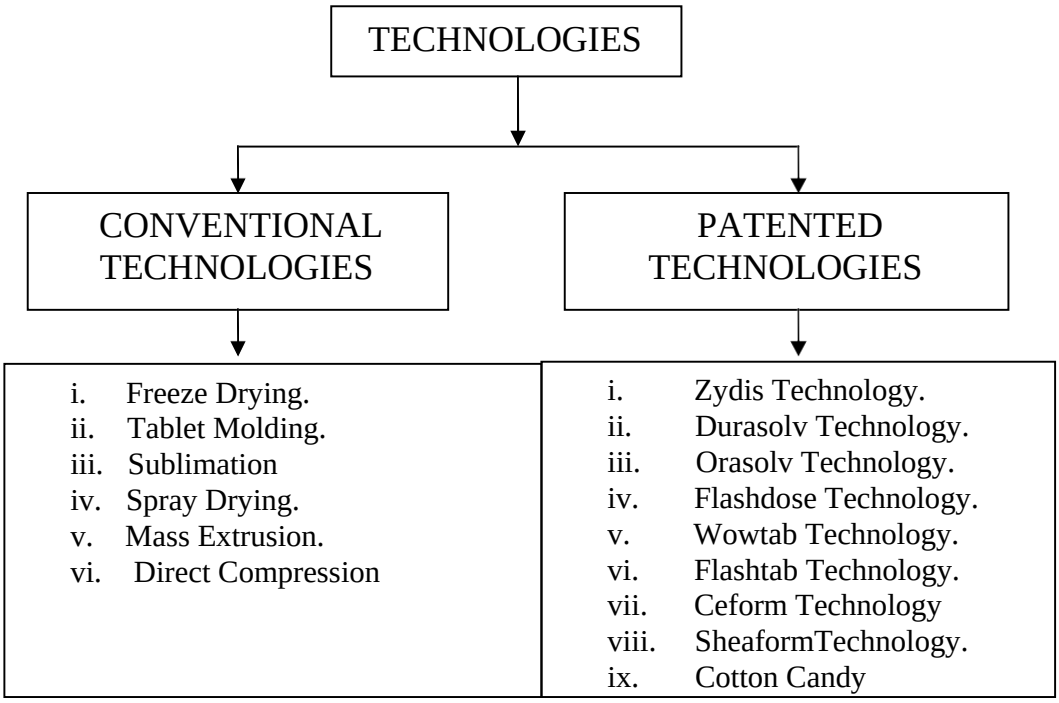
Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fractions of formulation.

VII. By enzymatic reaction

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

1.3 Technologies used to manufacture mouth dissolving tablets

The technologies used to manufacture mouth dissolving tablets can be classified as:



Various technologies used to manufacture mouth dissolving tablet.

1.4 Conventional technologies for preparing mouth dissolvingtablets[15-17]:

1.4.1 Freeze Drying:

A process in which water is sublimated from the product after freezing is called freeze drying. Freeze dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and sometimes to the drug, thereby enhancing the dissolution characteristics of the formulation. However, the use of freeze drying is limited due to high cost of the equipment and processing. Other major disadvantages of the final dosage forms include lack of physical resistance in

standard blister packs.

A tablet that rapidly disintegrates in aqueous solution includes a partially collapsed matrix network that has been vacuum dried above the collapse temperature of the matrix. The matrix is partially dried below the equilibrium freezing point of the matrix. Vacuum drying of the tablet above its collapse temperature instead of freeze drying below its collapse temperature provides a process for producing tablets with enhanced structural integrity, while rapidly disintegrating in normal amounts of saliva.

1.4.2 Molding:

Tablets produced by molding are solid dispersions. Physical form of the drug in the tablets depends whether and to what extent it dissolves in the molten carrier. The drug can exist as discrete particles or microparticles dispersed in the matrix. It can dissolve totally in the molten carrier to form solid solution or dissolve partially in the molten carrier and the remaining particles stay undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on the type of disintegrationor dissolution. Molded tablets disintegrate more rapidly and offer improved taste because the disintegrationmatrix is, generally made from water-soluble sugars. Molded tablets typically do not possess great mechanical strength. Erosion and breakage of the molded tablet often occur during handling and opening of blister packs.

1.4.3 Sublimation:

Because of low porosity, compressed tablets composed of highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in the water. Porous tablets that exhibit good mechanical strength and dissolve quickly have been developed. Inert solid ingredients

(E.g. urea, urethane, ammonium carbonate, camphor, naphthalene) were added to other tablet excipients and the blend was compressed into tablet. Removal of volatile material by sublimation generated a porous structure. Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. The tablets dissolve within 10-20 seconds and exhibit enough mechanical strength for practical use.

1.4.4 Spray Drying:

Highly porous and fine powders can be produced by spray drying, as the processing solvent is evaporated rapidly during spray drying. Spray drying technique is based upon a particulate support matrix and other components to form a highly porous and fine powder. This is then mixed with above ingredients and compressed to tablet. The fast dissolving tablets prepared form Spray drying technique disintegrated within 20 seconds.

1.4.5 Mass Extrusion:

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

1.4.6 Direct compression:

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also, high doses can be accommodated, and final weight of tablet can easily

exceed that of other production methods. Directly compressed tablet's disintegration and solubilization depends on single or combined action of disintegrants, water-soluble excipients and effervescent agent. Disintegrant efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and/or high friability and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus, all result from insufficient physical resistance.

Various commercially available superdisintegrants along with their properties.

Sr. no.	**Name**	**Type**	**Properties**	**Brand name**
1.	Crospovidone	Polyvinyl-pyrrolidone	Crossed linked Poly vinyl pyrrolidone Rapidly disperses and swells in water	PolyplasdoneXL, Kollidon CL
2.	Croscarmellose Sodium.	Modified cellulose	Cross linked sodium carboxy methylcellulose. Excellent swelling and water wicking properties.	Ac-di-sol, Primellose, Solutab.
3.	Sodium starch Glycolate	Modified Starch	Sodium salt of carboxy methyl ether of starch. High swelling capacity and rapid water Uptake	Primogel, Explotab, Glycolys.

1.5 Patented technologies for orodispersible or mouth dissolvingtablets[16,18]:

1.5.1 ZYDIS Technology:

Zydis formulation is a unique freeze-dried tablet in which drug is physically entrapped or dissolved within the matrix of fast-dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many materials designed to achieve several objectives. To impart strength during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength.

To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis units during freeze drying process or long-term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

1.5.2 DURASOLV Technology:

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring small amounts of active ingredients.

1.5.3 ORASOLV Technology:

CIMA labs have developed Orasolv Technology. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine are used to prepare the tablets. The tablets prepared are soft and friable and packed in specially designed pick and place system.

1.5.4 FLASH DOSE Technology:

This technology is based on the preparation of sugar-based matrix known as floss, which is made from a combination of excipients either alone or in combination of drugs. Two platform fuisz technologies called Sheaform or Ceform are currently being utilized in preparation of wide range of oral disintegrating product.Flash dose has been patented by Fuisz. Nurofen meltlet, a new form of Ibuprofen as melt-in-mouth tablets; prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consists of self-binding shearform matrix termed as “Floss”. Shearform matrices are prepared by flash heat processing.

1.5.5 WOWTAB Technology:

Wowtab Technology is patented by Yamanouchi Pharmaceutical Company WOW means “Without Water”. In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed intotablet.

1.5.6 FLASHTAB Technology:

Prographarm laboratories have patented the Flashtab technology. Tablets prepared by this system consist of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, microencapsulation, and extrusion-spheronisation. All the processing utilized conventional tableting technology.

1.5.7 CEFORM Technology:

In this, microspheres containing active ingredient are prepared. The manufacturing process involves placing a dry powder, containing either substantially pure drug material or a special blend of drug materials plus other pharmaceutical compounds, and excipients into precision engineered, and rapidly spinning machine. The centrifugal force throws dry blend at high speed through small, heated openings. The resultant microburst of heat liquifies the drug blend to form sphere. The microspheres are blended or compressed into preselected oral delivery dosage form. The microspheres can be incorporated into a wide range of fast dissolving dosage forms such as flash dose, or spoon dose, EZchew.

1.5.8 SHEARFORM Technology:

Shearform technology is based on preparation of floss that is also known as “Shearform Matrix”, which is produced by subjecting a feedstock containing a sugar carrier to flash heat processing. In this process, the sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal flow condition, which permits part of it to move with respect of the mass. The flowing mass exits

through the spinning head that flings the floss. The floss so produced is amorphous in nature, so it is further cropped and recrystallised by various techniques to provide uniform flow properties and then facilitates blending. The recrystallised matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet. The active ingredient and other excipients can be blended with floss before carrying out recrystallisation. The Shearform floss, when blended with the coated or uncoated microspheres, is compressed into tablets or EZ chewable tablets from standard tableting equipment.

1.5.9 COTTON Candy:

Cotton candy process is known as candy floss process. this technique forms the basis of flash dose (Fuisz technologies, Chantilly, VA) In this technology, saccharides or polysaccharides are processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The floss is then partially recrystallised to impart a good flow properties and compressibility the floss then can be milled and blended with active ingredient and other excipients and finally that compressed into MDT. Advantages of this process are that the tablet can be accommodate high doses and possess satisfactory mechanical strength. The candy floss are hygroscopic, hence, their manufacturing requires control of humidity conditions.

Comparison of some patented technologies for mouth dissolving tablets[19].

Technology	Novelty	Handling/Storage	Drug Release/ Bioavailability
Zydis (R.P. Scherer,Inc.)	First to market. Freeze Dried	Do not push tablet through foil. Do not use dosage form from damaged package. Sensitive to degradation at humidities >65%	Dissolves in 2 to 10 seconds. May allow for pre-gastric absorption leading to enhanced bioavailability
Orasolv (CIMA Labs, Inc.)	Unique taste masking. Lightly compressed	Packaged in patented foil packs	Disintegrates in 5 to 45 seconds depending upon the size of the tablet. No significant change in drug bioavailability
Durasolv (CIMA Labs, Inc.)	Similar to Orasolv, but with better mechanical strength	Packaged in foil or bottles. If packaged in bottles, avoid exposure to moisture or humidity	Disintegrates in 5 to 45 seconds depending upon the size of the tablet. No significant change in drug bioavailability
Wowtab (YAMANOUCHI Pharma Technologies, Inc.)	Compressed dosage form. Proprietary taste masking. Smoothmelt action gives superior mouthfeel	Package in bottles. Avoid exposure to moisture or humidity	Disintegrates in 5 to 45 seconds depending upon the size of the tablet. No significant change in drug bioavailability

List of commercially available orodispersible tablets

Trade Name	Active Drug	Manufacturer
Feldene Fast Melt	Piroxicam	Pfizer Inc., USA
Calritin Redi Tab	Loratidine	Schering Plugh Corp, USA
Maxalt MLT	Rizatriptan	Merck & Co. USA
Zyprexia	Olanzapne	Eli Lilly, Indianapolis, USA
Pepcid RPD	Famotidine	Merck & Co., NJ, USA
Zofran ODT	Ondansetron	GlaxoWellcome, Middlesex, UK
Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
TempraQuiclets	Acetaminophen	Bristol Myers Squibb, NY, USA
Febrectol	Paracetamol	Prographarm, Chateauneuf, France
Nimulid MDT	Nimesulide	Panacea Biotech, New Delhi, India
Romilast	Montelukast	Ranbaxy Labs Ltd., New Delhi, India
Benadryl Fastmelt	Diphenhydramine and pseudoephedrine	Warner Lambert, USA

1.6 DRUG PROFILE:

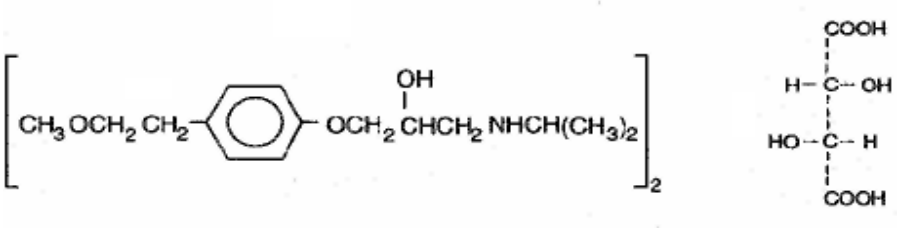
Metoprolol Tartrate[20-24]:

Chemical formula:

a) 1-(isopropylamino)-3-p-(2-methoxyethyl) phenoxy-2propanol (2:1) dextro-tartrate.

b) 1- Isopropylamino-3-[4-(2-methoxyethyl) phenoxy] propan-2-oltartrate.

Chemical structure:



Empirical formula	**:**	$(C_{15}H_{25}NO_3)_2C_4H_6O_6$
Molecular weight	**:**	684.82
Description	**:**	White crystalline powder or colorless crystals.
Melting point	**:**	120-123ºC
Solubility	**:**	Very soluble in water, soluble in ethanol and chloroform; practically insoluble in ether.
pH of 2% aqueous solution:	**:**	6.0 to7.0
Dissociation constant (pKa)	**:**	9.7

Therapeutic category : Antihypertensive

Antianginal, Antiarrhythmic

Mechanism of action : Metoprolol Tartrate is a β_1 selective antagonist. It suppresses the activation of the heart by blocking β_1 adreno receptors and they reduce the work of the heart by decreasing cardiac output & blood pressure.

Pharmacokinetics:

Absorption : Metoprolol is readily and completely absorbed from the gastrointestinal tract, but is subjected to very considerable first-pass metabolism in the liver and the bioavailability is only about 38%. Peak plasma concentrations vary widely and occur about 1.5 to 2 hrs after a single oral dose.

Distribution : Metoprolol is widely distributed. It crosses the blood brain barrier the placenta and is distributed into breast milk. The apparent volume of distribution ranges from about 2.5 liters/ kg to 5.0 liters/ kg and approximately 90% bound to plasma protein

Metabolism : It is extensively metabolized in the liver by oxidative deamination, O-dealkylation followed by oxidation and aliphatic hydroxylation

Excretion : The metabolites are excreted in the urine together with only small amounts of unchangedmetoprolol.

Indications : Angina pectoris, hypertension, migraine prophylaxis, arrhythmias,hyperthyroidism

Dosage and Administration : In hypertension: Initially 100mg daily taken withor immediately after meal. Increased to 400mg once or twice daily according to the patient response.

Maintenance dose: 100-200mg daily

Angina: 50-100mg; 2-3 times daily.

Arrhythmias: usually 50mg; 2-3 times daily; up to 300mg daily in divided doses if necessary

Side Effects : Constipation, nausea, vertigo, dizziness, headache,fatigue, dry mouth, skin rashes & Insomnia.

Marketed Brands :

- ToprolXL (Astra Zeneca) : - 100 and 200
- Lopressor (Novartis India) : - 200 mg
- BetalocSA (Astra Zeneca) : - 200 mg

1.6 POLYMER PROFILES:

1.6.1 Crospovidone[25]:

Nonproprietary Names : BP: Crospovidone

PhEur: Crospovidone

USPNF:Crospovidone

Synonyms : Cross linked povidone, polyvinyl polypyrrolidone,PVPP,

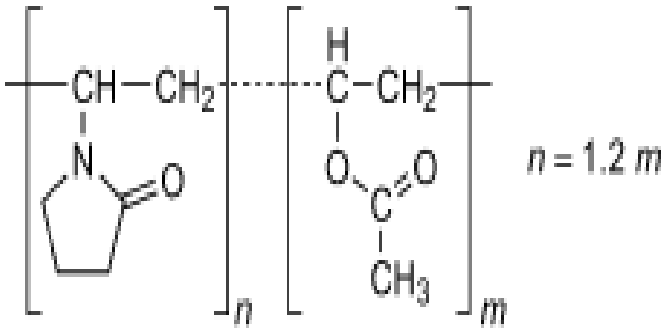
Chemical Name and

CAS Registry Number : 1-Ethenyl-2-pyrrolidinone homopolymer[9003-39-8]

Empirical Formula : The USPNF 23 describes Crospovidone as a water insoluble synthetic crosslinked homopolymer of *N*-vinyl- 2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material

$(C_6H_9NO)_n$>1 000000

Structural Formula :



Functional Category **:** Superdisintegrant.

Description **:** Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Applications in pharmaceutical formulation or technology:

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry- granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of Crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, Crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to Crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

1.6.2 Croscarmellose sodium[25]:

Nonproprietary Name : USPNF: Croscarmellosesodium.

Synonyms : Ac-Di-sol; cross-linked carboxy methylcellulose Sodium; Primellose

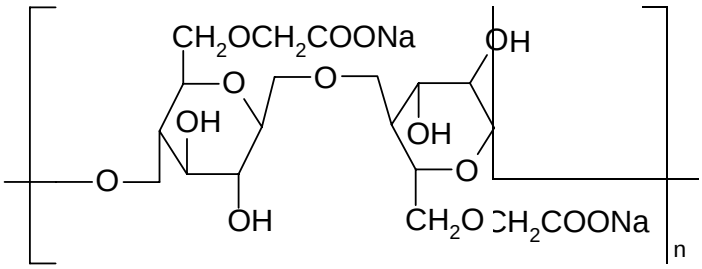
Functional category : Tablet and capsule disintegrant

Chemical name : Cellulose, carboxymethyl ether, sodium salt, cross-linked

CAS Registry Number : 74811-65-7.

Description : Croscarmellose sodium occurs as an odourless, white-coloured powder.

Structural formula:



Molecular weight : 90000-700000.

pH (1%w/v dispersion) : 5.0-7.0.

Solubility : Insoluble in water. Although croscarmellose sodium rapidly swells to 4-8 times of its original volume on contact with water.

Stability and storage condition : Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with Croscarmellose sodium as disintegrant, showed no significant difference in drug dissolution after storage at 30^0C for 14months.

Incompatibilities : The efficacy of disintegrants, such as Croscarmellose sodium may be slightly reduced in tablet formulations prepared by wet granulation or direct compression process which contain hygroscopic material such as sorbitol.

Safety : Croscarmellose is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amount of Croscarmellose sodium may have a laxative effect although the quantities used in solid dosage formulations are unlikely to cause suchproblems.

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

1.6.3 Sodium starch glycolate[25]:

Synonyms : Explotab, Primogel.

Nonproprietary Name : BP: Sodium starchglycolate

USPNF: Sodium starch glycolate

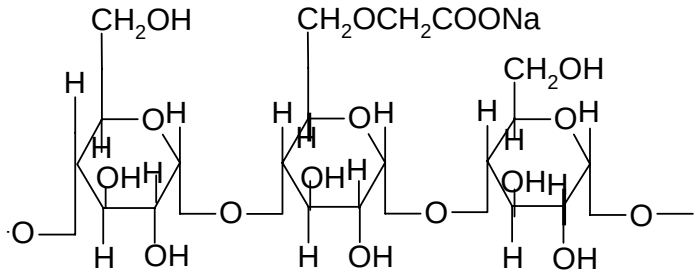
Functional Category : Tablet and capsule disintegrant.

Chemical Names : Sodium carboxy methyl starch.

CAS Registry Number : 9063-38-1

Description : Sodium Starch Glycolate is a white to off-white, odourless, tasteless, free flowing powder. It consists of oval or spherical granules, 30-100 µm in diameter with some less spherical granules ranging from 10-35 µm in diameter.

Structural Formula:



Solubility	**:**	Practically insoluble in water; sparingly soluble in ethanol (95%). In water it swells up to 300 times its volume
Stability and Storage Conditions	**:**	It is a stable material. It should be stored in a well closed container to protect from wide variations in humidity and temperature that may cause cracking.
Incompatibilities	**:**	Incompatible with ascorbic acid.
Safety	**:**	It is generally regarded as a non-toxic and non-irritant material. However, oral ingestion of large quantities may be harmful.
Applications	**:**	As a disintegrant in tablet (wet granulation and direct compression) and capsule formulation in 2-8% concentration

1.6.4 Indion 414:

Description **:** INDION414 is a high purity pharmaceutical grade weak acid cation exchange resin supplied as a dry powder in potassium form. It is suitable for use in pharmaceutical application such as tablet disintegration and taste masking bitter drugs. Indion 414 is based on a crosslinked polyacrylic acid

Applications

Tablet Disintegration **:** Indion 414 is an extremely effective tablet disintegrant which provides the necessary hardness and chemical stability to the tablet. the product swells up to a very great extent (about 700%) when in contact with water or gastro-intestinal fluids, causing rapid disintegration without the formation of lumps. Depending on the formulation, the use of Indion 414 is recommended for effective disintegration of tablet.

Characteristics

Appearance **:** White to pale cream powder

Matrix **:** Crosslinked acrylic co-Polymer

Functional Group: Carboxylic acid

Ionic form as supplied : Potassium

Solubility : In soluble in water and in common solvents

Specifications

Particle size distribution

Retained on 100 BSS mesh (150 microns) : 1%maximum

Retained on 200 BSS mesh (75 microns) : 30%minimum

Moisture Content : 10% Maximum

Sodium Content : 0.2% Maximum

Potassium Content : 20.6-25.1%

pH of 10% Slurry : 7.0-9.0

Iron content as Fe : 100 ppm, Maximum

Heavy Metals content as Pb : 20 ppm , Maximum

Arsenic content : 3 ppm, Maximum

Toxicity : Indion 414 is a high molecular weight polymer. It is therefore not absorbed by body tissues and is totally safe for human consumption. Test for toxicological tolerance show that it does not have any pronounced physiological action at recommended dosage level and is non–toxic. Experiments on mice have shown LD 50 value of Indion 414 to be approximately 10,000 mg/kg body weight

Storage : Indion 414 is hygroscopic in nature. It is therefore essential to store it in a tightly packed container to prevent absorption of atmospheric moisture. If moisture is absorbed, the indion414 can be dried at 90^0 to 100^0C for approximately 6 hours to reduce the moisture content below 10%.

1.6.5 Microcrystalline cellulose (AVICEL PH 102) [25]:

Nonproprietary Name : NF: Microcrystalline cellulose.

USP: Microcrystalline cellulose.

Functional Category : Tablet and capsule diluents, tablet disintegrant, suspending and/or viscosity increasing agent.

Synonyms : Cellulose gel: Crystalline cellulose: Avicel PH101,102,

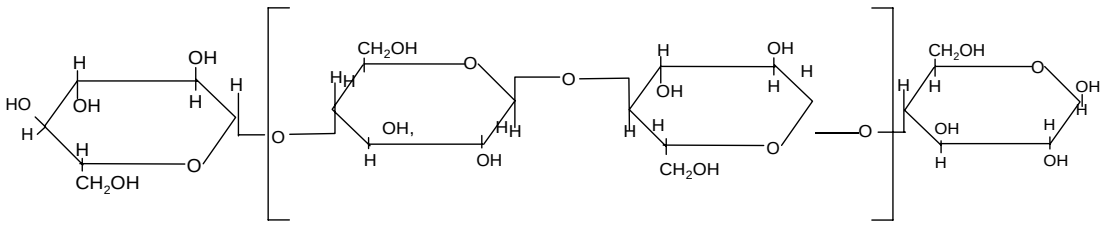
Chemical names : Cellulose

CAS Registry number : 9004-34-6

Empirical Formula : (C6H10O5) n n=220

Molecular Weight : 36,000(approx)

Structural formula:

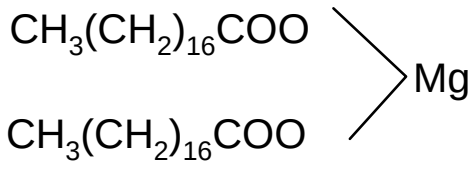


Microcrystalline Cellulose

Description	**:**	Purified, partially depolymerized cellulose occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.
Density	**:**	Apparent density - 0.28g/cm^3 Tap density-0.43g/cm^3
Solubility	**:**	Insoluble in water, dilute acids and most organic solvents, slightly soluble in 5% w/v NaOH solution.
Stability and Storage Conditions	**:**	Stable, hygroscopic. Store in a well closed container
Incompatibilities	**:**	None cited in the literature.
Safety	**:**	Generally regarded as safe
Applications	**:**	Tablet binder/ diluents (wet or dry granulation) 5 to 20% Tablet disintegrant & Glidant 5 to15% Anti Adherent 5 to20%

1.6.6 Magnesium stearate[25]:

Nonproprietary Name	**:**	NF : Magnesium stearate. BP/EP: Magnesium stearate
Synonyms	**:**	Metallic stearic; Magnesium salt.
Functional Category	**:**	Tablet and capsule lubricant.
Chemical Names	**:**	Octadecanoic acid; Magnesium salt; Magnesium stearate
CAS Registry Number	**:**	557-04-0
Empirical Formula	**:**	$C_{36}H_{70}MgO_4$
Molecular Weight	**:**	591.3
Structural Formula	**:**	



Magnesium Stearate

Description	**:**	It is a fine, white, precipitated or milled, impalpable Powder of low bulk density, having a faint characteristic odour and taste. The powder is greasy to touch and readily adheres to the skin.
Density	**:**	1.03-1.08 g/Cm^3
Bulk volume	**:**	3.0-8.4 g/ml
Tapped volume	**:**	2.5-6.2 g/ml
Solubility	**:**	Practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in benzene and warm ethanol (95%).
Stability and Storage Conditions	**:**	Stable, non-self-polymerizable. Store in a cool, dry place in a well closed container
Incompatibilities	**:**	Incompatible with strong acids, alkalies, iron salts and with strong oxidizing materials

1.6.7 Camphor[26]:

Camphor is a ketone obtained from cinnamon camphora (Linne) Nees et Ebermaier (family- Lauraceae) (Natural Camphor) or produced synthetically (synthetic camphor).

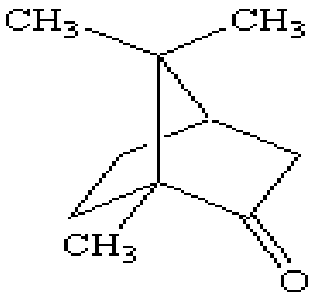
Chemical Names : Bicycle[2.2,1]heptane-2-one,1,7,7-trimethyl camphor

Synonyms : Gum Camphor

Empirical Formula : $C_{10}H_{16}O$

Molecular Weight : 152.23

Structural Formula :



Melting point : 174^0-179^0 C

Description : Colorless or white crystalline solid, fragrant penetrating odour

Specific Rotation	**:**	Between +410 and + 430 for natural camphor
Solubility	**:**	1 in 10 solution in Hexane is clear
Packaging and Storage	**:**	Preserve in tight container and avoid exposure to extensive heat
Application	**:**	As a rubefacient, as a plasticizer for cellulose esters and ethers, explosives and pyrotechnics, as a mouth repellent, as a preservative in pharmaceuticals and cosmetics

1.6.7 Talc[25]:

Non Proprietary Name : Purified talc

Synonym : Powdered talc.

Empirical Formula : $Mg_6(Si_2O_5)_4(OH)_4$

Specific Surface Area : 2.41-2.42m^2/g

Description : Talc is very fine, white to greyish-white colored, odorless, impalpable, hydrophobic, crystalline powder. It adheres readily to the skin, is soft to touch, and free from grittiness.

Functional Category : Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant

Pharmaceutical Applications : It is commonly used as a lubricant in tablet and capsules

Concentrations of talc to be used in various applications

Use	Concentration (%)
Dusting powder	90-99
Glidant and tablet lubricant	1-10
Tablet and capsule diluents	5-30

Stability and Storage Conditions : Talc is a stable material. It should be stored in a well-closed container in a cool, dry place.

Incompatibilities : Incompatible with quaternary ammonium compounds

Safety : Following oral ingestion talc is not absorbed systemically and may be thus regarded as an essentially nontoxic material

1.6.9 Aspartame[27]:

Functional Category	**:**	Sweetening agent
Synonyms	**:**	APM, Aspartyl phenyl amine methyl ester, Equal, Canderel, Nutrasweet, Sanecta,Tri-sweet.
Description	**:**	It occurs as white, almost odorless crystalline powder
Solubility	**:**	Slightly soluble in ethanol (95%), sparingly soluble in water. Solubility increases at higher temperature and at more acidic pH
Stability and Storage Conditions	**:**	It is stable in dry conditions. In presence of moisture, hydrolysis occurs. Degradation also occurs during prolonged heat treatment. Bulk material should be stored in a well-closed container, in a cool, dry place
Incompatibilities	**:**	Incompatible with dibasic calcium phosphate

Safety	**:**	The WHO has set an acceptable daily intake of 40 mg/kg body weight. Reported adverse effects are headache, grandmal seizures, memory loss, gastrointestinal and dermatological symptoms
Applications	**:**	It is used as an intense sweetening agent in tablets and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste and has sweetening powder of 180-200 times that of sucrose

CHAPTER -2

OBJECTIVE

2.1 Need of the Study:

The concept of mouth dissolving drug delivery system emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatincapsules[15].

In some cases, such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablet may bedifficult[16].

Such problems can be resolved by means of mouth dissolving tablets, which disintegrates or dissolve in saliva without the need for water. As tablet disintegrates or dissolve in saliva without the need for water[17]. As tablet disintegrates in mouth, this could enhance the clinical effect of the drug through pre-gastric absorption from the mouth, pharynx and esophagus, in such cases bioavailability of drug is significantly greater than those observed from conventional tablet dosage form by avoiding first pass livermetabolism[15].

Moreover, they cover the swallowing difficulty associated with geriatric, pediatric, or psychiatric patients and for the conditions where patients may not have ready access to water, thus it provides convenience of administration, greater patient compliance and quick onset ofaction[18].

Therefore, in the present study an attempt will be made to formulate mouth dissolving tablets of Metoprolol Tartrate, is 1-(isopropylamino)-3-p-(2- methoxyethyl) phenoxy-2propanol(2:1)dextro-tartrate β_1 selective antagonist, antianginal with a view to provide a convenient means of administration to those patients suffering from difficulties in swallowing such as pediatric, geriatric, uncooperative and mentally illpatients[19,20].

2.2 Objectives of the Study:

1. Preparation of mouth dissolving tablets of Metoprolol Tartrate by direct compression using different concentration of superdisintegrants like Indion 414, cross-linked Carboxy Methyl Cellulose (AC-di-sol), Sodium Starch Glycolate (Explotab) and Crospovidone (polyphasdoneXL).
2. Drug-excipients interaction using FTIR studies.
3. Mouth dissolving tablets of Metoprolol Tartrate were also prepared by sublimation method using camphor as subliming agent and Indion 414, Croscarmellose Sodium (Ac-di-sol), Sodium Starch Glycolate (Explotab) and crosprovidone (Polyplasdone XL) as superdisintegrants.
4. Mouth dissolving tablets of Metoprolol Tartrate were evaluated for hardness, friability, weight variation, disintegration time, drug content, water absorption ratio, water absorption time.
5. To characterize the formulation with respect to drug-excipients interaction (using DSC).
6. Study *in vitro* dissolution of Metoprolol Tartrate from the formulated mouth dissolving tablets.

CHAPTER-3

REVIEW OF LITERATURE

Amin P et al [28] studies on Indion 414 as superdisintegrant in formulation of mouth dissolve tablets. Experiments were carried out to evaluate the disintegrant property of Indion 414 by incorporating Indion 414 in fast disintegrating dosage form like mouth dissolve tablets and Indion 414 was compared with the conventional disintegrants to determine its relative efficacy. The comparison of disintegrants were done with various quality control parameters like appearance, taste, mouth feel, hardness, weight variation, *in vitro* disintegrationtime, drug content and drug release.

Uddhav Set al[29].describes manufacturing technologies for mouth dissolving tablets showing that incorporation of an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety and improved patient compliance. In these studies, they had described different types of technologies employed for the formulation of mouth dissolving tablets i.e. freeze drying, spray drying, sublimation and comparison of sugar-based excipients with their dissolution rate and compressibility.

Barone MR et al [30] develop the rapidly dispersing tablet of a poorly wettable compound–formulation DOE and mechanistic study of effect of formulation excipient on wetting of celecoxib. In this work a tablet was placed in water and the turbidity of the resulting “dynamic” suspension was measured. They describe the novel method to enhance the dissolution rate for poorly soluble compounds by reduction in particle size, with screening formulation statistical design of experiments, mechanistic studies, optimization design of experiments and analytical methods like turbidity test, contact

angle analysis, microscopic test.

Patel NV et al[31] formulate oxcarbazepine fast release tablet by melt granulation technique. This work describes as a melt granulation technique to improve the dissolution characteristic of a poorly water-soluble drug Oxcarbazepine. They concluded that melt granulation has been proved to be a viable process to produce a fast release dosage form for oxcarbazepine, using PEG4000 as a melt binder, without using solvent orwater.

Chaudhari PD et al[32] formulate and evaluated taste masked orodispersible dosage form of levocetirizine. An attempt was made to mask the taste, by complexation technique using ion-exchange resin, tulsion 335 formulate in to an orodispersible dosage form. The drug loading onto ion exchange resin was optimized for concentration of resin, swelling time of resin, stirring time, pH of resin solution, stirring temperature. Shows bitter drug successfully taste masked using suitable ion exchange resin. The drug resin complex orodispersible tablets were formulated and the evaluated for drug content, content uniformity, weight variation, hardness, friability, water absorption ratio, *in vitro* and *in vivo* drugrelease

Abdelbary C et al[33] determine the *in vitro* disintegration profile of RDT and correlate with oral disintegration. They evaluated the disintegration profile of RDT manufactured by main commercialized technologies, using texture analyzer. The evaluation of quantitative values as the disintegration onset (t_1) and total disintegration time (t_2), the characterization of effects of test variables as the disintegration medium and temperature on the disintegration time of RDT and correlation between *in vitro* and *in vivo* oral disintegration times. Which showed that the use of the texture analyzer *in vitro* determination of the disintegration behaviors

different RDT was shown very successful, convenient andprecise.

Prabhu NB et al[34] studies on taste masking of drotaverine hydrochloride by the complexation technique. The drug loading process was optimized for taste masking and drug: resin ratio, the resinate was evaluated for bulk density, tap density, taste and characterization was done using DSC. The taste masked drotaverine complex was incorporated into palatable melt in mouth tablet and evaluated various quality control parameters. The mouth dissolve tablets had optimum physiochemical property with complete release of drug with 30 min.

Chakraborty Set al[35] studied the effect of a natural superdisintegrant isolated mucilage of *Planteegoovata*and synthetic superdisintegrant like Sodium Starch Glycolate and croscarmellose sodium on formulation of fast dissolving tablet. The tablets were evaluated weight variation, hardness, disintegration time, drug content, friability, dissolution and swelling index was investigated with an aim to compare the swelling property of mucilage *Planteegoovata*with SSG and Ac-di-sol. Concluded that natural super disintegrates like *Planteegoovatel*mucilage showed better disintegration property than the super disintegrants like SSG and Ac-di-Sol in FDTS.

Devi VK et al[36] prepared orodispersible fluconazole tablets using voltatilizable agent such as an ammonium bicarbonate / camphor, mannitol as a diluents and polyethylene glycol 4000 as a binder. Evaluated for parameters like friability, weight variation, hardness, the best formulation choosen and compared with marketed conventional tablet. Showed no significant difference between the technological properties of the prepared formulation and the marketed tablets.

Lakade SH et al[37] formulate mouth dissolving tablets of ondansetron hydrochloride by direct compression method. Tablets of ondansetron hydrochloride with β-cyclodextrin were prepared by using different concentration of dilusents like MMC, mannitol, lactose. Showed superior organoleptic properties along with excellent *in vitro* disintegrationtime and drug release as compared to other formulation.

Mulla JA et al[38] prepared promethazine hydrochloride mouth disintegrating tablet that have been used for prevention of emesis and nausea using disintegrants like Ac-di-sol, explotab, polyplasdone and MCC along with other additives by directly compression techniques. It was observed that the concentration of the superdisintegrants influenced disintegration time and *in vitro* dissolution time and *in vitro* dissolution characteristics. Ac-di-sol was found to be better as compared to other superdisintegrants used in study.

Jacob Set al[39] used co-processed excipient of mannitol and microcrystalline cellulose for fast dissolving tablets of glipizide. Co-processed excipient prepared by incorporating one excipient to the particle structure of another excipient using co-drying process. These attributes improve the binding of tablet increase water uptake and thereby decrease the disintegration time of the tablet.

Lalla JK et al[40] prepared fast dissolving Rofecoxib tablets by wet granulation methods using lactose, Avicel PH 102. The inclusion complex of Rofecoxib with β-cyclodextrin using ball milling technique and the evaluation was done with DSC. Tablet evaluated for weight variation, hardness, friability, disintegration time. Comparison between formulated fast dissolving tablets of Rofecoxib with a

conventional released marketed tablet. It was observed that combination of three disintegrants gave the desired rapid disintegration. The dissolution study show that the formulation prepared either by wet granulation or by direct compression showed complete release of drug within 12 min in both media.

Chaudhari PD et al[41] studied the bitter taste of famotidine was masked using Eudragit in different ratio. The different superdisintegrants like Ac-di-sol and polyplasdone with their varying concentration used for disintegration of tablet in mouth. After dissolution study he concluded that all formulation showed faster release rate than marketed formulation.

Zhao N et al[42] compare disintegration efficiency and to develop a discriminating model for 3 classes of superdisintegrants represented of AC-Di-Sol, primoses and polyplasdone X L 10. The study was thus providing a closer look at the functionality of superdisintegrants in promoting tablet disintegration and development of model formulation with examinated by videography and dissolution profile. AC-Di-Sol was found to disintegrate tablet rapidly into apparently primary particles. 3 disintegrants representing each of the 3 main classes of superdisintegrants differed in their ability to disintegrate model tablets into their primary particles.

Patel DM et al[43] prepared fast dissolving Etoricoxib tablet by sublimation method using camphor as a subliming agent along with the exicipients. The tablets were evaluated for percentage friability and disintegration time and 3^2 full factorial designs were applied to investigate the combine effect of 2 formulation variables. The optimized tablet formulation was compared with conventional marketed tablets for percentage drug dissolved in 30 min. From the result they concluded that fast dissolving tablet with improved etoricoxib dissolution could be prepared by

sublimation containing suitable subliming agent.

Mishra DN et al[44] formulate rapidly disintegration oral tablet of poor aqueous soluble valdecoxib by direct compression technique. Using crospovidone, Sodium Starch Glycolate and cross camellose sodium as disintegrants. He found that hardness of all prepared tablets was found to be satisfactory. Tablet containing crosspovidone shows only lesser hardness as compare to other disintegrants. He concluded that fast disintegrating tablets of voldecoxib can be successfully prepared using selected superdisintegrants.

Nandgude TD et al[45] prepared diphenhydramine tannate fast dissolving tablet by wet granulation method after incorporating superdisintegrants like sodium glycolate and Crospovidone in different concentration. The tablets are subjected to evaluation with post compressional parameters like weight variation, hardness and friability, tensile strength, water absorption ratio, *in vitro* disintegrationtime, *in vivo* disintegrationtime. Concluded that conventional tablet shows 100% release after 7 hrs whereas mouth disintegration tablet achieved maximum release 3-4 hrs. Tablet containing SSG show superior organoleptic properties along with excellent *in vitro* dispersiontime.

Bhagawati ST et al[46] cefixime dispersible tablets were prepared by using corscarmellose sodium, crosspovidone and Sodium Starch Glycolate as disintegrants, starch and PVPK-30 as a binder by direct compression technique. A total number of nine formulations were prepared. The tablet prepares by croscarmellose sodium showed drug release of 99.80%, 98.3%, 97.28% respectively after 15min. He concluded that in all nine formulations tablet prepared by croscarmellose sodium as disintegrants shows rapid drugrelease.

Setty CM et al[47] developed fast dispersible Aceclofenac tablets and study the effect of superdisintegrants on wetting time, disintegration time, drug content, *in vitro* release and stability parameter using direct compression technique. The parameters were tested for significance by using analysis of variance (ANOVA: Single factor). The stability study showed that tablet containing superdisintegrants were sensitive to high humidity condition. He also concluded that although functional differences existed between the superdisintegrants, the fast dispersible aceclofenae tablets could be prepared by using any of the superdisintegrants used.

Fini A et al[48] developed eight formulations containing Ibuprofen in the form of orally disintegrating tablets. To prevent bitterness of drug he masked the taste of drug using taste masking agents. Aspartame used as a sweeter in formulation, mannitol used as a binder and explotab were added as superdisintegrant and compacted under low compression force. Dissolution profile suggest that the combined action of hydrophobic lecithin and coating delay the release of the drug from tablets with respect to when it is free or in the form of simplegranules.

Sharma Set al[49] developed carvediolol fast dissolving tablet by using solid disintegrationin polyethylene glycol. The tablet was prepared by direct compression technique and evaluated for thickness, hardness, uniformity of weight, friability wetting time, disintegration time, drug content, *in vitro* release. Concluded that prepared tablet gives benefit in terms of patient compliance, low dosing and good stability.

Bhatti A et al[50] prepared taste masked granules using aminoalkyl methacrylate

copolymer by the extrusion method and formula rapidly disintegrating tablet by direct compression method. The tablet prepared by using microcrystalline cellulose and Sodium Starch Glycolate as disintegrant. Concluded that tablet had a good taste and rapidly disintegrated in the mouth were useful and practical for pediatric and geriatric population.

Swamy PV et al[51] used superdisintegrants such as croscarmellose sodium. Crosprovidone and Sodium Starch Glycolate and prepared amoxycillinetrihydrate capsule. Concluded that formulation contain crosspovidone show good dissolution rate as compare to market product. They also concluded that croscarmellose sodium can be used for enhancing the *in vitro* dissolution rate of poorly water-soluble drug amoxycilline trihytrate.

Narazaki R et al[52] studied and developed a simple and suitable disintegration method specific for rapid disintegrating tablet. Manufacture several storage conditions in order to obtain RDTs with wide range disintegration time. Compared the disintegration time of several methods. In conclusion they claimed that able to establish a simple method for RDTs having good correlation with disintegration in human mouth.

Rao TV et al[53] prepared mouth dissolving tablet of simavastatin by effervescent technique. Used sodium bicarbonate and citric acid an effervescent agent with mannitol, Magnesium stearate used as exicipient. Four formulation prepared simavastatin tablet improve the patient compliance and palatability moisture activation was successfully employed in tablet. Having a balance over the hardness and disintegration time of tablet using economic lab feasiblemethod.

Mizumoto T et al[54] tries to develop novel fast-disintegration tablet as a user-friendly dosage form for the aged. Used mannitol, lactose, glucose, magnesium stearate as excipient. Prepared many formulations using different exicipients in different formulation, various parameters checked and compare. They concluded that tablet contain mannitol, glucose and lactose showed quick disintegration time, but very low hardness and tablet contain maltose and mannitol having high hardness but slow disintegration time.

Patel DM et al[55] studied in formulation of orodispersible tablet of Rafecoxib. The superdisintegrants sodium starch glycolate. Croscarmellose sodium used in different formulation. Granulation was carried out by deposition method. And prepared granules directly compressed. He concluded that the tablet containing Crospovidone exhibit quick disintegrating time and wetting time followed by tablet containing croscarmellose sodium and sodium starch glycolate.

Swamy PV et al[56] developed orodispersible tablet of meloxicam using different superdisintegrants. Combinations of sodium starch glycolate-croscarmellose sodium or sodium starch glycolate–Crospovidone were used along with directly compressible mannitol. The prepared batches evaluated for hardness, friability, wetting time, water absorption ratio like various parameters. He concluded that the formulation prepared using 2% w/v Sodium Starch Glycolate and15% croscarmellose sodium was found better formulation compare to conventional tablet.

Jeong SH et al[57] developed fast dissolving tablet using various polymer coated ion-exchange resin complexes. Complex of ion exchange resin and model drug

prepared using different particle size of the resin. A high shear granulation method was used to prepare the granules containing coated resin particles. The tablets were examined using SEM. He concluded that as the resin particle becomes smaller. The time needed to reach equilibrium was shorter than of bigger particles and drug release rate increased due to the increased surface area of the resin complexes.

Kuchekar BS et al[58] prepared orodissolving tablet of promethazine HCl using Ac-di-sol and SSG as disintegrants and mannitol, MCC as a diluent, tablet is prepared by direct compression technique. The prepared tablet is evaluated for hardness friability, drug contents, and disintegrationtime. Author found that tablet contains SSG and croscarmellose sodium was to get best result.

Rampure MV et al[59] prepared rapidly disintegrating tablet at Alfuzosin by effervescent method using sodium bicarbonate and citric acid. Crospovidone, Sodium Starch Glycolate and croscarmellose sodium used as superdisintegrants. The prepared tablet evaluated for different parameters and compare market product. He showed that the formulation containing Crospovidone along with mixture at 24% w/w of sodium bicarbonate and 18% w/w citric acid as overall best formulation.

Kuchekar BS et al[60] prepared mouth dissolving tablets of salbutamol sulphate a novel drug delivery system. Formulations were designed by factorial design technique. Sodium starch glycolate, croscarmellose sodium and treated agar were used as superdisintegrants while microcrystalline cellulose was used as diluent. Formulations containing Sodium Starch Glycolate along with other superdisintegrants, showed rapid in-vitro and in-vivo disintegrationtime, when compared to other formulations.

Righi MF et al[61] have developed glyburide fast-dissolving of tablets by exploiting the solubilizing effect of different cyclodextrins above or in combination with hydrophilic polymers. Tablets containing binary and ternary systems were prepared by direct compression and evaluated for technological properties and dissolution behaviour in comparison with a reference formulation containing the plain drug. Better results were obtained with ternary systems. Polyvinyl pyrrolidone emerged as the most effective polymer, and tablets with drug-PVP- hydroxypropyl-β-CD coevaporated products showed the best dissolution profiles, reaching of 100% dissolved drug within only 15 minu.

Raghavendra Rao NG et al[62] have formulated fast dissolving tablets of poorly soluble carbamazepine by direct compression technique with β-cyclodextrin complexes using various superdisintegrants like Indion-414, croscarmellose sodium, Crospovidone and sodium starch glycolate. The prepared tabletswere evaluated for hardness, friability, drug content, weight variation, disintegration time, wetting time, *in vitro* dissolution studies and were characterised by DSC, FTIR and stability studies. Concluded that the formulation containing 10% of croscarmellose sodium is over all the best formulation.

Jacob S et al [63] have assessed the potential of a natural polysaccharide, pectin to mask the bitter taste of ambroxyl hydrochloride, by microencapsulation technique, and its possibility to formulate as a fast disintegrating dosage form. The prepared microspheres by emulsion solvent evaporation technique possessed good sphericity, smooth surface morphology, uniform and narrow size distribution (10 – 90 μm). This study demonstrated that pectin could be a right choice in developing patient favored

formulations for bitter drugs and can be utilized in fast disintegrating dosage forms as well.

Deshmukh SS et al[64] have tried to prepare ziprasidone hydrochloride fast dissolving tablets. For enhancing solubility of drug, inclusion complexes of drug were prepared using βCD and HPβCD. To aid the fast disintegration of tables, superdisintegrants in different ratios were used and their effect on disintegration was studied. The inclusion complexes with HPβCD prepared by microwave method exhibited highest enhancement in solubility and showed fastest dissolution profile (100% drug release in 5min).

Vamshi Priya VA et al[65] have investigated the efficiency of superdisintegrants in promoting the tablet disintegration and drug dissolution of topiramate immediate release tablets. The efficiency of superdisintegrants was tested by considering four concentrations viz., 2%, 3%, 4% and 5% in the formulation. The dissolution profile of the formulation containing 4% Sodium Starch Glycolate and lactose monohydrate as a diluent was like that of a marketed product.

Jacob Set al[66] have prepared fast dissolving effervescent tablets of glibenclamide by the modification of non-reactive liquid-based wet granulation technique. Citric acid was coated with plastic materials such as polyethylene glycol (PEG), which provide a physical barrier to the reaction. The inherent hygroscopic nature of PEG could decrease the affinity for moisture of effervescent mixtures and can provide a stabilizing effect. Sodium bicarbonate was blended with sugar alcohol like mannitol, which could give a protective coating. PEG 1000 melts at body temperature and thereby does not delay the reaction between acid source and base.

Balasubramanium J et al[67] evaluated effect of superdisintegrants on dissolution of cationic drugs. Study revealed that Crospovidone demonstrated a more rapid dissolution rate for the model cationic drugs, irrespective of their aqueous solubilities because Crospovidone is a nonionic disintegrant, no ionic interaction occurs between it and the cationic drugs. However, ionic interaction between cationic drugs and anionic superdisintegrants may delay drug release to such an extent as to fail the Q tolerance of the compendial dissolution method for this product.

Chen CR et al[68] investigated the dissolution difference between acidic and neutral media of acetaminophen tablets containing a super disintegrant and a soluble excipient. A formula containing acetaminophen and Crospovidone with or without sucrose, did not show big dissolution difference between acidic and neutral media, which correlates well with the disintegration study. In contrast, a formula containing acetaminophen, sucrose and croscarmellose sodium caused longer disintegration and slower dissolution in the acidic medium than those in the neutral medium.

CHAPTER -4

MATERIAL AND METHODS

4.1 MATERIALS:

Sl. No.	Material	Source
1.	Metoprolol Tartrate	Gift sample from Emcure Pharma, Pune.
2.	Croscarmellose sodium	Gift sample from Signet, Mumbai.
3.	Crospovidone	Gift sample from Cipla, Kurkhumb.
4.	Sodium starch glycolate	Signet, Mumbai.
5.	Microcrystalline cellulose	SD Fine Chemi Ltd. Mumbai.
6.	Mannitol	LobaChemie, Mumbai.
7.	Camphor	SD Fine Chem. Ltd., Mumbai.
8.	Aspartame	Gift sample from Cipla, Kurkhumb.
9.	Magnesium stearate	SD Fine Chem Ltd., Mumbai.
10.	Talc	LobaChemie, Mumbai.
11.	PotasiumDihydrogenPthalate	SD fine Chem Ltd., Mumbai.
12.	Sodium hydroxide	SD fine Chem Ltd., Mumbai.

4.2 EQUIPMENT:

Sl. No.	Equipment	Make / Model
1.	Tablet compression machine	Rimek, minipress 10 station rotary machine, Karnavathi engineering ltd, Gujarat.
2.	Hardness tester	Pfizer hardness tester, Servewell instruments and equipmentspvt. ltd., Bangalore.
3.	Friability Test Apparatus	020334 -Veego Digital
4.	Tablet Dissolution Test Apparatus	220307-Electrolab USP (XXIII)
5.	UV visible spectrophotometer	UV-1700 Shimadzu corporation, Japan.
6.	Balance	BT 220H -Shimadzu Digital Balance, Japan
7.	pH meter	5291679-Hanna Instruments, Italy
9.	Thickness tester	Screw Gauze
10.	FT-IR Spectrometer	Perkin Elmer Instruments, USA
11.	DSC	DSC60 Shimadzu Corporation, Japan.

4.3 METHODS

4.3.1 Analytical method for estimation of Metoprolol Tartrate:

Identification of drug was carried out by FTIR (Perkin Elmer Instruments, USA). Standardization of the drug was carried out by using UV visible spectrophotometer (1700-Shimadzu, Japan). Differential scanning calorimetry (DSC) studies were also carried out to assess drug excipient compatibility.

4.3.2 Determination of λ_{max} for Metoprolol Tartrate:

100mg of pure drug transferred into 100ml of distill water in a volumetric flask. Withdrawn 10ml from this solution and diluted to 100ml it make 100mcg/ml (stock solution) then concentration made by withdrawing 0.5, 1, 1.5, 2, 2.5,3 ml from stock solution and diluted to 10ml it makes solution of concentration 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml , 25µg/ml, 30µg/ml.

Separately, absorbance was measured for each solution at λ_{max} of 223nm using Shimadzu UV/visible 1700 spectro photometer, graph was plotted for absorbance versus concentration of Metoprolol Tartrate.

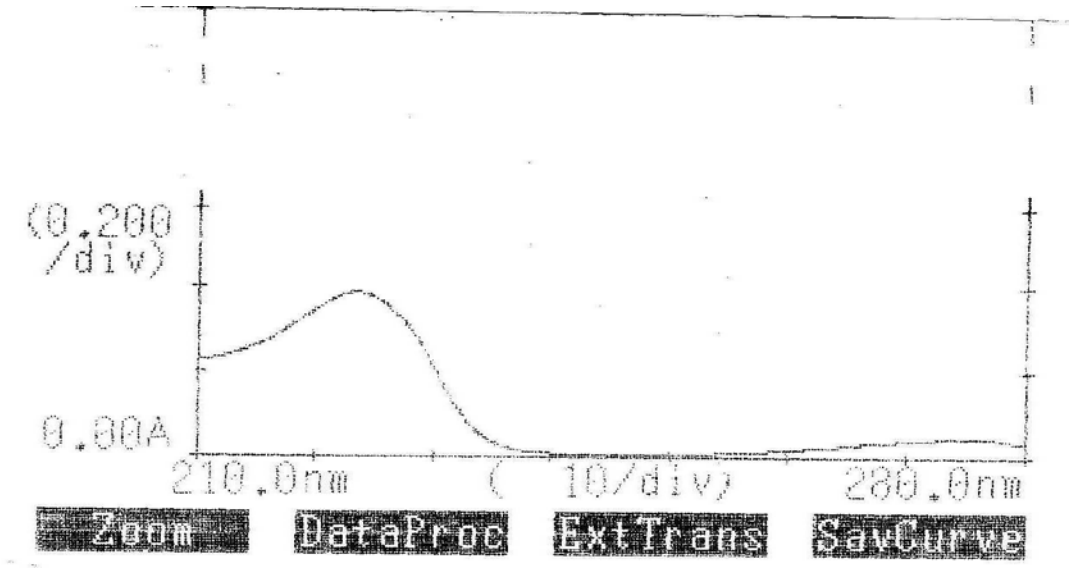


Figure 1: Scanning of Metoprolol Tartrate in distilled water.

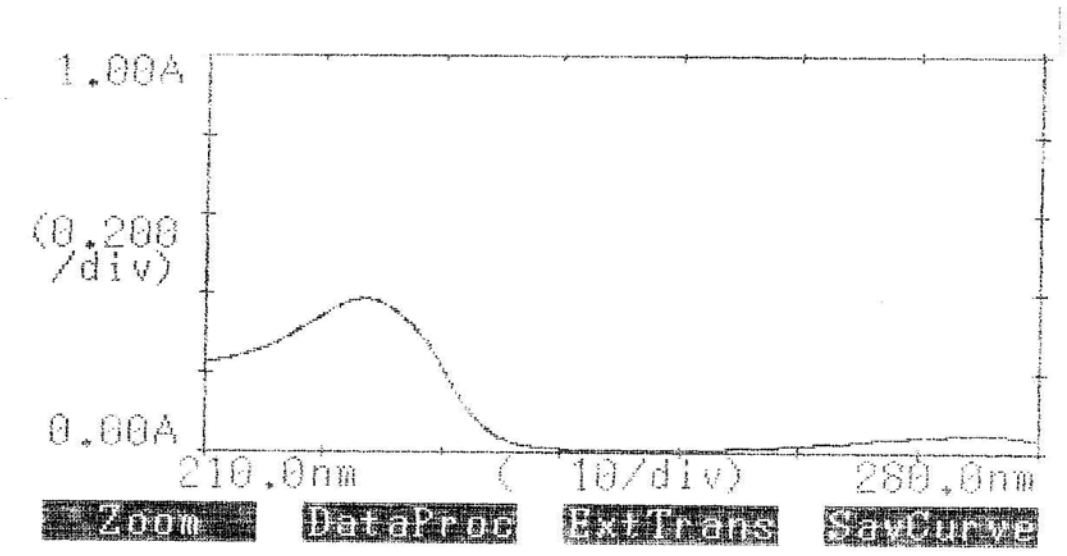


Figure 2: Scanning of Metoprolol Tartrate in pH 6.8-phospate buffer.

4.3.3 Standard calibration curve of Metoprolol Tartrate in phosphate buffer pH 6.8[69]:

- Solution ranging from 5 to 30 μg/ml were prepared using phosphate buffer (pH 6.8); separately, absorbance was measured for each solution at λ_{max} of 223nm using Shimadzu UV/visible 1700 spectrophotometer, graph was plotted for absorbance versus concentration of metoprolol tartrate.

Procedure:

100mg of pure drug transferred into 100ml of distill water in a volumetric flask. Withdrawn 10ml from this solution and diluted to 100ml it make 100mcg/ml (stock solution) then concentration made by withdrawing 0.5, 1, 1.5, 2, 2.5,3 ml from stock solution and diluted to 10ml it makes solution of concentration 5μg/ml, 10μg/ml, 15μg/ml, 20μg/ml , 25μg/ml,30μg/ml.

From the standard curve of Metoprolol Tartrate (table no. 1, fig. 3), it was observed that the drug obeys Beer's law in concentration range of 5 –30μg/ml in phosphate buffer pH 6.8. The linear regression equation generated was used for the calculation of amount of drug.

Table 1: Standard calibration curve of Metoprolol Tartrate in 6.8 pH buffer solution at λ_{max}223nm

Sl. No.	Concentration (µg/ml)	Absorbance
1.	00	0.000
2.	05	0.176
3.	10	0.354
4.	15	0.538
5.	20	0.740
6.	25	0.897
7.	30	0.993

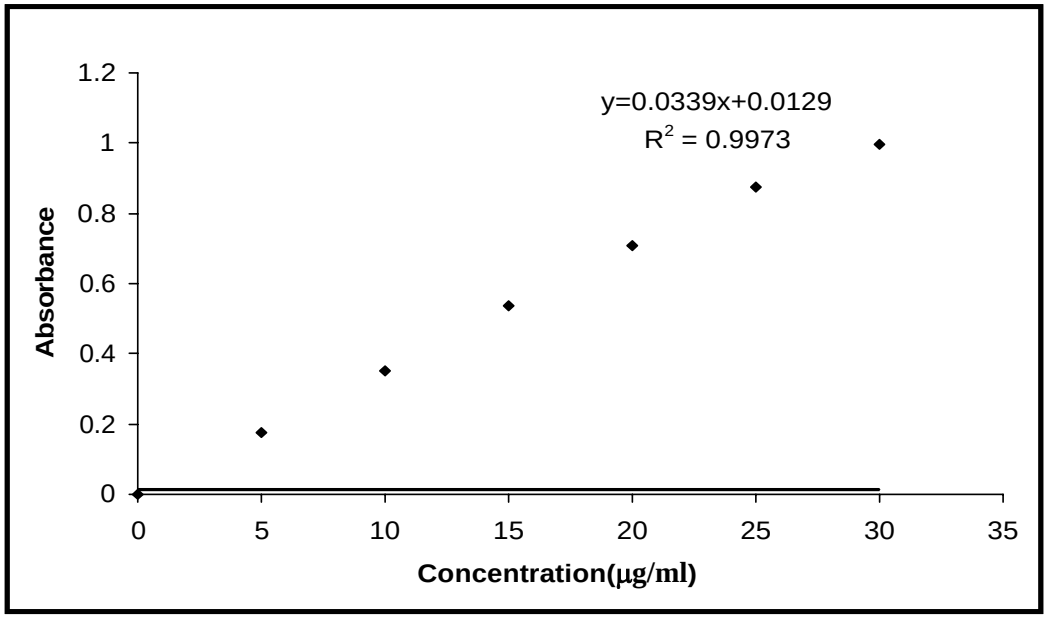


Figure 3: Standard calibration curve of Metoprolol Tartrate in 6.8 pH buffer solution at λ_{max}223nm

4.4 PREFORMULATIONSTUDY:

I) Pre-compression parameters:

a) Angle of Repose.

b) Bulk density.

c) Tapped density.

d) Hausner's ratio.

e) Compressibility index(%)

II) Drug polymer interaction study:

a) FTIR studies.

b) DSC studies.

PRE-COMPRESSION PARAMETERS:

4.4.1 Angle of Repose (θ)[72,73] :

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

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

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

Where, θ is the angle of repose

his height of pile

r is radius of the base of pile

Different ranges of flowability in terms of angle of repose (Table No. 9) are given below.

Relationship between Angle of Repose (θ) and flow properties.

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

Method:

A funnel was filled to the brim and the test sample could flow smoothly through the orifice under gravity. From the cone formed on a graph sheet was taken to measure the area of pile, thereby evaluating the flowability of the granules. Height of the pile was also measured.

4.4.2 Bulk Density[72]:

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

Method:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of accurately weighed powder (bulk) from each formula, previously shaken to break any agglomerates formed was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder could fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The taping was continued until no further change in volume was noted. LBD and

TBD were calculated using following formula;

$$LBD = \frac{\text{Weight of the powder}}{\text{Volume of packing}} \qquad \text{--------- (a)}$$

$$TBD = \frac{\text{Weight of the powder}}{\text{Tapped volume of packing}} \qquad \text{---------- (b)}$$

4.4.3 Tapped Density[72]:

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated using the following formula

$$\rho_t = \frac{M}{V_t}$$

4.4.4 Hausner's Ratio[60]:

Hausner ratio is an indirect index of ease of power flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{\rho^t}{\rho_d}$$

Where ρ_t is tapped density and ρ_d is bulk density. Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

4.4.5 Carr's compressibilityindex[72]:

The compressibility index of the granules was determined by Carr's compressibility index.

(%) Carr's Index can be calculated by using the following formula

$$\text{Carr's Index (\%)} = \frac{\text{TBD - LBD}}{\text{TBD}} \text{ x100 ----------(c)}$$

Grading of the powders for their flow properties according to Carr's Index

Consolidation Index (Carr %)	Flow
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to passable
23 – 35	Poor
33 – 38	Very poor
>40	Very very poor

4.4.6 Drug Polymer Interaction Studies:

- **FTIR STUDIES:**

IR spectra for pure drug, formulations DCI 1, DCI3, DCC4, SBI1, SBC4, and SBP1 were recorded in a Fourier transform infrared (FTIR) spectrophotometer (Shimadzu corporation 8600, Japan) with KBr pellets **.**

- **DSC Studies:**

DSC studies were carried out pure drug and best formulations DCI 1, DCI3, DCC4, SBI1, SBC4, and SBP1. DSC scan of about 5mg, accurately weighed Metoprolol Tartrate and optimized formulations were performed by using an automatic thermal analyzer system. (DSC60 Shimadzu Corporation, Japan) Sealed and perforated aluminium pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as for the sample was used as a reference. The entire samples were run at a scanning rate of 10°C/min from 50-300°C.

4.5 METHODS OF PREPARATION OF MOUTH DISSOLVING TABLETS:

1. Direct compression method.
2. Sublimation method.

4.5.1 Preparation of mouth dissolving tablets by direct compression technique[60]:

Method: Mouth dissolving tablets of Metoprolol Tartrate were prepared by direct compression method according to the formula given in table no: 5.

All the ingredients were passed through 60 mesh sieves separately. The drug and microcrystalline cellulose were mixed by small portion of both each time and blending it to get a uniform mixture kept aside. Then the ingredients were weighed and mixed in geometrical order and tablets were compressed of 8mm sizes flat round punch to get tablet using Rimek Compression Machine.

4.5.2 Sublimation method[70,71]:

Method: Metoprolol Tartrate tablets were prepared by sublimation technique. The basic principle involved in preparing mouth dissolving tablets by sublimation technique is inert solid ingredients (E.g. urea, urethane, ammonium carbonate, camphor, naphthalene) were added to other tablet excipients and the blend was compressed into tablet.

Removal of volatile material by sublimation generated a porous structure. Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. The tablets dissolve within 10-20 seconds and exhibit enough mechanical strength for practical use.

Sixteen formulations were developed by varying concentration of subliming agent i.e. camphor.

Accurately weighed ingredients were sifted through sieve no.44 and thoroughly mixed for 10 min and magnesium stearate and other ingredients were added to the blend and thoroughly mixed. The tablets were compressed using Rimek tablet punching machine. The compressed tablets were than subjected to sublimation at 80°c for 30 min. The tablets were evaluated for disintegration time and mean tablet weight.

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Schematics figure of sublimation method for design of mouth dissolving tablets

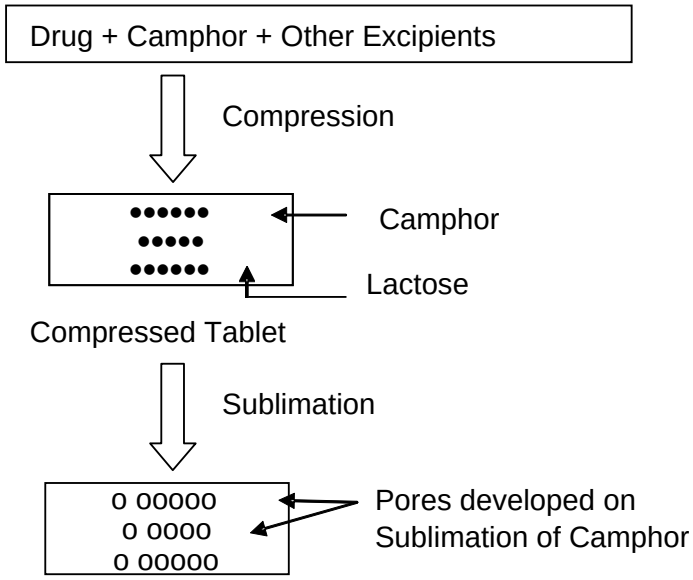


Table 2: Formulation of Metoprolol Tartrate mouth dissolving tablets prepared by Direct Compression Method (1-tablet)

Ingredients (mg)	Formulation code															
	DCI_1	DCI_2	DCI_3	DCI_4	DCC_1	DCC_2	DCC_3	DCC_4	DCP_1	DCP_2	DCP_3	DCP_4	DCS_1	DCS_2	DCP_3	DCS_4
Metoprolol Tartrate	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Indion 414	6	12	18	24	-	-	-	-	-	-	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	-	6	12	18	24	-	-	-	-	-	-	-	-
Crosprovidone	-	-	-	-	-	-	-	-	6	12	18	24	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	-	-	-	-	-	6	12	18	24
Aspartame	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Mg stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Methyl cellulose	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
MCC (Avicel PH-102)	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
D- Mannitol	94	88	82	76	94	88	82	76	94	88	82	76	94	88	82	76
Total	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

Table 3: Formulation of Metoprolol Tartrate mouth dissolving tablets prepared by Direct Compression Method (50-tablets)

Ingredients (mg)	Formulation code															
	DCI_1	DCI_2	DCI_3	DCI_4	DCC_1	DCC_2	DCC_3	DCC_4	DCP_1	DCP_2	DCP_3	DCP_4	DCS_1	DCS_2	DCP_3	DCS_4
Metoprolol Tartrate	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250
Indion 414	300	600	900	1200												
Croscarmellose sodium	-	-	-	-	300	600	900	1200	-	-	-	-	-	-	-	-
Crospovidone	-	-	-	-	-	-	-	-	300	600	900	1200	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	-	-	-	-	-	300	600	900	1200
Aspartame	750	750	750	750	750	750	750	750	750	750	750	750	750	750	750	750
Mg stearate	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Talc	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250
Methyl cellulose	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150
MCC (Avicel PH-102)	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500
D- Mannitol	4700	4400	4100	3800	4700	4400	4100	3800	4700	4400	4100	3800	4700	4400	4100	3800
Total	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000

Table 4: Formulation of Metoprolol Tartrate mouth dissolving tablets prepared by Sublimation Method (1-tablet)

Ingredients (mg)	Formulation code															
	SBI_1	SBI_2	SBI_3	SBI_4	SBC_1	SBC_2	SBC_3	SBC_4	SBP_1	SBP_2	SBP_3	SBP_4	SBS_1	SBS_2	SBS_3	SBS_4
Metoprolol Tartrate	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Indion 414	6	12	18	24	-	-	-	-	-	-	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	-	6	12	18	24	-	-	-	-	-	-	-	-
Crospovidone	-	-	-	-	-	-	-	-	6	12	18	24	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	-	-	-	-	-	6	12	18	24
Aspartame	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Mg stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Camphor	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
MCC (Avicel PH-102)	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
D- Mannitol	74	68	62	56	74	68	62	56	74	68	62	56	74	68	62	56
Methyl cellulose	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Total	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

Table 5: Formulation of Metoprolol Tartrate mouth dissolving tablets prepared by Sublimation Method (50-tablets)

Ingredients (mg)	Formulation code															
	SBI_1	**SBI_2**	**SBI_3**	**SBI_4**	**SBC_1**	**SBC_2**	**SBC_3**	**SBC_4**	**SBP_1**	**SBP_2**	**SBP_3**	**SBP_4**	**SBS_1**	**SBS_2**	**SBS_3**	**SBS_4**
Metoprolol Tartrate	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250
Indion 414	300	600	900	1200												
Croscarmellose sodium	-	-	-	-	300	600	900	1200	-	-	-	-	-	-	-	-
Crospovidone	-	-	-	-	-	-	-	-	300	600	900	1200	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	-	-	-	-	-	300	600	900	1200
Aspartame	750	750	750	750	750	750	750	750	750	750	750	750	750	750	750	750
Mg stearate	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Talc	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250
Camphor	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
MCC (Avicel PH-102)	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500
D- Mannitol	3700	3400	3100	2800	3700	3400	3100	2800	3700	3400	3100	2800	3700	3400	3100	2800
Methyl cellulose	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150
Total	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000

Figure 4: Tablets prepared by Direct Compression Method

Figure 5: Tablets prepared by Sublimation Method

4.6 EVALUATION OF TABLETS:

I) Post-compression parameters:

1. Hardness.
2. Friability.
3. Weight variation.
4. Uniformity of thickness.
5. Drug content uniformity.
6. Wetting time.
7. Water absorption ratio.
8. *In vitro* disintegration time.
9. *In vitro* dissolution studies.

POST-COMPRESSION PARAMETERS:

4.6.1 Hardness Test[73]:

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

4.6.2 Friability Test[72,73]:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition.

The friability of tablets was determined by using Veego Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to100revolutions. The tablets were weighed again(W_{final}).The percentage friability was then calculated by

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} X\ 100 \text{ ----------(d)}$$

% friability of tablets less than 1% is considered acceptable.

4.6.3 Weight Variation Test[73]:

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Percentage deviation in weight variation

Average weight of a tablet	Percentage deviation
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
324 mg or more	5

In all the formulations the tablet weight was more than130mg and less than 324 mg, hence 7.5% maximum difference allowed.

4.6.4 Uniformity Of Thickness[73]:

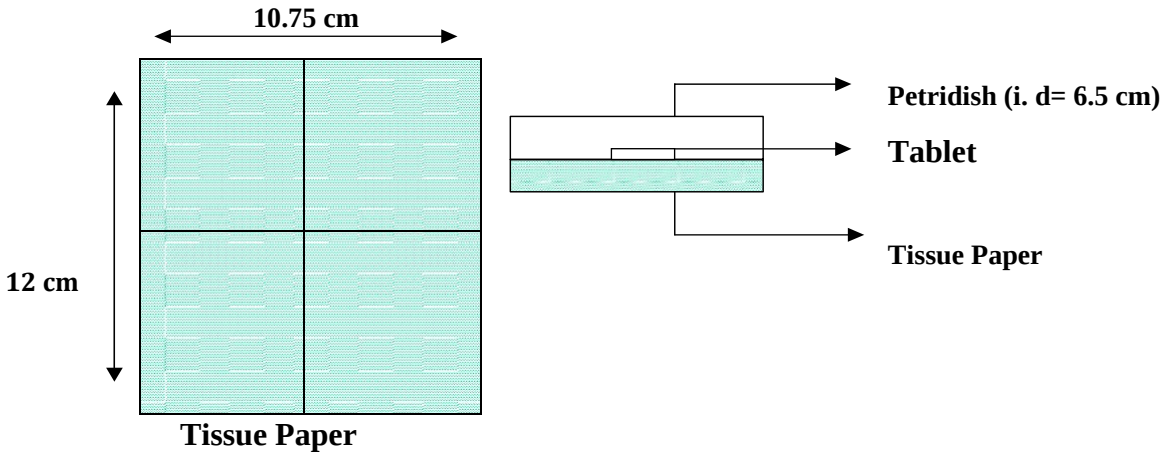
The crown thickness of individual tablet may be measured with a micrometer, which permits accurate measurements and provides information on the variation between tablets. Other technique employed in production control involves placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding caliper scale. The tablet thickness was measured using screw gauge.

4.6.5 Drug Content Uniformity[74]:

Four tablets weighed and crushed in a mortar then weighed powder contain equivalent to 100mg of drug transferred in 100ml distill water. Its concentration 1000 mcg/ml. 10ml from this stock solution taken and diluted to 100ml distilled water, it makes 100µg/ml. Then 20µg/ml solution prepared by taking 2ml from stock solution and diluted to 10ml. Absorbance measure at223nm.

4.6.6 Wetting Time[75]:

The method was applied to measure tablet wetting time. A piece of tissue paper folded twice was placed in a small petri dish (i.d. = 6.5 cm) containing 10 ml of water, a tablet was placed on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined. The method was reported by Yunxia Bi et al.



Simple method for the measurement of wetting time of a tablet.

4.6.7 Water Absorption Ratio[75]:

A piece of tissue paper folded twice was placed in a small petri dish containing 6ml of water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation.

$$R = 100 (W_a - W_b)/W_b \text{ ----------(g)}$$

Where, W_b – weight of tablet before absorption

W_a – weight of tablet after absorption

Three tablets from each formulation were performed and standard deviation was also determined.

4.6.8 *In Vitro* Disintegration Time[73]:

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications.

I.P. Specifications: Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37°±2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37°±2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

4.6.9 In Vitro Dissolution Studies[76]:

Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rmp) using 900ml of phosphate buffer pH (6.8) as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5°C, aliquot of dissolution medium was withdrawn at every 1 min interval and filtered. The absorbance of filtered solution was measured by UV spectro photometric method at 223 nm and concentration of the drug was determined from standard calibration curve.

***In Vitro* Drug Release Studies Details :**

Apparatus used	:	USP XXIII dissolution test apparatus
Dissolution medium	:	6.8 pH phosphate buffer solution.
Dissolution medium volume	:	900 ml
Temperature	:	37±0.5°C
Speed of basket paddle	:	50 rpm
Sampling intervals	:	1min
Sample with draw	:	5 ml
Absorbance measured	:	223nm

CHAPTER-5

RESULTS AND DISCUSSION

5.1 Result of pre-compression parameter for tablet prepared by direct compression and sublimation methods

Pre-Compression Parameters:

Powder ready for compression containing drug and various excipients were subjected for pre-compression parameters to study the flow properties of granules, to achieve uniformity of tablet weight. The results of all the preformulations parameters are given Tables no 6 and 7.

5.1.1 Angle Of Repose(θ):

The data obtained from angle of repose for all the formulations were found to be in the range of $26^0.52`$ and $30^0.87`$. All the formulations prepared by both the methods showed the angle of repose less than 30^0, which reveals good flow property. As mentioned earlier in the literature[65,66].

5.1.2 Bulk Density:

Loose bulk density (LBD) and tapped bulk density (TBD) for the blend was performed. The loose bulk density and tapped bulk density for the entire formulation blend varied from 0.517 gm/cm^3 to 0.558 gm/cm^3 (direct compression method) and 0.498 gm/cm^3 to 0.557 gm/cm^3 (sublimation method) respectively.

5.1.3 Hausner's Ratio:

Hausner's ratio of entire formulation showed between 1.14 to 1.215 indicates better flow properties[58].

5.1.4 Carr's Consolidation Index:

The results of Carr's consolidation index or compressibility index (%) for the entire formulation blend ranged from 13.87% to 20.68%. The directly compressible granulations had shown excellent compressibility index values up to 15% result in good to excellent flow properties. As shown in previous research work[65].

Table 6: Pre-compression parameters of Direct Compression Method

Formulation code	Bulk Density (g/cc) ±SD, n=3	Tapped Density (g/cc) ±SD, n=3	Angle of Repose (degree) ±SD, n=3	Carr's Index (%) ±SD,n=3	Hausner's Ratio ±SD, n=3
DCI_1	0.52 ± 0.007	0.63 ± 0.01	29.25 ± 1.56	17 ± 1	1.21 ± 0.03
DCI_2	0.53 ± 0.007	0.63 ± 0.01	30.02 ± 1.20	15 ± 1.51	1.18 ± 0.04
DCI_3	0.53 ± 0.007	0.64 ± 0.02	30.1 ± 1.70	17 ± 1.20	1.20 ± 0.03
DCI_4	0.55 ± 0.007	0.65 ± 0.01	30.20 ± 0.88	15 ± 2.51	1.18 ± 0.03
DCC_1	0.50 ± 0.007	0.63 ± 0.01	28.43 ± 1.48	20 ± 1.58	1.26 ± 0.03
DCC_2	0.52 ± 0.007	0.63 ± 0.02	30.72 ± 1.22	17 ± 1.55	1.21 ± 0.04
DCC_3	0.51 ± 0.007	0.62 ± 0.38	329.87 ± 1.32	17 ± 1.39	1.21 ± 0.04
DCC_4	0.54 ± 0.007	0.65 ± 0.02	28.04 ± 1.34	16 ± 2.20	1.20 ± 0.03
DCP_1	0.52 ± 0.007	0.62 ± 0.01	26.28 ± 1.26	16 ± 2.01	1.19 ± 0.03
DCP_2	0.52 ± 0.007	0.63 ± 0.01	27.52 ± 1.20	17 ± 2.12	1.21 ± 0.04
DCP_3	0.54 ± 0.007	0.64 ± 0.02	29.19 ± 1.26	15 ± 1.51	1.18 ± 0.03
DCP_4	0.55 ± 0.007	0.65 ± 0.01	28.26 ± 1.20	15 ± 1.39	1.14 ± 0.03
DCS_1	0.52 ± 0.007	0.62 ± 0.02	29.03 ± 1.56	16 ± 1.20	1.19 ± 0.04
DCS_2	0.53 ± 0.007	0.63 ± 0.01	28.72 ± 1.41	15 ± 1.67	1.18 ± 0.02
DCS_3	0.51 ± 0.007	0.62 ± 0.02	28.85 ± 1.33	17 ± 1.41	1.21 ± 0.03
DCS_4	0.52 ± 0.007	0.63 ± 0.02	30.14 ± 1.67	17 ± 2.51	1.21 ± 0.03

* Average of three determinations

Table 7: Pre-compression parameters of powder blend of Sublimation Method

Formulation code	Bulk Density (g/cc) ±SD, n=3	Tapped Density (g/cc) ±SD, n=3	Angle of Repose (degree) ±SD,n=3	Carr's Index(%) ±SD,n=3	Hausner's Ratio ±SD, n=3
SBI_1	0.49 ± 0.007	0.65 ± 0.01	29.25 ± 1.56	17 ± 1	1.30 ± 0.03
SBI_2	0.52 ± 0.007	0.62 ± 0.01	28.02 ± 1.20	16 ± 1.51	1.19± 0.04
SBI_3	0.53 ± 0.007	0.61 ± 0.02	29.11 ± 1.70	13 ± 1.20	1.15 ± 0.03
SBI_4	0.53 ± 0.007	0.64 ± 0.01	30.20 ± 0.88	17 ± 2.51	1.20 ± 0.03
SBC_1	0.50 ± 0.007	0.63 ± 0.01	26.43 ± 1.48	20 ± 1.58	1.26 ± 0.03
SBC_2	0.54 ± 0.007	0.65 ± 0.02	27.72 ± 1.22	16 ± 1.55	1.20 ± 0.04
SBC_3	0.52 ± 0.007	0.63 ± 0.38	29.87 ±1.32	17 ± 1.39	1.21 ± 0.04
SBC_4	0.51 ± 0.007	0.62 ± 0.02	29.04 ± 1.34	17 ± 2.20	1.21 ± 0.03
SBP_1	0.53 ± 0.007	0.63 ± 0.01	30.28 ± 1.26	15 ± 2.01	1.18 ± 0.03
SBP_2	0.52 ± 0.007	0.65 ± 0.01	27.52 ± 1.20	18 ± 2.12	1.25 ± 0.04
SBP_3	0.51 ± 0.007	0.62 ± 0.02	30.19 ± 1.26	17 ± 1.51	1.21 ± 0.03
SBP_4	0.55 ± 0.007	0.65 ± 0.01	29.26 ± 1.20	15 ± 1.39	1.14 ± 0.03
SBS_1	0.52 ± 0.007	0.62 ± 0.02	30.03 ± 1.56	16 ± 1.20	1.19 ± 0.04
SBS_2	0.53 ± 0.007	0.63 ± 0.01	29.72 ± 1.41	15 ± 1.67	1.18 ± 0.02
SBS_3	0.51 ± 0.007	0.62 ± 0.02	28.85 ± 1.33	17 ± 1.41	1.21 ± 0.03
SBS_4	0.53 ± 0.007	0.64 ± 0.02	28.14 ± 1.67	17 ± 2.51	1.20 ± 0.03

* Average of three determinations

5.2 RESULTS FOR DRUG POLYMER INTERACTION STUDIES

5.2.1 FTIR Studies:

The pure drug Metoprolol Tartrate (Racemic mixture) exhibited characteristic "OH" absorption at 3454^{-1} cm. which is the normal range of absorption for aliphatic hydroxyl group. Secondary ammine (NH) has given a weak absorption in the form of a hump. Merged with aromatic C-H at 3030^{-1} cm. and aliphatic C-H of CH_3 and OCH3 at 2980^{-1} cm. The C-O absorption is found at 1589^{-1}cm. merged with C=C of aromatic. These data are in support of the structure of the drug taken for study.

The IR spectra of DCI_1 and DCI_3 revealed the factor that the hydrogen binding has taken place between the drug OH group and C=O of Indian 414 which has resulted into shifting of peak for OH from 3454^{-1}cm to 3400^{-1}cm. the NH absorption has given an absorption peak at 3290^{-1}cm. However, 'C=O' of Indion 414 which is part of the tricyclic ring system has shown a strong absorption at1735^{-1}cm.

The IR spectra of DCC_8 revealed presence of all the absorption peaks of drug along with a strong C=O of carboxylic cluster peak at 1734^{-1}cm. It is clear from these observations that tablet that we obtain is a physical mixture containing 'H' bonding between drug and the 'CCS'.

The IR spectra of SBI_1 revealed that changes were not at all noticed suggesting that formulation process has not led to any chemical reaction by changing their proportions.

The IR peak of SBC_8 these formulated product is very similar to one obtain during the previous experiment. In this case also broad peaks were obtained around3400 $^{-1}$cm and 2950 $^{-1}$cm and number of peaks around 1700 $^{-1}$cm.

The SBP_9 showing additional peaks in FTIR corresponding to various constituents a strong and broad peak as appear at 3402^{-1}cm.due to the numberof hydroxyl group present in the components of the formulation., so also very broad peak has been noised at 2909^{-1} cm. because of C-H systems are present. The strong C=O is noticed near 1700 $^{-1}$cm and 1650^{-1}cm due to the C-O of the ketones and cyclic ketones.

Suggesting that it is the IR of mixtures but not of any reaction product and there was no interference in the functional groups as the principle peaks of the Metoprolol Tartrate were found to be unaltered in the spectra of the drug-polymer physicalmixture.

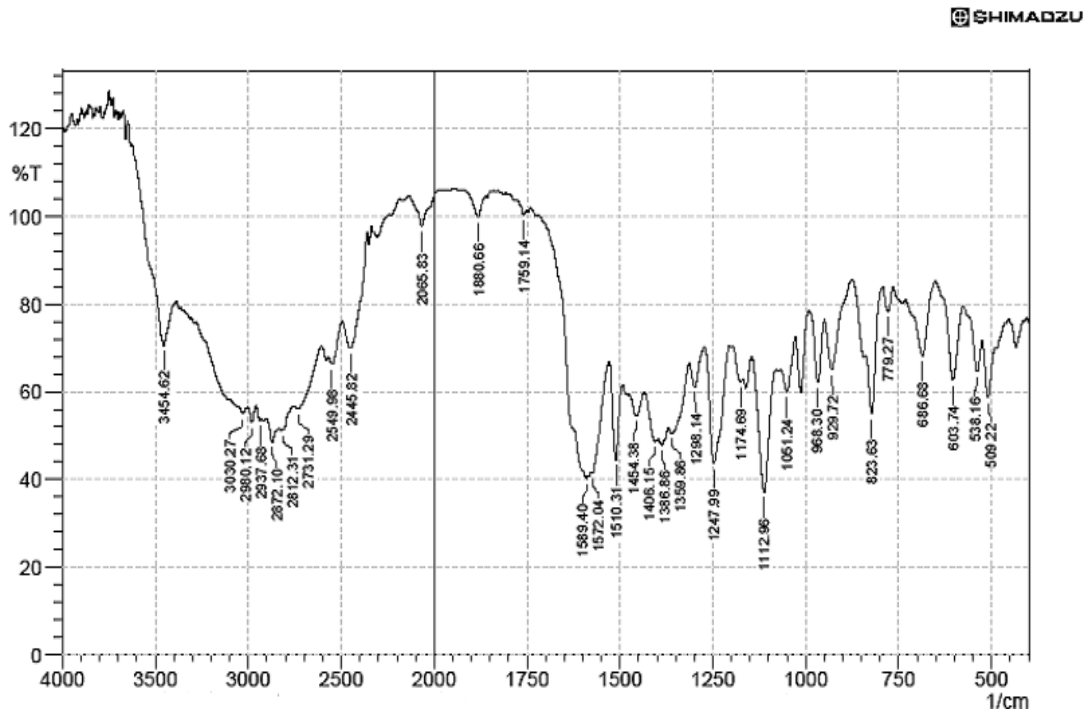


Figure 6: IR Spectra Metoprolol Tartrate

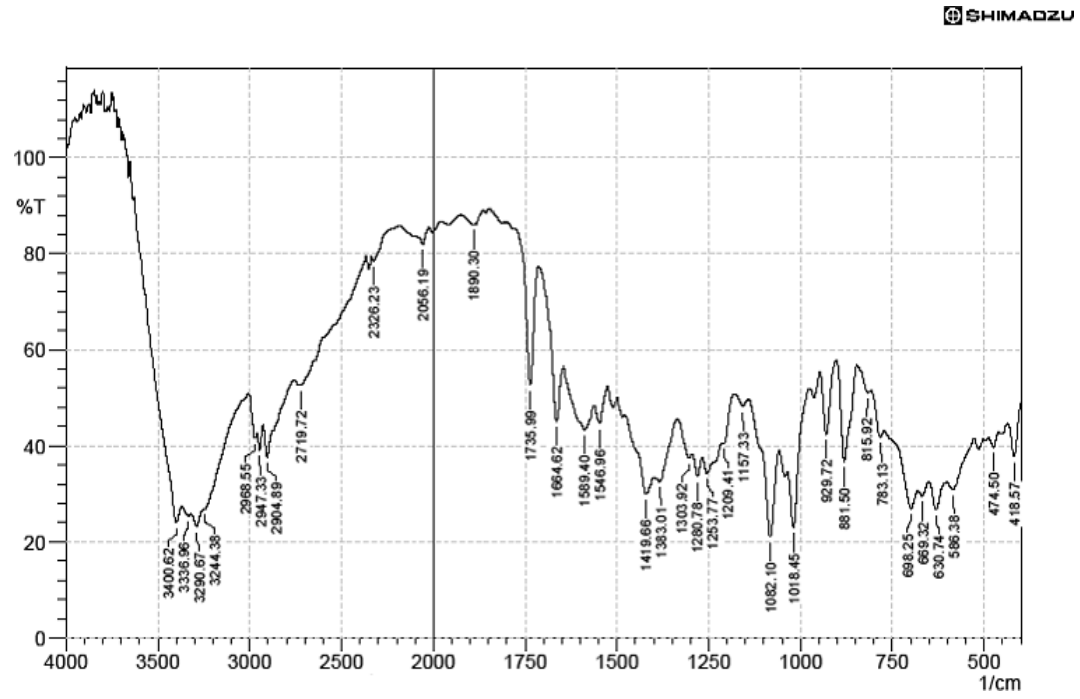


Figure 7: IR Spectra of formulation (DCI_1)

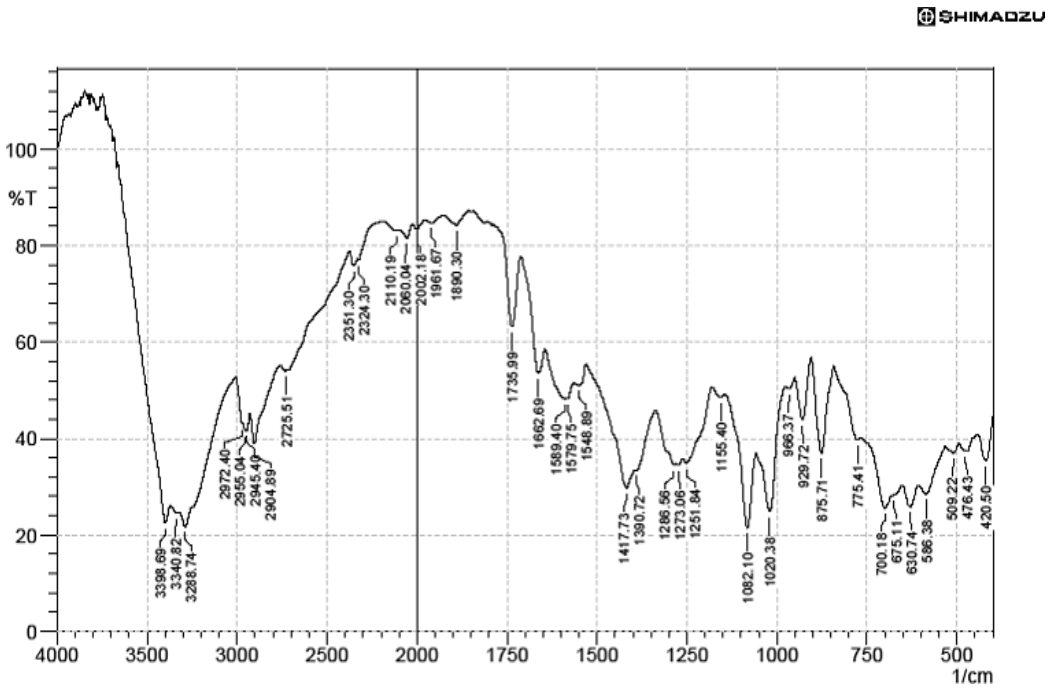


Figure 8: IR Spectra of formulation (DCI_3)

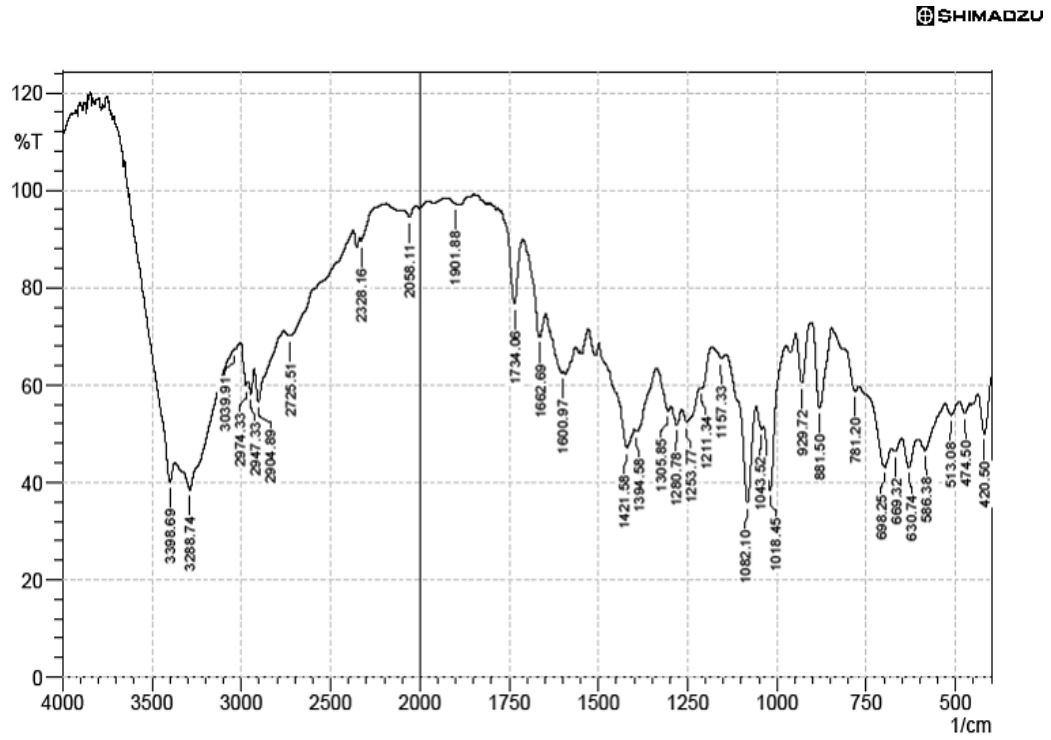


Figure 9: IR Spectra of formulation (DCC_4)

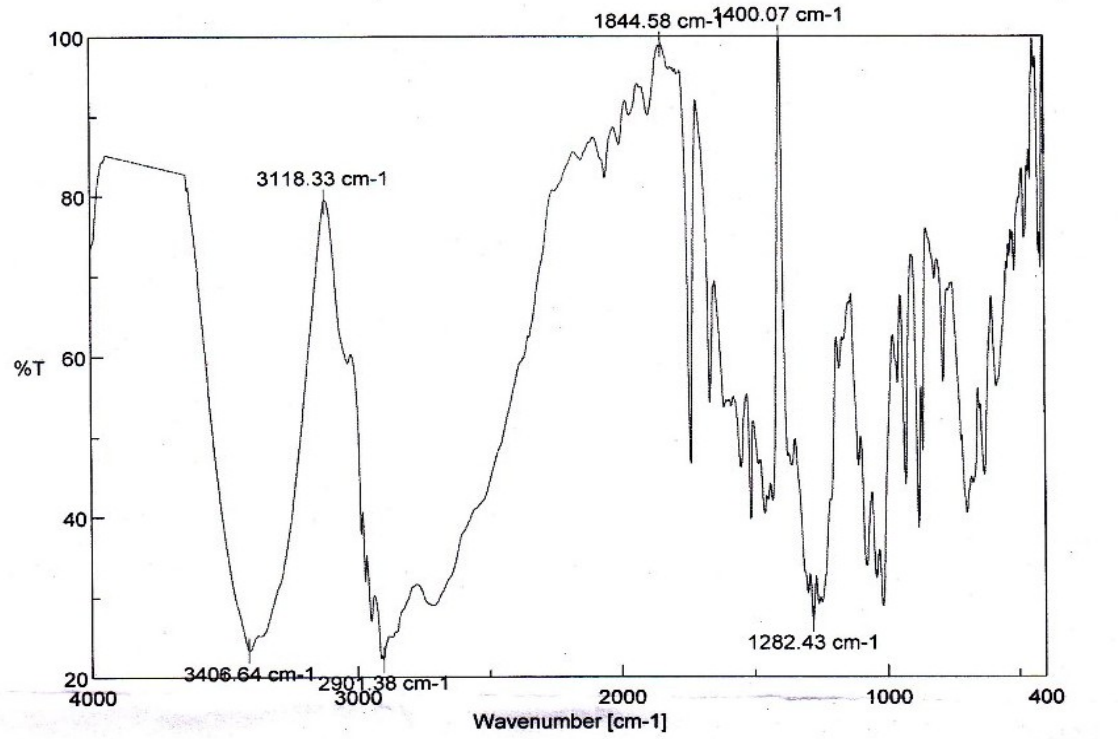


Figure 10: IR Spectra of formulation (SBI_1)

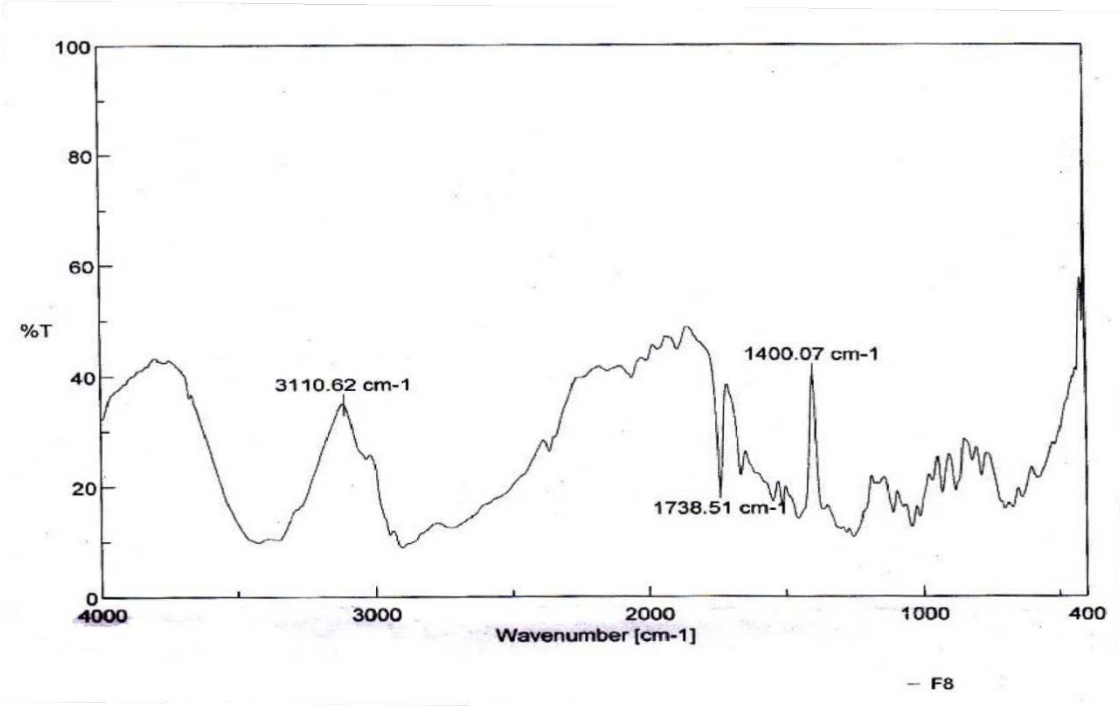


Figure 11: IR Spectra of formulation (SBC_4)

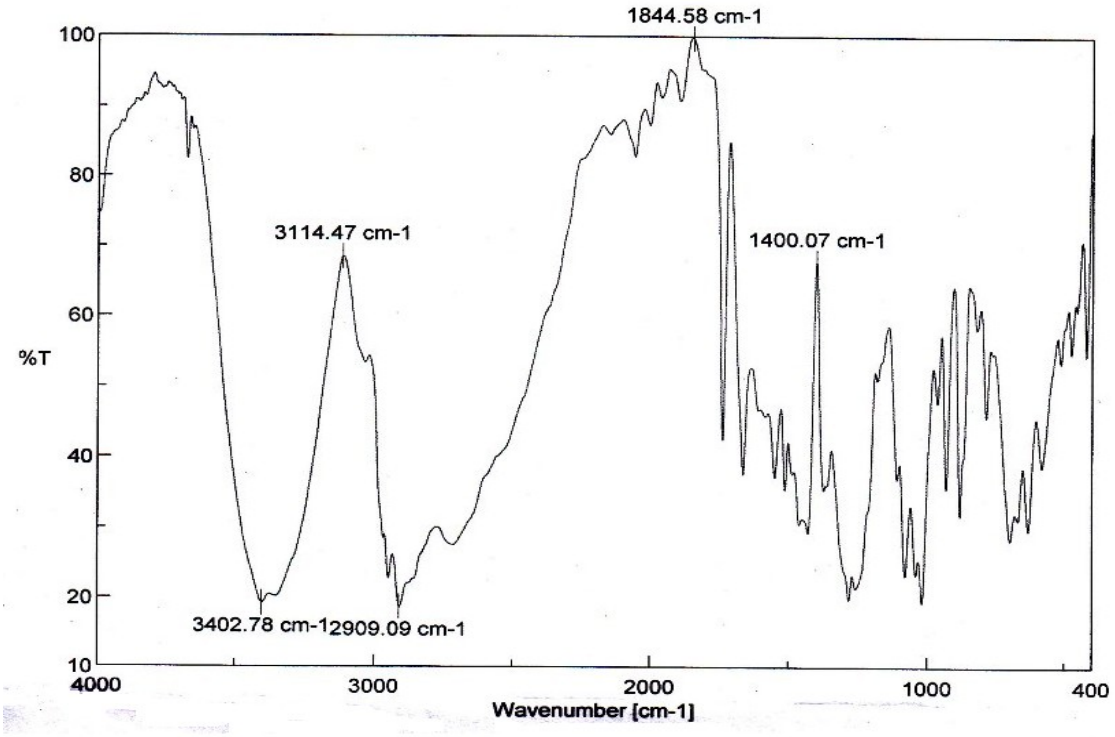


Figure 12: IR Spectra of formulation (SBP_1)

5.2.2 DSC Studies

The DSC shows that when the drug Metoprolol Tartrate is taken to study its properties at higher temperature it has exhibited melting peak at 123^0C with very little variation with the literature reported temperature. This is probably due to the error in experimental determination.

The DSC of DCI_1 and DCI_3 shows slow melting is observed since it is a mixture of two organic molecules.

The formulation DCC_4 it has started melting slowly at 162^0C to 167^0C since tablet contains mixture of the drug and CCS in almost equiproportion which has resulted in a physical mixture.

The DSC of SBI_1 shows physical mixture started melting at 163 °C taking longer time to complete the process of melting at 165 °C but the process of softening starts at 160 °C suggesting that it takes almost 5 °C to melt completely.

The formulation SBC_4 it has not given sharp melting range but very broad range of melting process due to the croscarmellose sodium.

The DSC studies of SBP_1 suggested that it has not given sharp melting range but very broad range of melting process.

DSC studies of all above formulations suggesting that in all these formulations no chemical constituents has not undergone to give any reaction product

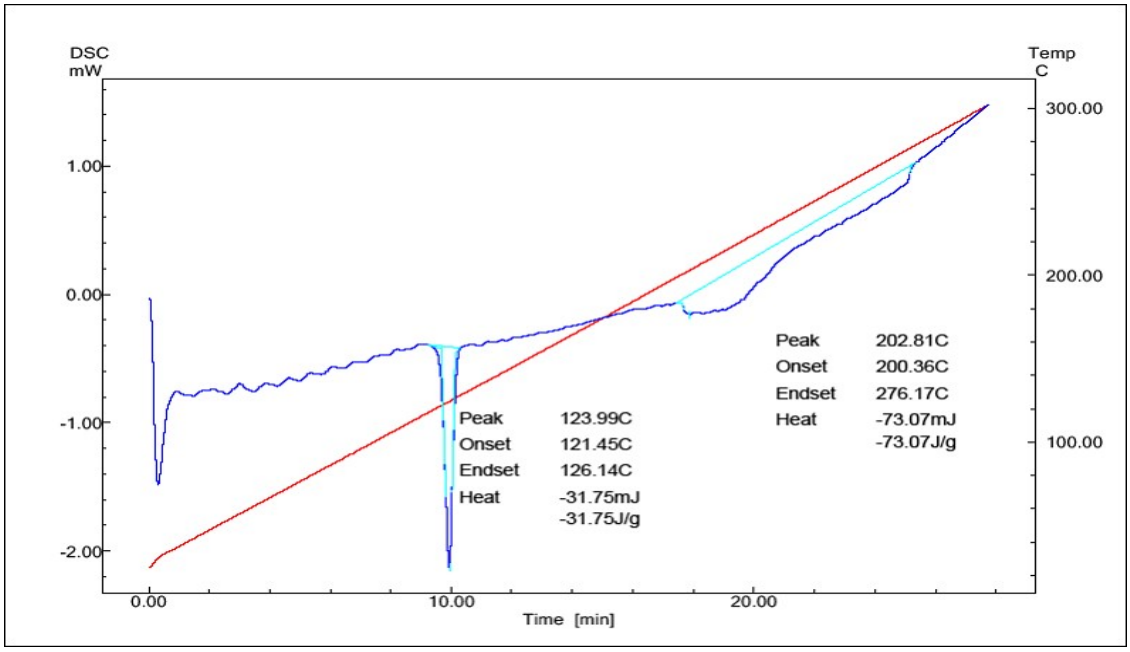


Figure 13: DSC Of Metoprolol Tartrate

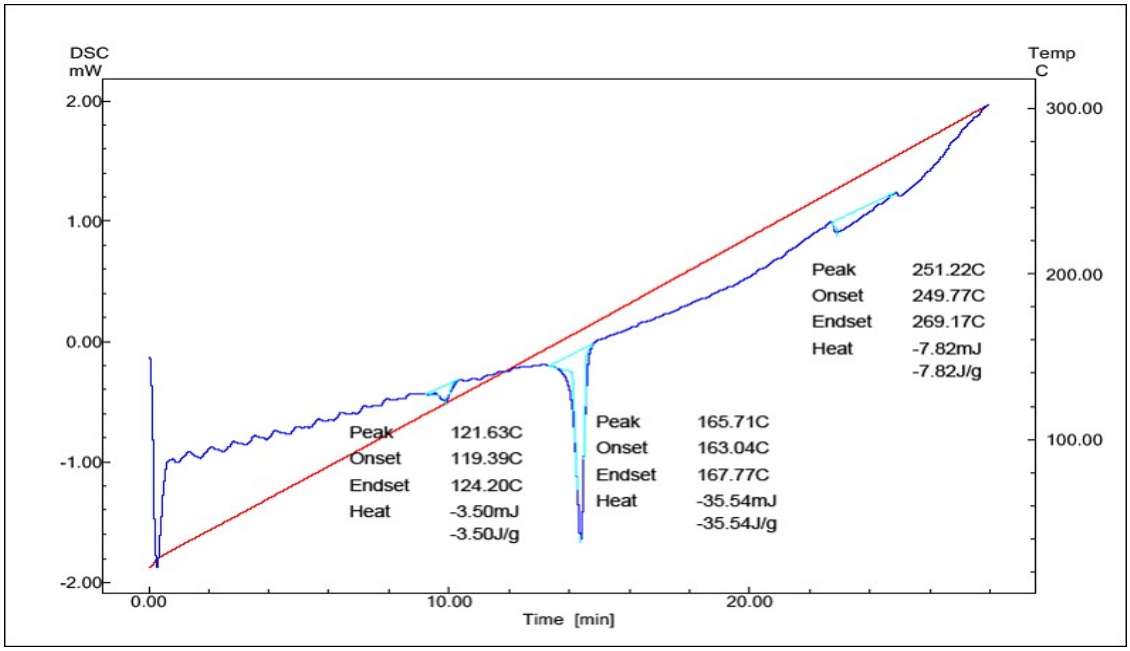


Figure 14: DSC of formulation (DCI_1)

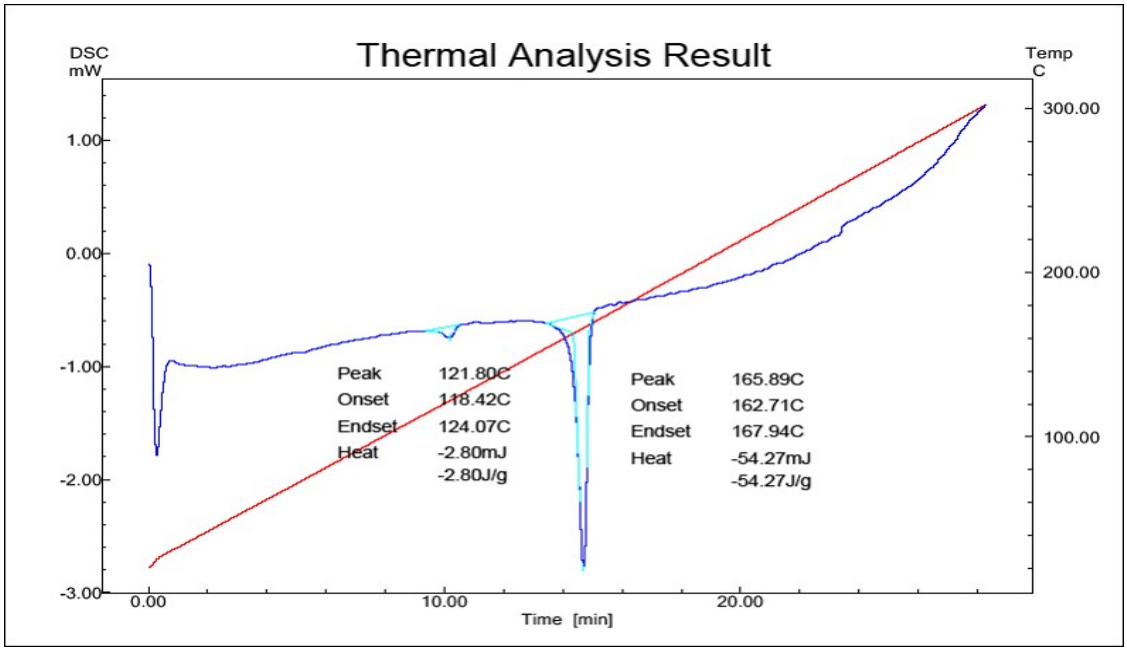


Figure 15: DSC of formulation (DCI_3)

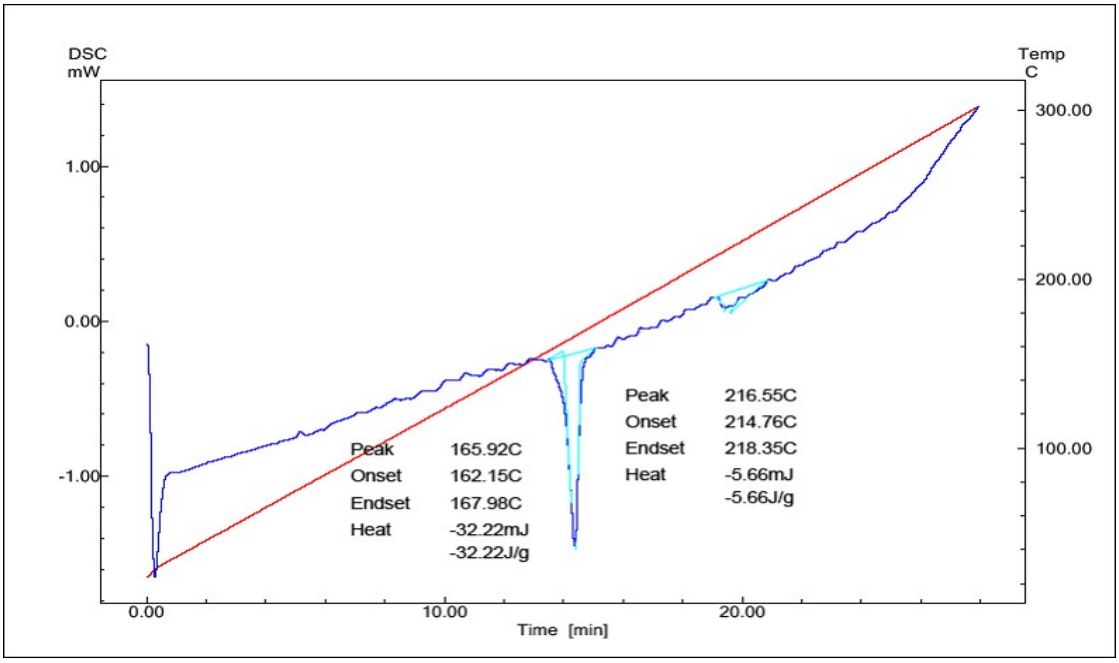


Figure 16: DSC of formulation (DCC_4)

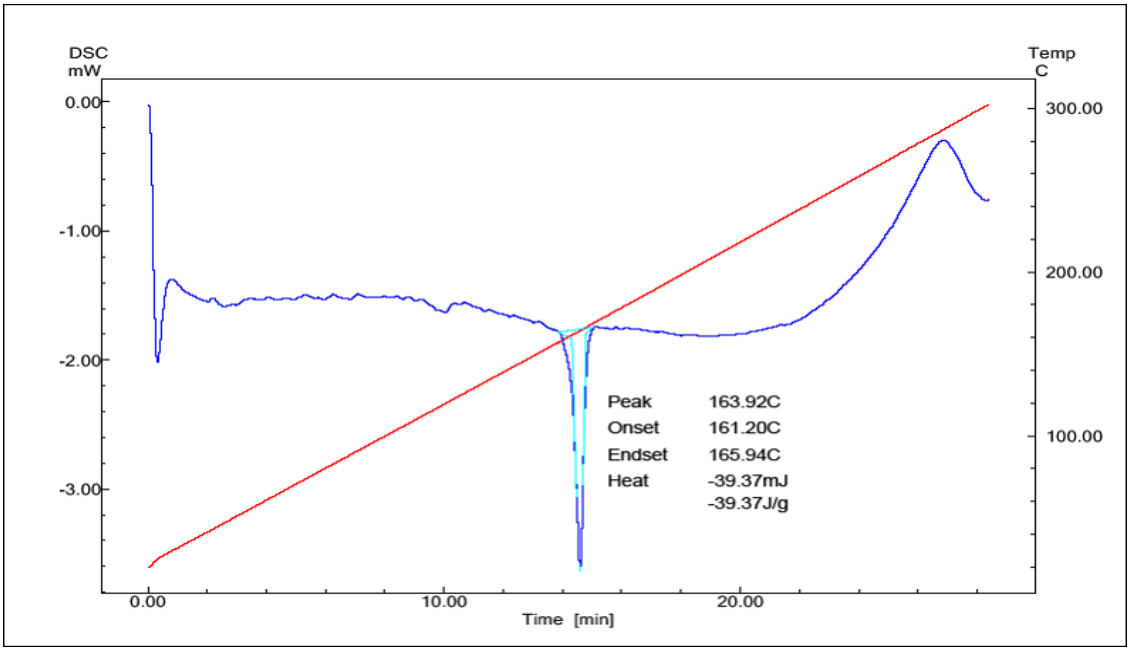


Figure 17: DSC of formulation (SBI_1)

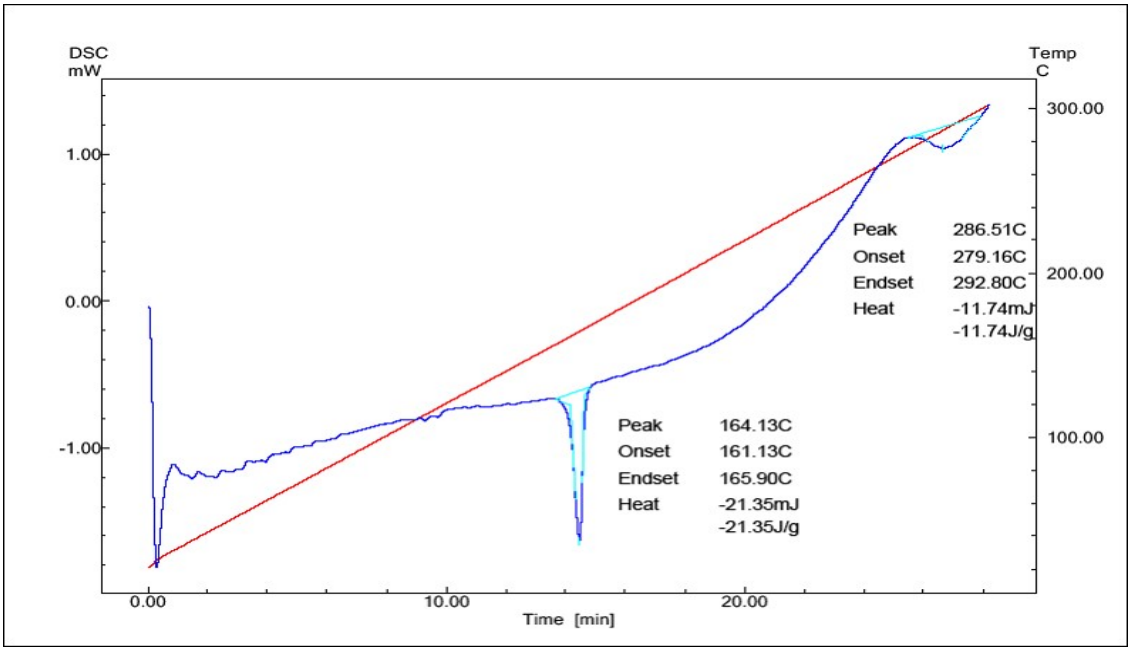


Figure 18: DSC of formulation (SBC_4)

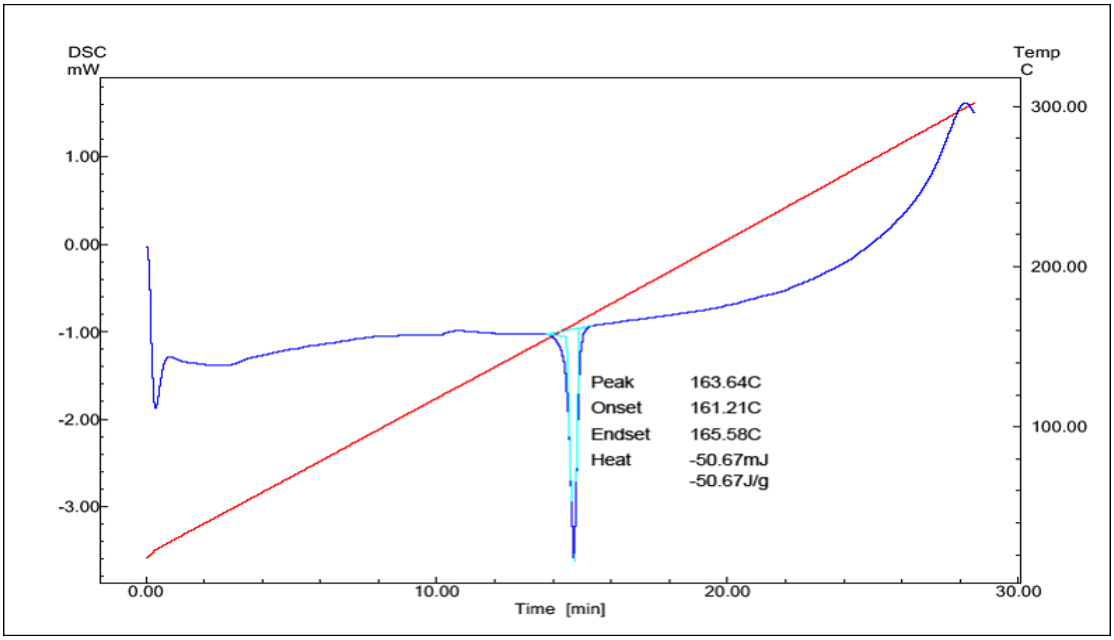


Figure 19: DSC OF formulation (SBP_1)

5.3 RESULTS OF POST-COMPRESSIONAL TABLETS PREPAREDBY DIRECT COMPRESSION AND SUBLIMATION METHODS

Post-Compression Parameters:

5.3.1 Hardness:

The hardness of all the tablets prepared by both methods was maintained within the 2.00 ± 0.10 kg/cm^2 to 2.8 ± 0.18 kg/cm^2. The mean hardness test results are tabulated in table no. 8 and 9.

5.3.2 Friability Test:

The friability was found in all designed formulations in the range 0.52 to 0.82% to be well within the approved range (<1%). The friability study results were tabulated in table no 8 and9.

5.3.3 Weight Variation Test:

The weight variation was found in all designed formulations in the range 196 ± 1.69 to 205 ± 1.62 mg. The mean weight variation test results are tabulated in table no. 8 and 9.

All the tablets passed weight variation test as the average percentage weight variation was within 7.5% i.e. in the pharmacopoeial limits.

5.3.4 Thickness:

The mean thickness was (n=3) almost uniform in all the formulations and values ranged from 4.60 ± 0.064 mm to 4.87 ± 0.015 mm. The standard deviation values indicated that all the formulations were within the range. The results of thickness for tablets were shown in table no. 8 and9.

5.3.5 *In Vitro* Disintegration Time:

The *in vitro* disintegration time is measured by the time taken to undergo uniform dispersion. Rapid disintegrationwithin several minutes was observed in all the formulations. The *in-vitro* disintegration data is tabulated in the table no. 10 and 11. The *in vitro* disintegration time of Metoprolol Tartrate prepared by direct compression and sublimation method were found to be in the range of 18 to 59 sec fulfilling the official requirements.

Based on the *in vitro* disintegration time, formulation DCI_3 (9% Indion 414) and SBI_1 (3% Indion 414) were found to be promising and showed a disintegration time of 21 and 18 sec respectively. Disintegrating study showed that the disintegrating times (Table 10 and 11) of the tablets decreased with increase in the concentration of croscarmellose sodium, Crospovidone and indion-414[78].However, disintegration times increased with increase in the concentration Sodium Starch Glycolate in the tablets. It indicates that increase in the concentration Sodium Starch Glycolate had a negative effect on the disintegration of the tablets. The results are in consistent with other results [79,80]. The results of comparison of Indion 414, CCS, SSG, CP superdisintegrants in the mouth dissolving tablets showed that the Indion 414 shows least disintegration time for the Roxithromycin, Dicyclomine and Montelukast sodium[26]. In case of Aceclofenac mouth dissolving tablets *in vitro* disintegration time of tablet deceased from (41-34 sec) with increase in concentration of CCS. *In vitro* disintegration time increased with increase in concentration of Sodium Starch Glycolate in tablets, at higher level formation of viscous gel layer by SSG might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration or leakage of tablet contents. In case of tablet containing CP increasing the level of CP had no much

greater effect on *in vitro* disintegration times of the tablets[47]. In case of mouth dissolving tablets of carbamazepine, the CCS shows least *in vitro* disintegration time with increasing the concentration of CCS in comparison with indion 414, CP, SSG[62]. The disintegration times of Crospovidone and indion-414 containing tablets are comparatively lower than tablets containing crosscarmellose sodium and Sodium Starch Glycolate due to its rapid capillary activity and pronounced hydration with little tendency to gel formation [42] with crospovidone. Thus, these results suggest that the disintegration times can be decreased by using wicking type disintegrants (crospovidone). As the method of preparation of tablets changed to sublimation, the disintegration time decreased significantly regardless of the diluent used. It is because tablets prepared by sublimation method rapidly exhibits high pores and disintegrate the tablet rapidly. Above results shows that tablets prepared with 5 % superdisintegrant and 20 % camphor (sublimation method) showed least disintegration time (Table 11) in comparison with the all other formulations because of their lowest hardness and the porous structure is responsible for faster water uptake, hence it facilitates wicking action of croscarmellose sodium in bringing about faster disintegration [81].

5.3.6 Wetting Time:

Wetting time is closely related to the inner structure of the tablet. The results of wetting time are shown in table no. 10 and 11. The wetting time of Metoprolol Tartrate prepared by direct compression and sublimation method were found to be in the range of 37 to 50 sec. Promising formulations DCI_3 (9% Indion 414) and SBI_1 (3% Indion 414) showed a wetting time of 48 and 37 sec respectively, which facilitate the faster dispersion in the mouth.

5.3.7 Water Absorption Ratio:

The formulations prepared by both the technique shows wetting time in the range 48 to 85 % formulations containing only 3% of superdisintegrant shows lower water absorption ratio when compared to formulations 12% of superdisintegrant, the water absorption ratio also decreases due to less swelling property. It was observed that as concentrations of CCS increases water absorption ratio increases due to CCS is made by cross- linking reaction of sodium CMC. This cross linking greatly reduced water solubility of sodium CMC while permitting material to swell and absorbs water many times of its weight [32]. The values of water absorption ratio shown in table no. 10 and 11.

5.3.8 Drug Content:

The drug content uniformity was performed for all the 32 formulations and results are tabulated in table No. 10 and 11. Three trials from each batch were analyzed spectrophotometrically. The average value and standard deviations of all the formulations were calculated. The percentage drugs content of the tablets was found to be between 99.08±0.15 to 100.76 ± 0.27% of Metoprolol Tartrate. The results were within the range and that indicated uniformity of mixing.

Table 8: post-compressional parameters for Direct Compression Method

Formulation Code	Hardness * (Kg/cm^2) ±SD	Friability (%)	Thickness* (mm) ±SD	Weight variation* (mg) ±SD
DCI_1	2.5 ± 0.11	0.56	4.60 ±0.12	202 ± 1.78
DCI_2	2.3 ± 0.11	0.66	4.75 ±0.15	203 ± 1.32
DCI_3	2.2 ± 0.10	0.62	4.71 ±0.10	198 ± 0.56
DCI_4	2.1 ± 0.12	0.58	4.80 ± 0.10	204 ± 1.97
DCC_1	2.8 ± 0.18	0.57	4.85 ± 0.17	201 ± 0.65
DCC_2	2.1 ± 0.10	0.67	4.87 ± 0.15	200 ± 1.93
DCC_3	2.1 ± 0.15	0.75	4.72 ± 0.12	196 ± 1.21
DCC_4	2.3 ± 0.21	0.78	4.65 ± 0.09	199 ± 1.50
DCP_1	2.2 ± 0.10	0.59	4.61 ± 0.19	200 ± 0.18
DCP_2	2.3 ± 0.21	0.65	4.58 ± 0.21	203 ± 1.62
DCP_3	2.2 ± 0.15	0.60	4.64 ± 0.15	200 ± 1.85
DCP_4	2 ± 0.10	0.52	4.71 ± 0.25	197 ± 0.96
DCS_1	2.1 ± 0.05	0.61	4.69 ± 0.14	196 ± 1.69
DCS_2	2.2 ± 0.20	0.73	4.73 ± 0.28	200 ± 1.73
DCS_3	2.4 ± 0.15	0.82	4.59 ± 0.20	205 ± 1.62
DCS_4	2.5 ± 0.42	0.77	4.65 ± 0.08	198 ± 1.45

* Average of three determinations

Table 9: post-compressional parameters of Sublimation Method

Formulation Code	Hardness * (Kg/cm^2) ±SD	Friability (%)	Thickness* (mm) ±SD	Weight variation* (mg) ±SD
SBI_1	2 ± 0.11	0.58	4.69 ±0.12	200 ± 0.78
SBI_2	2.1 ± 0.11	0.54	4.82 ±0.15	201 ± 1.02
SBI_3	2.3 ± 0.10	0.75	4.74 ±0.10	199 ± 1.56
SBI_4	2.2 ± 0.12	0.57	4.85 ± 0.10	203 ± 0.97
SBC_1	2.8 ± 0.18	0.51	4.59 ± 0.17	205 ± 1.75
SBC_2	2.1 ± 0.10	0.68	4.69 ± 0.15	200 ± 0.63
SBC_3	2.1 ± 0.15	0.65	4.72 ± 0.12	196 ± 1.42
SBC_4	2.1 ± 0.21	0.58	4.58 ± 0.09	198 ± 0.50
SBP_1	2.1 ± 0.10	0.59	4.67 ± 0.19	204 ± 1.38
SBP_2	2.4 ± 0.21	0.75	4.72 ± 0.21	205 ± 0.82
SBP_3	2.5 ± 0.15	0.69	4.78 ± 0.15	201 ± 0.25
SBP_4	2 ± 0.10	0.58	4.71 ± 0.25	199 ± 1.92
SBS_1	2.3 ± 0.05	0.60	4.60 ± 0.14	197 ± 0.69
SBS_2	2.2 ± 0.20	0.77	4.73 ± 0.28	204 ± 1.43
SBS_3	2.4 ± 0.15	0.73	4.79 ± 0.20	201 ± 0.59
SBS_4	2.6 ± 0.42	0.81	4.63 ± 0.08	198 ± 0.65

* Average of three determinations

Table 10: post-compressional parameters for Direct Compression Method

Formulation Code	In vitro disintegration Time* (sec) ±SD	Wetting Time* (sec) ±SD	Water Absorption Ratio* ±S. D	Drug Content* (%) ±SD
DCI_1	27 ± 2.78	47 ± 2.51	80 ± 1.54	99.18 ± 0.72
DCI_2	25 ± 1.0	49 ± 2.0	83 ± 1.86	99.81 ± 1.07
DCI_3	21 ± 1.0	48 ± 2.40	85 ± 1.35	99.54 ± 0.50
DCI_4	30 ± 2.0	40 ± 1.89	78 ± 1.58	98.12 ± 0.73
DCC_1	41 ± 1.5	50 ± 2.20	67 ± 1.21	99.30 ± 0.87
DCC_2	40 ± 1.7	48 ± 1.0	70 ± 1.57	99.23 ± 0.90
DCC_3	39 ± 2.8	43 ± 2.25	72 ± 1.20	100.03 ± 1.07
DCC_4	34 ± 1.45	44 ± 2.15	76 ± 1.05	99.63 ± 0.39
DCP_1	49 ± 1.28	46 ± 1.0	61 ± 1.73	99.50 ± 0.77
DCP_2	52 ± 1.11	42 ± 2.25	58 ± 1.85	99.96 ± 0.27
DCP_3	50 ± 2.15	40 ± 1.75	63 ± 1.88	99.56±0.76
DCP_4	53 ± 1.55	41 ± 1.35	57 ± 1.15	100.09±0.76
DCS_1	45 ± 2.10	42 ± 1.21	60 ± 1.18	100.65±1.23
DCS_2	52 ± 1.21	47 ± 1.79	55 ± 1.08	99.08±2.65
DCS_3	59 ± 1.08	49 ± 1.71	52 ± 1.05	100.76±0.33
DCS_4	52 ± 2.0	42 ± 2.41	48 ± 1.81	99.99±1.79

* Average of three determinations

Table 11: Post-compressional parameters of Sublimation Method

Formulation Code	In vitro disintegration Time* (sec) ±SD	Wetting Time* (sec) ±SD	Water Absorption ratio* ±SD	Drug Content* (%) ±SD
SBI_1	18 ± 2.78	37 ± 2.51	85 ± 1.75	99.58 ± 0.85
SBI_2	21 ± 1.0	39 ± 2.0	82 ± 1.52	99.41 ± 1.57
SBI_3	22 ± 1.0	48 ± 2.40	81 ± 1.35	99.34 ± 1.07
SBI_4	26 ± 2.0	40 ± 1.89	78 ± 1.58	98.65 ± 0.74
SBC_1	33 ± 1.5	50 ± 2.20	67 ± 1.21	99.41 ± 1.87
SBC_2	30 ± 1.7	48 ± 1.0	70 ± 1.57	99.31 ± 1.08
SBC_3	27 ± 2.8	43 ± 2.25	72 ± 1.20	99.43 ±1.46
SBC_4	25 ± 1.45	41 ± 2.15	80 ± 1.05	99.13 ± 0.49
SBP_1	19 ± 1.28	40 ± 1.0	81 ± 1.73	99.47 ± 1.47
SBP_2	22 ± 1.11	42 ± 2.25	58 ± 1.85	99.11 ± 0.43
SBP_3	30 ± 2.15	40 ± 1.75	63 ± 1.88	98.56 ± 1.32
SBP_4	38 ± 1.55	41 ± 1.35	54 ± 1.15	99.09 ±0.10
SBS_1	43 ± 2.10	42 ± 1.21	66 ± 1.18	100.65 ±1.43
SBS_2	37 ± 1.21	47 ± 1.79	55 ± 1.08	99.38 ±1.75
SBS_3	48 ± 1.08	49 ± 1.71	51 ± 1.05	100.56 ±0.43
SBS_4	44 ± 2.0	41 ± 2.41	46 ± 1.51	99.59 ±1.61

* Average of three determinations

Figure 20: *In Vitro* Disintegration Of Tablets

0second **10seconds**

15seconds **20seconds**

5.4 DISSOLUTION STUDY

5.4.1 *In Vitro* Dissolution Studies:

Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rmp) using 900ml of phosphate buffer pH (6.8) as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5°C, aliquot of dissolution medium was withdrawn at every 1-minute interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 223nm and concentration of the drug was determined from standard calibrationcurve.

The dissolution of Metoprolol Tartrate from the tablets is shown in figure 19- 26. (Table 12 – 13) shows the $t_{50\%}$ and $t_{90\%}$ of the release profiles. These values changed with change of method of preparation of tablets.

In case of tablets prepared by direct compression technique the $t_{50\%}$ and $t_{90\%}$ values decreased with increase in the concentration of crosscarmellose sodium, Crospovidone and Indion-414. However, $t_{50\%}$ and $t_{90\%}$ values increased with increase in concentration of sodium starch glycolate. The rapid increase in dissolution of Metoprolol Tartrate with the increase in crosscarmellose sodium may be due to rapid swelling and disintegrating tablets rapidly into apparently primary particles [82,83]. While tablets formulated with sodium starch glycolate, disintegrate by rapid uptake of water, followed by rapid and enormous swelling [83] into primary particle but more slowly [84] due to the formation of a viscous gel layer by Sodium Starch Glycolate [85]. Crospovidone and Indion- 414 containing tablets rapidly exhibits high capillary activity and

pronounced hydration with a little tendency to gel formation [83] and disintegrates the tablets rapidly but into larger masses of aggregated particles[82]. Thus, difference in the size distribution generated with different superdisintegrants might have contributed to difference in the $t_{50\%}$ and $t_{90\%}$ values with the same amount of superdisintegrants in the tablets.

Although, disintegration times are lesser in Crospovidone and Indion-414 containing tablets, comparatively higher $t_{50\%}$ and $t_{90\%}$ values are observed in Crospovidone containing tablets.

As the method of preparation of tablets changed to sublimation, the dissolution of the drug from the tablets prepared by camphor sublimation method was quicker than those prepared by other method. This may be due to their lowest hardness and the porous structure is responsible for faster water uptake, hence it facilitates wicking action of crosscarmellose sodium in bringing about faster disintegration [28]. All the formulations showed rapid % drug release (69.12% - 99.83%) due to fast disintegration of tablets.

Table 12: Release profile of Metoprolol Tartrate mouth dissolving tablets prepared by Direct Compression Method

Formulation Code	$T_{50\%}$ (min)	$T_{90\%}$ (min)
DCI_1	0.40 ±1.42	2.05 ±0.65
DCI_2	0.35 ± 1.08	1.70 ±1.11
DCI_3	0.20 ±0.67	1.10 ±1.84
DCI_4	0.35 ±0.54	2.05±0.56
DCC_1	0.40 ± 1.97	5.05 ±0.75
DCC_2	0.45 ± 0.89	4.75 ±0.71
DCC_3	0.40 ±1.08	5.15 ±1.21
DCC_4	0.40 ± 0.65	3.60 ±1.08
DCP_1	0.35 ± 0.21	3.55 ±1.46
DCP_2	0.40 ± 0.42	5.05 ±1.69
DCP_3	0.40 ± 0.57	5.45 ±1.03
DCP_4	0.40 ± 1.02	5.05 ±0.42
DCS_1	0.40 ± 1.46	5.35±0.59
DCS_2	0.40 ± 1.86	6.35 ±1.90
DCS_3	0.45 ± 1.31	6.30 ±0.43
DCS_4	0.40 ± 1.70	6.25 ±0.62

5.4.2 DISSOLUTION STUDY OF SUBLIMATIONMETHOD:

Table 13: Release profile of the Metoprolol Tartrate mouth dissolving tablets prepared by Sublimation Method

Formulation Code	$T_{50\%}$ (min)	$T_{90\%}$ (min)
SBI_1	0.30 ±0.49	1.20±0.24
SBI_2	0.35±0.31	2.05±0.33
SBI_3	0.35±0.76	1.25±0.52
SBI_4	0.35±0.42	2.35±0.39
SBC_1	0.40±0.21	4.45±0.23
SBC_2	0.40±0.22	4.55±0.78
SBC_3	0.40±0.56	4.65±0.43
SBC_4	0.40±0.42	3.75±0.11
SBP_1	0.35±0.87	3.70±0.56
SBP_2	0.40±1.61	5.20±0.76
SBP_3	0.40±0.40	5.05±1.21
SBP_4	0.40±0.31	5.10±0.31
SBS_1	0.45±1.42	5.10±1.58
SBS_2	0.45±1.11	6.40±0.31
SBS_3	0.45±1.56	6.05±1.34
SBS_4	0.45±0.96	6.10±1.87

Figure 21: Release profile of formulations containing Indion 414 (DCI_1 - DCI_4)

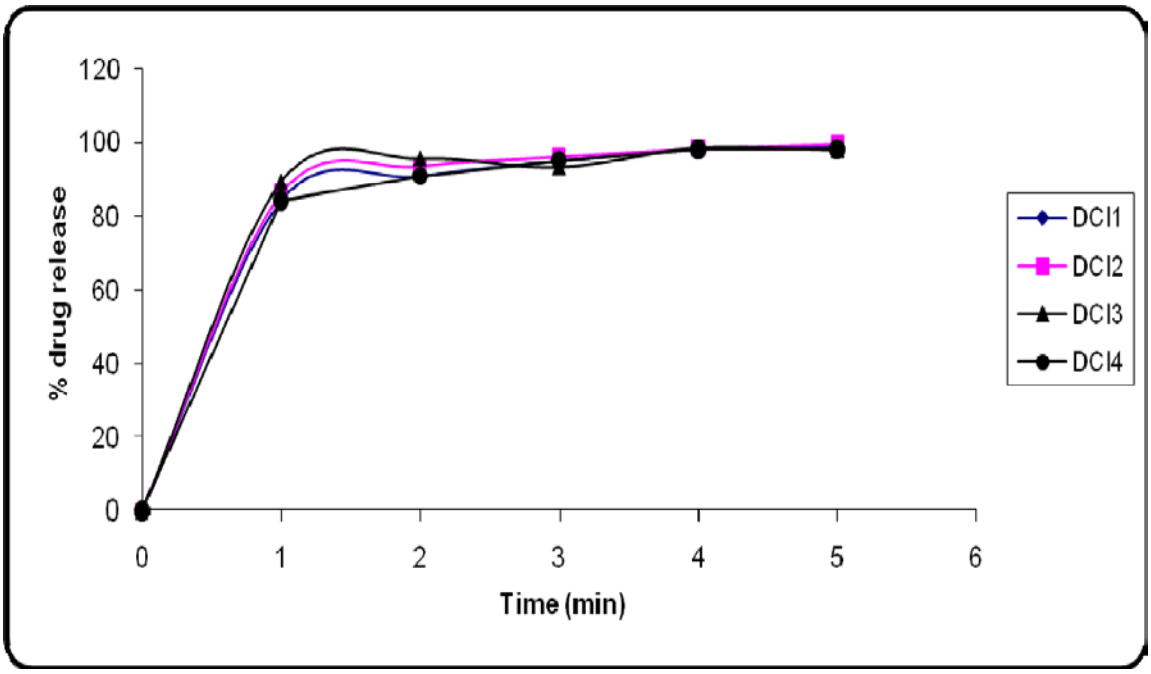


Figure 22: Release profile of formulations containing Croscarmellose Sodium (DCC_1 – DCC_4)

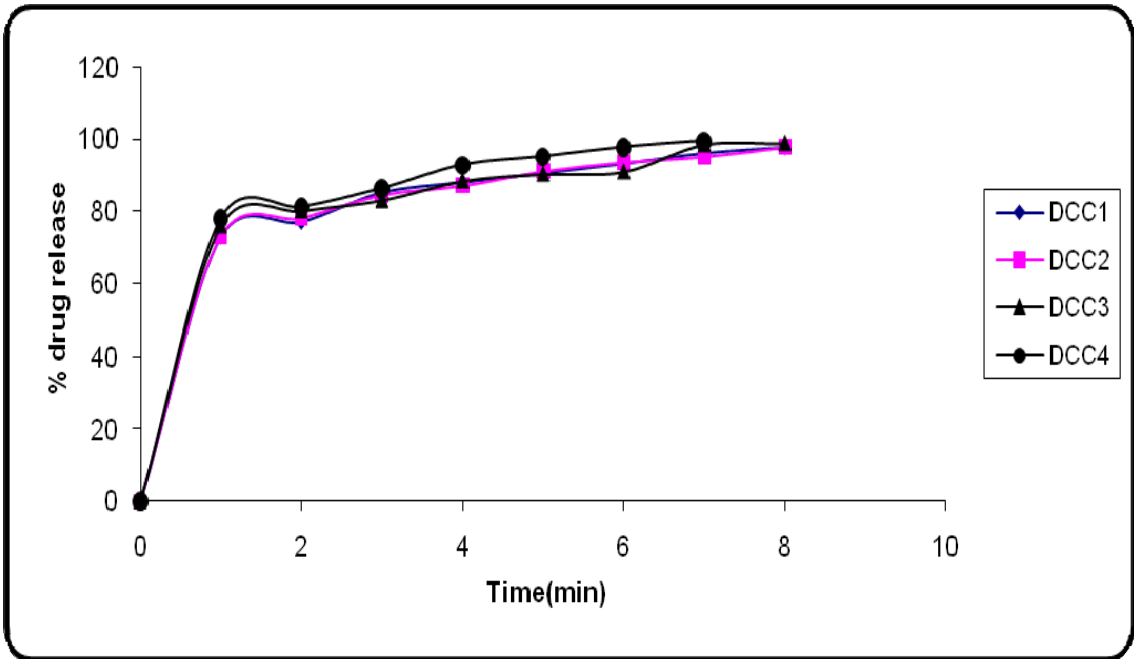


Figure 23: Release profile of formulations containing Crospovidone (DCP_1 – DCP_4)

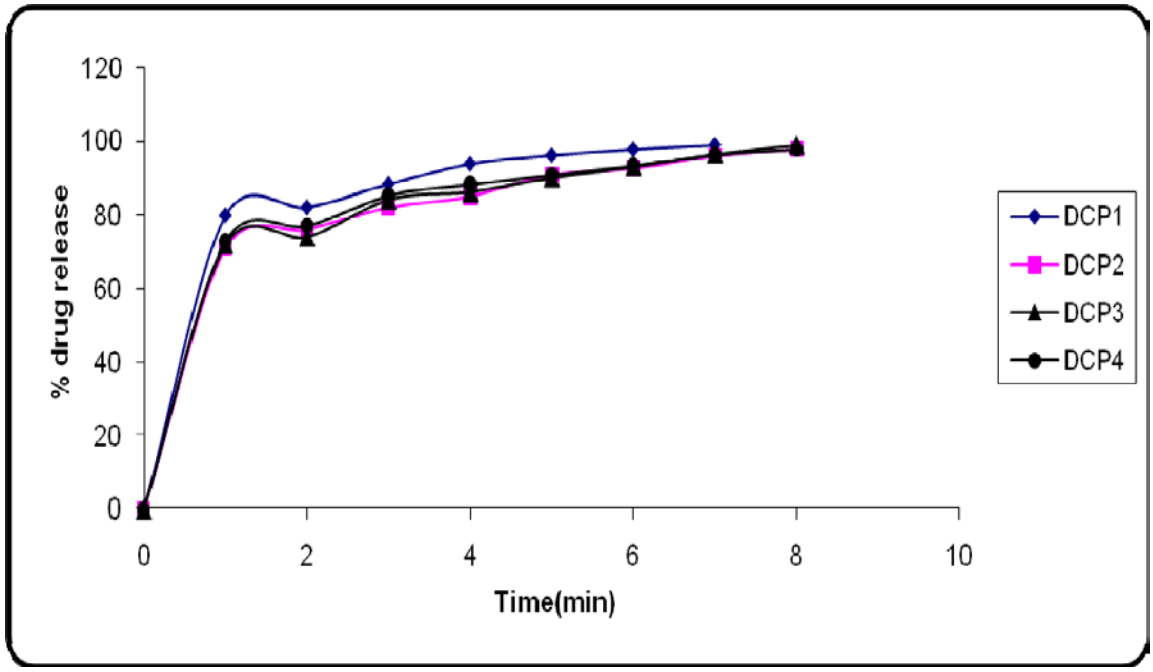


Figure 24: Release profile of formulations containing Sodium Starch Glycolate (DCS_1 – DCS_4)

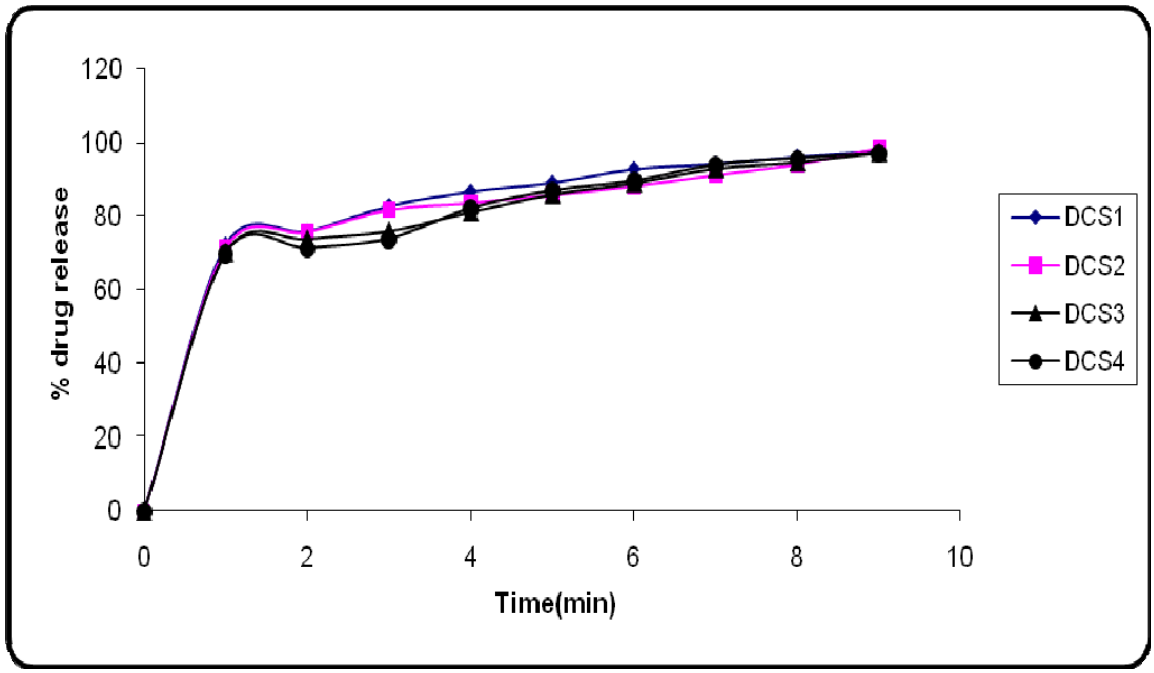


Figure 25: Release profile of formulations containing Indion 414 (SBI_1- SBI_4)

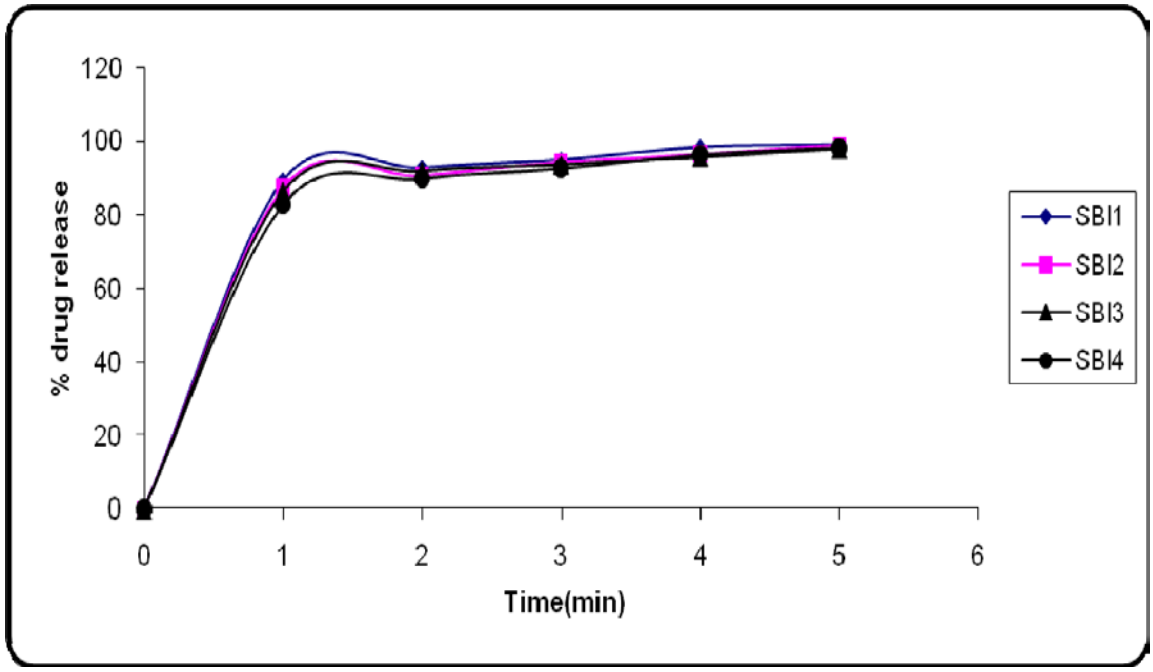


Figure 26: Release profile of formulations containing Croscarmellose Sodium (SBC_1 – SBC_4)

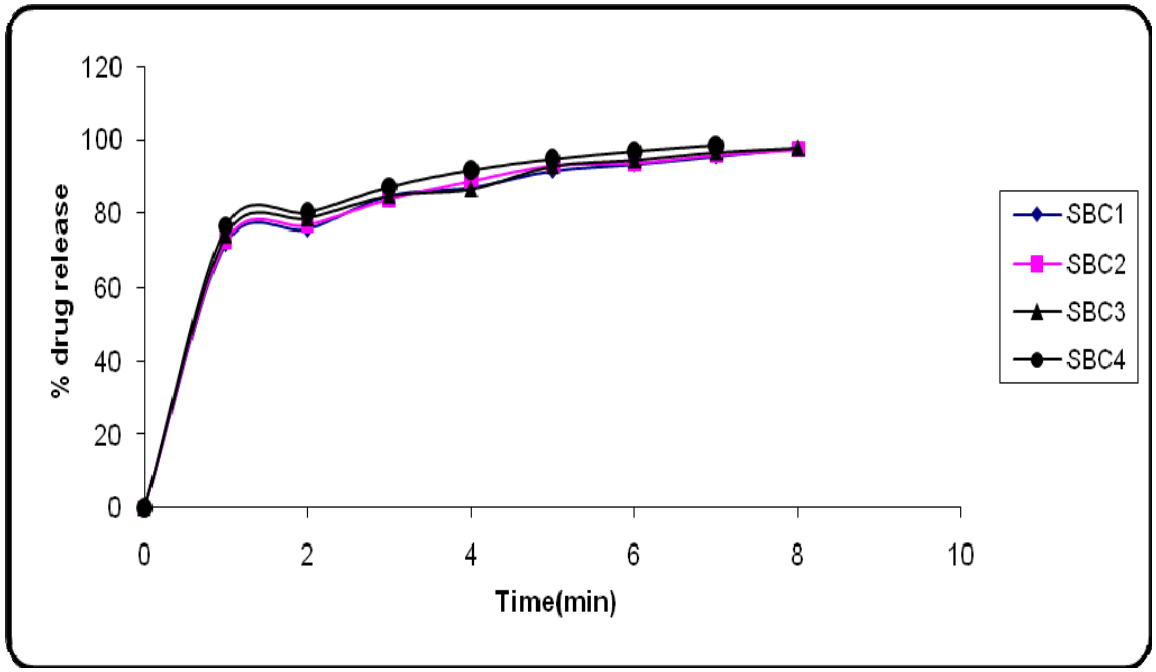


Figure 27: Release profile of formulations containing Crospovidone (SBP_1 – SBP_4)

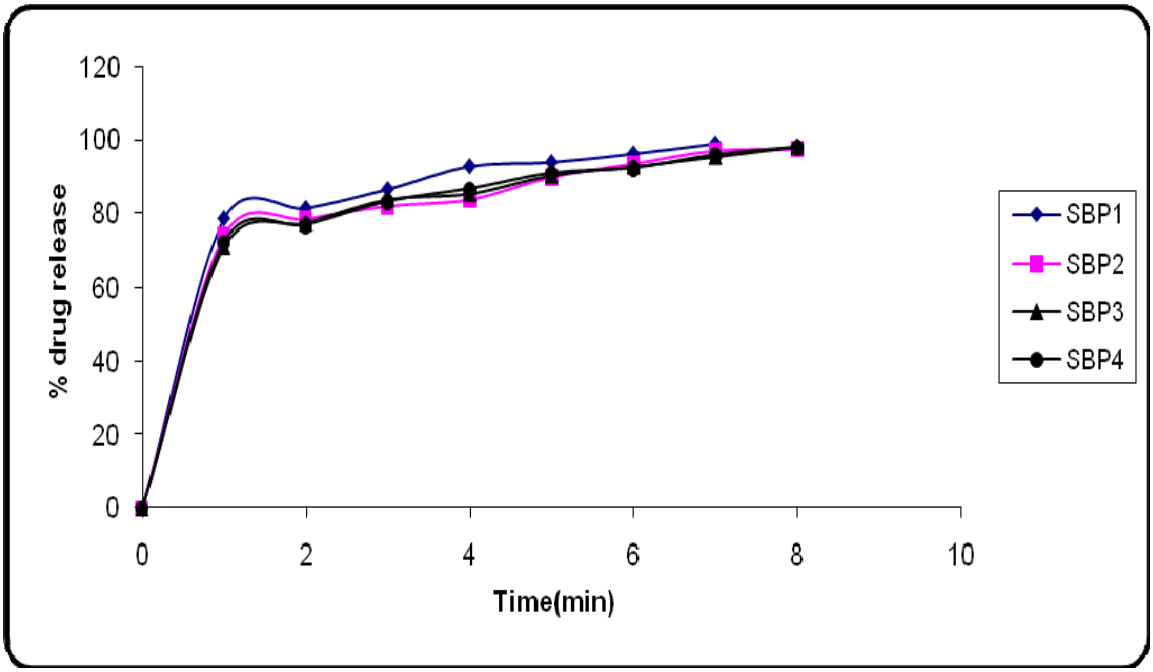
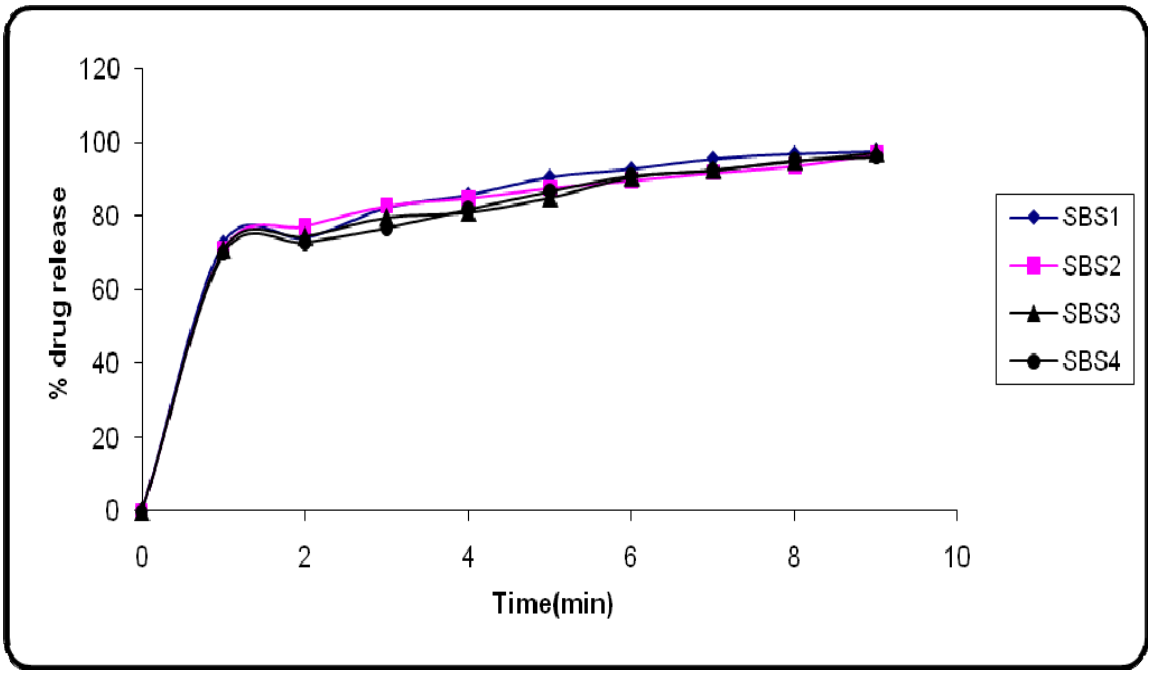


Figure 28: Release profile of formulations containing Sodium Starch Glycolate (SBS_1 - SBS_4)



CHAPTER 6

SUMMARY&CONCLUSION

The most popular solid dosage forms are being tablets and capsules;one important drawback of these dosage form for some patients, is the difficulty to swallow. Drinking water plays an important role in swallowing of oral dosage forms. For these reasons tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Orodispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people. Orodispersible tablets are those when put on tongue, disintegrates instantaneously releasing the drug, which dissolves or disperse in saliva.

The concept of formulating mouth dissolving tablets containing Metoprolol Tartrate offer a suitable and practical approach in serving the desired objective of faster disintegration and dissolution characteristic with increase bioavailability.

Metoprolol Tartrate is a selective beta1-adrenoreceptor blocking agent, by blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, Metoprolol reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the management of angina pectoris and in acute myocardial infarction. However, in patients with heart failure, beta-adrenergic blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure.

Mouth dissolving tablets of Metoprolol Tartrate were prepared using various superdisintegrants such as indion 414, croscarmellose sodium, sodium starch glycolate, crospovidone, Microcrystalline cellulose and camphor (as subliming agent)

in different ratio.

Prepared tablets were subjected to different evaluation parameters such as hardness, friability, weight variation, drug content uniformity, wetting time, water absorption ratio, *in-vitro* disintegration time, *in-vitro* dissolution studies.

Results revealed that the tablet of all formulations have acceptable physical parameters .The tablet prepared by direct compression method passes weight variation was found in the range 196 to 205 mg which is below ±7.5%, hardness 2 to 3 Kg / cm^2, percentage friability of 0.54 to 0.81 %, *in vitro* disintegration time of 21 to 59 sec, drug content uniformity was in between 99.08 to 100.76%, water absorption ratio were found between 46.77 to 85.64% and wetting time between 37 to 50 seconds. Shows maximum drug release within 5 min.

The tablet prepared by sublimation method passes weight variation was found in the range 197 to 204 mg which is below ±7.5%, hardness 2.1 to 2.9kg/cm^2, percentage friability of 0.53 to 0.85, *in vitro* disintegration time of 18 to 48 sec, drug content uniformity was in between 98.56 to 100.65%, water absorption ration were found between 51.15 to 85.15% and wetting time between 37 to 50 sec. Shows maximum drug release within 5 min.

The FTIR spectra and DSC studies of formulation shows that no interaction between drug and excipient.

Conclusion:

In the present work mouth dissolving tablets of Metoprolol Tartrate were prepared by direct compression and sublimation methods using superdisintegrants such as indion 414, sodium starch glycolate, croscarmellose sodium and crospovidone. In sublimation method, camphor is used as sub limingagent.

All the tablets of Metoprolol Tartrate were subjected to weight variation, hardness, friability, *in vitro* dispersion, drug polymer interaction, drug content uniformity, water absorption ratio, wetting time, and *in vitro* drug release.

Based on the above studies following conclusions can be drawn:s

- Tablet prepared by direct compression and sublimation methods were found to be good and were free from chipping and capping.
- The low values of the standard deviation of average weight of the prepared tablets indicate weight uniformity within the batches prepared.
- The hardness of the prepared tablets was found to be in the range of 2 to 3 Kg/cm^2.
- The friability values of the prepared tablet were found to be less than1%.
- IR spectroscopic and DSC studies indicated that the drug is compatible with all the excipients.
- The *in vitro* disintegration time of Metoprolol Tartrate prepared by direct compression and sublimation method were found to be in the range of 18 to 59 sec fulfilling the official requirements.
- Based on the *in vitro* disintegration time, formulation DCI_3 (9% Indion 414) and SBI_1 (3% Indion 414) were found to be promising and showed a disintegration time of 21 and 18 sec, wetting time of 48 and 37 sec

respectively, which facilitate the faster disintegration in the mouth.

- TheformulationDCI$_3$andSBI$_1$havedisplayedgoodwaterabsorptionratioof 85.77 and 85.15%, which indicate better and faster swelling ability of the disintegrants in presence of little amount of water.
- The drug content of tablets was uniform in all the batches and was between 98.12 to 100.76%.
- The drug release from mouth dissolving tablets of Metoprolol Tartrate prepared by direct compression and sublimation methods were found to be in the range of 96.05 to 99.56% and the result of DCI$_3$ and SBI$_1$ showed 97.83% and 99.01% drug release within 5minutes.
- Among the two methods used namely direct compression and sublimation, the sublimation method was found to be superior to direct compression method.
- Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. Removal of volatile material by sublimation generated a porous structure. The tablets dissolve within 10-20 seconds and exhibit enough mechanical strength for practical use, which is effective than the direct compression method.

CHAPTER 8

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