# "DISSOLUTION ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS USING COMPLEXATION TECHNIQUE"

**A Thesis Submitted to**

**NIRMA UNIVERSITY**

**In Partial Fulfillment for the Award of the Degree of**

## MASTER OF PHARMACY

## IN

## PHARMACEUTICAL TECHNOLOGY &

## BIOPHARMACEUTICS

**BY**

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**MAY-2016**

# CERTIFICATE

*This is to certify that the dissertation work entitled "DISSOLUTION ENHANCEMENT OF POORLY WATER SOLUBLE DRUG USING COMPLEXATION TECHNIQUE" submitted by Mr.GAURAV GUPTA with Regn. No. (14MPH105) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutical Technology and Biopharmaceutics" is a bonafide research work carried out by the candidate at the Department of Pharmaceutics, Institute of Pharmacy, Nirma University under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.*

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Gaurav Gupta

# Abbreviations

| | |
|---|---|
| CPR | Cumulative Percentage Release |
| HPMC | Hydroxy propyl Methyl Cellulose |
| PVP | Polyvinyl Pyrrolidine |
| CD | Cyclodextrin |
| IC | Inclusion complexation |
| FTIR | Fourier transform Infrared Red |
| DSC | Diffraction Scanning Colorimetry |
| XRD | X-ray diffraction. |
| PM | Physical Mixture |
| MCC | Micro crystalline Cellulose |
| ABS. | Absorbance |
| CONC. | Concentration |

# Dissolution Enhancement of Poorly Water Soluble Drugs.

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## ABSTRACT:

Aim of present work was to enhance the dissolution rate of poorly water soluble drugs using complexation technique. Complexation is a reversible association between two or more molecules to form a non-bonded entity with a well-defined stoichiometry. Cyclodextrins are large molecules with molecular weight greater than 1000Da and are consists of glucose monomers arranged in a donut ring shaped. Cyclodextrins consists of ring which has hydrophilic exterior and lipophilic core in which drug entraps. Phase solubility curve was prepared with different molar concentrations. Complexation was done using kneading method in which drug and cyclodextrin were mixed with addition of solvent to make paste to facilitate drug penetration in hydrophobic cavity of cyclodextrin.Various parameters were optimized like drug to beta cyclodextrin ratio, type and amount of solvent (water: methanol). Effect of addition of hydrophilic components along with complexation using hypromellose was also studied. Phase solubility curve showed that drug: beta cyclodextrin ratio 1:2 was required for complexation. Optimization of various factors could improve dissolution rate and > 85% drug release was obtained with drug: beta cyclodextrin: hypromellose 5 cps in a ratio of 1:2:1. Tablets showed acceptation parameters and improve dissolution rate when compared to marketed product and pure drug. Thus, it can be concluded that complexation can successfully be used for solubility enhancement of hydrophobic drugs.

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# CHAPTER-1

# AIM AND OBJECTIVE

## AIM & OBJECTIVE

Carvedilol is a non-selective β-adrenergic blocking agents used in treatment of hypertensive diseases, Congestive heart failure. It is practically insoluble in water, gastric and intestinal fluids. Drugs belongs to this class has low solubility and high permeability hence dissolution rates becomes the factor i.e governing for its oral bioavailability.These drugs has low solubility and dissolution rate and need to enhanced the solubility by using complexation technique, solid dispersion techniques.Main aim of this complexation technique is to enhanced the solubility and dissolution of the BCS Class-II drugs.These are anti-hypertensive drugs and needs to be deliver the drugs in the systemic circulation in faster period of time.

### OBJECTIVES:

- To compared the effects of tablets with the marketed products.
- To carry out phase solubility and pre formulation study.
- To study the effect of various process parameters.
- To enhanced the dissolution by using complexation techniques.

# Chapter-2
# INTRODUCTION

## 2. INTRODUCTION TO DISSOLUTION ENHANCEMENT: [1]

Materials are absorbed by active transport across the intestinal barrier, but absorption by passive diffusion is far more important. Regardless of the mode of transport, it is concluded that the drug must be in solvated state to diffuse into and across the enterocytes lining the intestinal lumen. Thus, solubility and rate of dissolution of drugs are major of importance and we can find many approaches for absorption enhancement.

### 2.1. SOLUBILITY: [2]

Drug solubility is defined as amount of the solute to dissolve in a specific solvent to form a homogeneous solution. It is also defined as a chemical property referring to the ability for a given substance of the solute to dissolve in the solvent. The U.S Pharmacopeia and National formulary described solubility as number of milliliters of solvent required to dissolve 1 gram of the solute. The solubility may be expressed as percentage on weight or volume basis, concentration, molality, mole fraction, mole ratio etc. It is one of important parameter for achieving the desired concentration of drug in systematic circulation for enhancing the bioavailability of drugs. The solubility values were expressed as log units of molar solubility (mol /ltr). A poor aqueous solubility is likely to hamper the bioavailability of drugs.

**Table 2.1: Solubility Criteria According to USP and BP**

| **Descriptive term** | **Parts of solvent required per part of solute.** |
|---|---|
| Very soluble | Less than 1 |
| Freely soluble | From 1 to 10 |
| Soluble | From 10 to 30 |
| Sparingly soluble | From 30 to100 |
| Slightly soluble | From 100 to 1000 |
| Very slightly soluble | From 1000 to 10000 |
| Practically insoluble | 10000 and over |

**2.1.1. Factors affecting the solubility of the drugs**:

**1) Temperature:**

Solubility is directly proportional to the temperature. Temperature affects the solubility of both solid and gases. Hence, solubility increases with the increasing the temperature.

**2) Polarity:**

Solutes dissolves in the solvent that have a similar polarity. Chemist used a popular aphorism to describe features of solute and solvents. 'Like dissolves like'.Non-polar solutes do not dissolves in polar solvents.

**3) Pressure:**

**a) Solid and liquid solutes:** For majority of solid and liquid solutes, pressure do not affect the solubility.

**b) Gas Solutes:** As for gases the Henry's law states that solubility of gas is directly proportional to pressure of gas. When the gas pressure is decreased the solubility of that gas is also decreased. Pressure affects the solubility of gas in liquid but never of solid dissolve in liquid.

**c).Molecular size:** Larger the molecules of solute, the larger is their molecular weight and their size .It is more difficult it is for solvent molecules to surround bigger molecules. Smaller the molecular size, larger the surface area and hence more solubility of solutes get increased.

**4) Stirring increases the speed of dissolving:** Stirring only increases the speed of the process-it increases move of the solvent what exposes solute to fresh portions of it, thus enabling solubility. Hence, solute get more exposed on the solvent and increased the solubility.

## 2.2. Theory of Dissolution:[23]

Dissolution is a process in which solid substances solubilizes in a given solvent i.e. mass transfer from solid surface to liquid phase. Several theories to explain drug dissolution have been proposed. Some of important ones are:

1. Diffusion layer
2. Danckwert's model
3. Interfacial barrier model.

### 2.2.1 Diffusion layer:

In this stagnant layer or diffusible layer is formed which is saturated with the drugs.The another steps is diffusion of soluble solute from stagnant layer to bulk of solution.

**NOYES AND WHITNEY EQUATION:**

$$Dc/dt=k (Cs – C_b)$$

Where,

Dc/dt = Dissolution rate of drug

K = dissolution rate constant (first order)

Cs = Concentration of drug in the stagnant layer (also called as saturation or maximum drug solubility)

$C_b$ = Concentration of drug in bulk solution at time "t"

### 2.2.2 Danckwert's Model (Penetration or Surface Renewal Theory):

This theory did not approve the existence of stagnant layer.It consist of mass of eddies or packets.These packets get replaced by new ones and exposed to new solid surface each time. Since the solvent packets are exposed to new solid surface each time, the theory is called as **surface renewal theory**. The Danckwert's model is expressed by equation

$$V\ dC/\ Dt = dm/dt=A\ (Cs\ -Cb)\sqrt{\gamma D}$$

Where,

dC/Dt=Dissolution rate of drugs.

### 2.2.3. Interfacial Barrier Model (Double Barrier or Limited Solvation Theory):

Based on the solvation mechanism it is a function of solubility rather than diffusion. The interfacial layer can be extended to both the diffusion layer model and danckwerts model.

$G = Ki (Cs – Cb)$

Where,

G= Dissolution rate per unit area

Ki=Effective interfacial transport constant.

Drug absorption as such depends upon the release of drug from the formulation. This affects the solubility and permeability in turn. The solubility and permeability depends upon nature of active compound. Based on different rate of solubility ad permeability they are divided into 4 classes. This classification is known as Biopharmaceutical Classification System which is classified on the bases of solubility and permeability of drug. They are classified as follows:

**Table A: Bio pharmaceutics Classification System and their formulation**

| Class | Solubility | Permeability | Oral dosage form approach |
|---|---|---|---|
| I | High | High | Simple solid oral dosage form |
| II | Low | High | Techniques to increase surface area like particle size reduction, solid solution, solid dispersion, inclusion complex Solutions using solvent or surfactants |
| III | High | Low | Include permeability enhancers, maximize local lumenal concentration |
| IV | Low | Low | Combination of class II and III |

**2.3. Importance of Dissolution:**

Oral route of administration especially oral dosage form is the most easy dosage form as it is easily administered high patient compliance, cost effectiveness, least sterility concern and flexibility of design dosage form. Due to these advantages many generic companies manufacture bio-equivalent oral dosage form. But, the major challenges of oral dosage form is its bioavailability. Bioavailability mainly depends on the aqueous solubility, drug permeability, dissolution rate, first pass metabolism and BCS class II drugs have low solubility which affects the bioavailability of drug. Solubility is one of the most important parameters to achieve the desired concentration of drug in systematic circulation for response. Generally low soluble drug require high dose to reach the therapeutic plasma concentration which often lead to toxicity. Hence, there is need to enhance the solubility of poorly soluble drugs.For BCS class II drugs, the rate limiting steps is its drug release and in returns its solubility in the gastric fluid. Hence, by increasing the solubility of drug, bioavailability also increases.

**2.4. Techniques for Solubility Enhancement:[23]**

1) Chemical modification:

a) pH adjustment

b) Salt formation

c) Co-crystallization

d) Co-solvency

e) Hydrotropic

f) Solubilizing agents

g)Nanotechnology

2) Physical modification:

a) Particle size Reduction:

b) Micronization

c) Nano suspension

3) Modification of crystal habit

a) Polymorphs

b) Pseudo-polymorphs

4) Complexation:

a) Use of complexing agents

5) Solubilizing by surfactants

a) Micro-emulsion

b) SMEDDS

6) Drug dispersion in carrier:

a) Solid solution

b) Solid dispersion

**2.4.1 Chemical modification:**

**2.4.1.1 pH adjustment:**

Molecule that can be protonated(base) or deprotonated(acid) can be dissolved in water by changing its pH are the good candidates for the process. They are majorily applied for crystalline and lipophilic drugs. They are easy to formulate and analyze. But, if the compound has tendency to undergo hydrolysis or catalysis with the change of pH then those drug can't be used.

**2.4.1.2 Salt formation:**

It is the technique the acidic or basic drugs are converted into its salt form to enhance the solubility and dissolution rate.These form has higher solubility and dissolution rate rather than that of the free acids or bases . For example: Hydrochloride salt of free base may initially dissolve at low pH in stomach.

**2.4.1.3 Co-crystallization:**

Co-crystallization can increase the physicochemical properties like solubility, dissolution rate, chemical stability and melting points.

**2.4.1.4 Co-solvents**:

Co-solvents are defined as water miscible organic solvents that are used in liquid drug formulation to increase the solubility of poorly water soluble compounds and also for the chemical stability of drugs.

**2.4.1.5 Hydrotropic:**

Hydrotrophy is a solubilization phenomenon where by addition of large amount of second solute results in an increase in aqueous solubility of another solute. Concentrated aqueous hydrotropic solution of sodium benzoate, sodium citrate and sodium acetate have been observed to enhance the aqueous

solubility of poorly water soluble drugs. Hydrotropes consists of hydrophilic part and a hydrophobic part (like surfactants) but the hydrophobic part is generally too small to cause spontaneous self-aggregation.

**2.4.1.6 Solubilizing agents:**

Different techniques are used to enhance the solubility such as:

1).Milling

2).Homogenization in water

3).Precipitation

4).Cryo-vaccum methods

5).Homogenization in non-aqueous solvent.

**2.4.2 Physical modification**:

**2.4.2.1 Particle size reduction**:

Particle size is inversely proportional to the surface area. Larger the particle size smaller is the surface area. Smaller the particle size higher is the surface area. As the surface area of drugs increases, the dissolution of the drug increases as it allows the greater exposure with the solubility enhancing solvent. The dissolution rate of drug proportionally increase with the increasing surface area. Conventional methods of particle size reduction are: grinding, milling, spray drying.

**2.4.2.2 Micronization**:

It is the process where reduction in particle size takes place. Micronization enhances the dissolution rate but not the equilibrium study. It is done by different process such as: Jet mill, rotor, stator, colloids mill

**2.4.2.3 Nano-suspension**:

It is another technique to change the normal size to Nano size for poorly soluble drugs. It is a process whereby the drug powder is converted to nano crystals of sizes 200-600 nm e.g amphotericin. Nano suspension are prepared by homogenization and wet milling process. These are prepared by homogenization and wet milling process.

### 2.4.3 Modification of Crystal habits:

#### 2.4.3.1 Polymorphs:

When a solid form can exists in more than one crystalline forms than they are designated as polymorphs and phenomenon as polymorphism. Polymorphs are of two types:

a).Enantiotropic polymorph:

These can be changed into another form by altering the temperature or pressure. e.g: sulphur

b)Monotropic polymorph:

It is the one which is unstable at all temperature and pressure.eg.Glyceryl stearate. The polymorph differ from each other with respect to their physical properties such as solubility, melting point, density, hardness, and compression characteristics. The existence of polymorphs can be determined by technique such as optical crystallography, X-ray-diffraction, Differential Scanning Colorimetry.

#### 2.4.3.2 Hydrates/Solvates (Pseudo-polymorphism):

The crystalline form of drug can be a polymorph or molecular adduct or both. The solvates can exists in different crystalline forms called as pseudo polymorphs. The overall phenomenon is called as pseudo polymorphism. When the solvent in association with the drug is water, the solvate is known as a hydrate.The anhydrous form of drug has greater aqueous solubility than the hydrates form.

### 2.4.4 Complexation:

Complexation are formed when guest molecule is partially or fully included inside a host molecules. The two types of complexation that are useful for increasing the solubility of drugs in aqueous media are staching and inclusion complexes.

#### 2.4.4.1 Staching complexes:

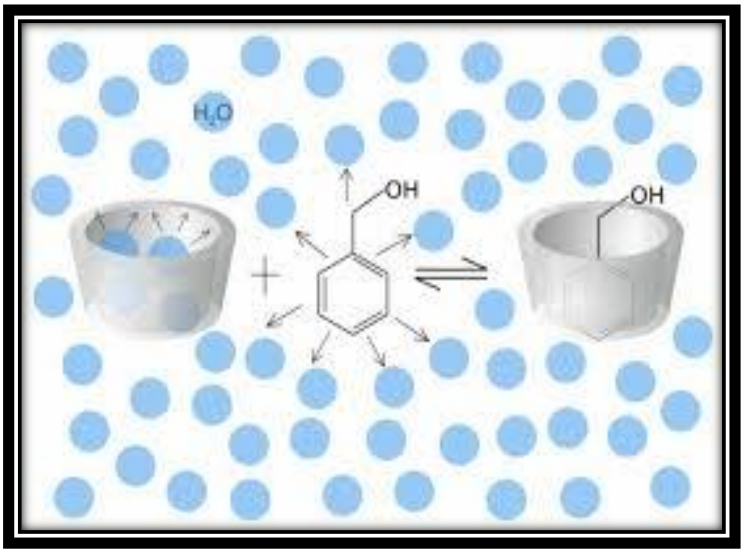
These complexes are formed by overlaps of planar region of aromatic molecules, while inclusion complex are formed when guest molecule enter inside a host molecules. The mathematical description for the equilibrium constant of a 1:1 complex, k1:1 is defined by:

K1:1= [SL]/[S] [L]

Where, S is the concentration of free solute, L is the concentration of free ligand & [SL] is the concentration of solute/ligand complex. The equilibrium constant is also commonly referred as stability constant or complexation constant.

**2.4.4.2 Inclusion complexation**:

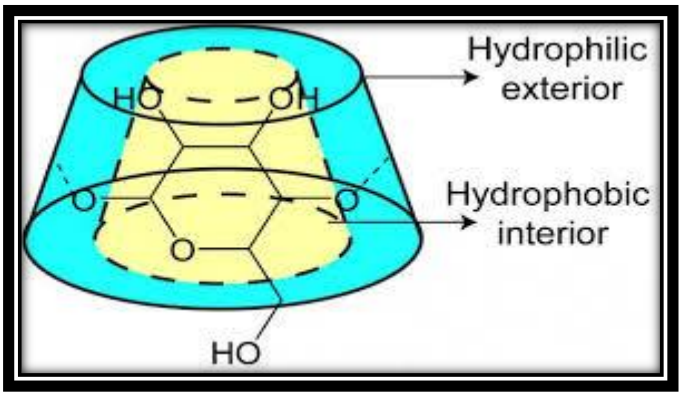
Inclusion complexation is produced by inclusion of the non-polar cavity known as host in which the guest molecules such as polar compounds get entrapped inside the cavity .When the guest molecules enters the host molecules the contact between the water and non-polar region both is reduced. Thus, inclusion phenomenon is a result of same driving force that produces the micellization. The host cavity must be large enough to accommodate the guest and small enough to eliminate water so that total contact between water and non-polar region of host and guest is reduced. The most commonly used host molecules are the cyclodextrins. These cyclic oligomers of glucose are relatively soluble in water and have cavity large enough to accept non-polar portions of common drug molecules.




**Elimination of water molecule from cyclodextrins**

**2.4.4.3 Cyclodextrins**:[4]

Cyclodextrins (sometimes called cyclo amyloses) are a family of compound made up of sugar molecules bound together in a ring (cyclic oligosaccharides). Cyclodextrin are produced from starch by means of enzymatic conversion. They are used in food, pharmaceutical, drug delivery, chemical industry, agricultural, environmental engineering. Cyclodextrin are a group of cyclic oligosaccharides which consists of hydrophobic cavity and outer portion is hydrophilic. They are formed by enzymatic degradation of starchbycyclodextrins-glucosyltransfers (CGT).These are versatile,crystalline complexing agent that have the ability to increase the solubility, bioavailability and stability of API mask the colour and taste of drugs and also prevent GI and ocular irritation. Thus, the molecularly encapsulated drug has improved aqueous solubility and dissolution rate.[4]




**Advantages of Cyclodextrins:**

1).They can retard degradation of the active compounds.

2).They have no effect on reactivity or they can accelerate the drug degradation.

3).They can mimic enzymatic catalysis or inhibition.

4).They can improved the stability of the active drug.

i).Heat stability

ii).Reduction of volatility

iii ).Oxidation resistance

5).They prevent the drugs from hydrolysis

### 2.4.5 Solubilization by Surfactants:

Surfactant acts as an absorption enhancer. This enhances the dissolution rate and rate of permeability of the poorly soluble drugs. Mechanism behind the enhancement of the dissolution is the wetting of drug and then penetration of dissolution fluid into the solid drug particle.

#### 2.4.5.1 Micro emulsions:

Micro emulsions consist of four components – external phase, internal phase, surfactant and co-surfactant. On the addition of surfactant to the internal phase, they form optically clear, isotropic, thermodynamically stable emulsion known as microemulsion. They are <0.1µ. some non-ionic surfactants with high HLB values like tweens are used to form o/w droplets during process.

#### 2.4.5.2 Self-Micro emulsifying Drug Delivery System (SMEDDs):

SMEDDS are the anhydrous system of the micro-emulsions. But they have only three components – oil, surfactant and co-surfactants. They form o/w micro-emulsions when dispersed in aqueous phase under constant agitation. Surfactants can also be non-ionic like polyoxyethylene surfactants like Brij, Sugar esters like span 80, etc. major factor which influences the drug bioavailability is its droplet particle size (6-80mm). But the main problem is its stability criteria.

### 2.4.6 Drug Dispersion in carriers

#### 2.4.6.1 Solid solution:

Solid Solution is a binary mixture of a solid solute molecularly dispersed into a solid solvent. In this system both the components gets crystallized together in one phase system homogenously, hence it is also known as molecularly dispersed or mixed crystals. As there is reduction in the particle size of the molecule, it shows nice solubility in the aqueous system. They are prepared using fusion method known as melts.

### 2.6.2 Solid dispersion:

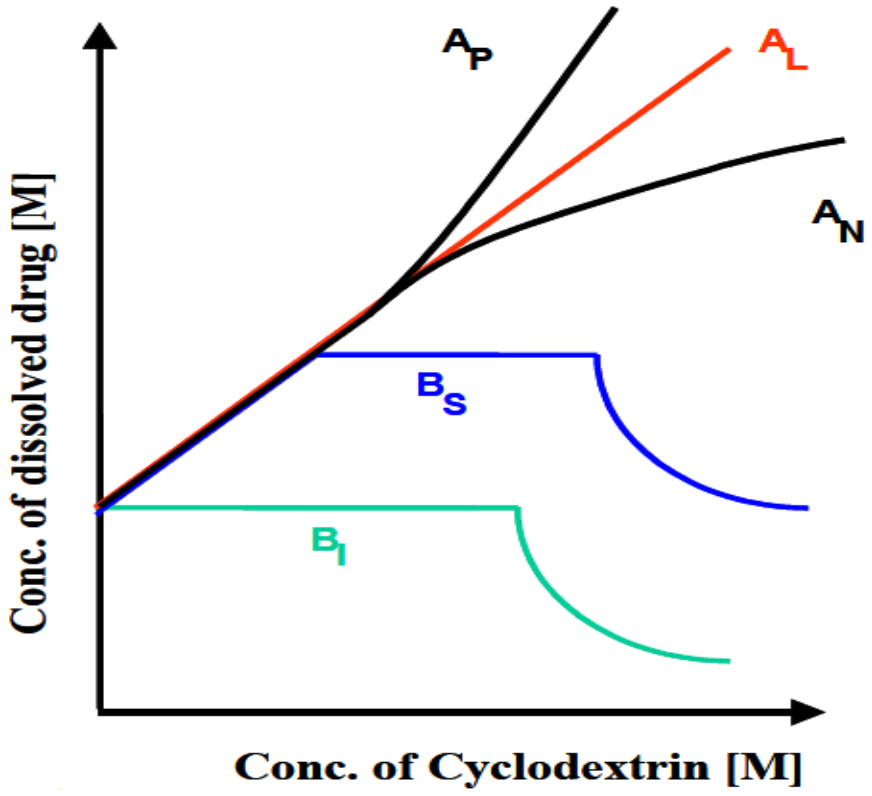
Dispersion of one or more active ingredient in a inert carrier or matrix at solid state prepared by melting,fusion, or solvent evaporation methods. This liquid solvent is removed by evaporation under reduced pressure or by freeze drying which results in amorphous precipitation of guest in

crystalline carrier. In this drug is precipitated in an amorphous form in former and then to crystalline form latter.

Preparation of solid dispersions also present several disadvantages:

- Carrier is hydrophilic and drug is hydrophobic it is difficult to find a common solvent to dissolved both the components.
- The product is often soft, waxy and has poor compressibility and flowability.
- Physical instability of the solid dispersions

## 2.7 Phase Diagram: [4]



There are two types of phase diagram:

I) Type A:

Solubility of drug increases with the increases cyclodextrins concentration. This type A is further classified into $A_L$ , $A_P$ , $A_N$

II) Type B:

It indicates the formation of complexes with limited solubility in aqueous complexation medium.. Type B phase diagram is further classified into Bi and Bs

### 2.7.1 $A_L$- type phase diagram:

Linear complex is formed when each complex contain only one molecule of complexing agents and complex is first order.

### 2.7.2 $A_P$ – type phase diagrams:

Formation of soluble complexes containing more than one molecules of ligand leads to a positive deviation from linearity, and such phase diagram are classified as Ap type.

### 2.7.3 $A_N$-type phase diagram:

Difficult to interpret.

### 2.7.4 B-types:

It indicates the formation of complexes with the limited solubility in aqueous complexation medium.

Note: Phase solubility profile do not verify formation of inclusion complex. They only describes how the increasing cyclodextrins concentration influences the drug solubility.

## 2.8 Applications of Cyclodextrins:[4]

**1.Toenhancedthe bioavailability:**These enhances the solubility,bioavailability and dissolution of the drugs of such compounds.

**2.For preparation of cholesterol free products**: In food industry, cyclo-dextrin are employed for preparation of cholesterol free products, the bulky and hydrophobic cholesterol molecules is easily lodged inside cyclodextrins ring and then removed.

**3. In health care**: European assessment report confirms that consumption of alpha-cyclodextrins can reduce blood sugar peaks following a high starch meal. Due to its surface-active properties, alpha cyclodextrins can be used as emulsifying fiber, for eg.in mayonnaise as well as whipping aid, for eg. in desserts and confectionery applications.

**4. Other food applications**: It includes the ability to stabilize volatile or unstable compounds and reduction of unwanted tastes and odour. Beta-cyclodextrins complexes with certain carotenoid food colorants have been shown to intensify colour, increase water solubility and improve light stability.

**5. Aerosols**: Aqueous cyclo- dextrin solution can generate aerosols in particle size ranges suitable for pulmonary depositions .Large quantities of aerosols can be nebulized in acceptable nebulization times.

## 2.9 Different properties of Cyclodextrins:

| **Property** | **α-Cyclodextrins** | **β- Cyclodextrins** | **γ- Cyclodextrins** |
|---|---|---|---|
| Number of glycol pyranose units | 6 | 7 | 8 |
| Molecular weight (g/mol) | 972 | 1135 | 1297 |
| Solubility in water at 25oc (%w/v) | 14.5 | 1.85 | 23.2 |
| Outer diameter (Ao) | 14.6 | 15.4 | 17.5 |
| Cavity diameter (Ao) | 4.7-5.3 | 6.0-6.5 | 7.5-8.5 |
| Height of torus (Ao) | 7.9 | 7.9 | 7.9 |
| Cavity volume (Ao) | 174 | 262 | 427 |
| Property | Irritating after intramuscular administration. | Less irritating after intramuscular administration | Insignificant irritating after intramuscular administration |
| Absorption (oral administration) | 2-3% | 1-2% | 0.1% |

## 2.10 Methods of Preparation:

| S. N. | Name of Technique | Detail of Technique |
|---|---|---|
| 1 | Physical blending | In this method a simple mixture of drug and cyclodextrin are mixed together in the mortar and pestle in different ratios such as 1:1, 1:2, 1:3 and then kneaded for particular period of time. |
| 2 | Kneading method | In this methods drugs and cyclodextrins are mixed in mortar and pestle in different ratios 1:1,1:2,1:3 with addition of little amount of water:methanol in ratio of 85:15.Then these mixture are kept for 24 hrs. in hot air oven and dried. |
| 3 | Solvent evaporation method | In this technique, the drug and the cyclodextrin is solubilized in two different mutually miscible solvents. Then these solvents are mixed together to get a molecular dispersion of drug and complexing agents. This solution is evaporated under vaccum for 24 hours at 45˚C to obtain a solid powder. It is considered to be an alternative to spray drying method. |
| 4 | Lyophilization / freeze drying technique | In this technique, the solvent system is removed from the solution used through a primary freezing and subsequent drying of the solution containing both drug & CD at less pressure. This method is best used for thermolabile substance to make it is complex. Few of the limitations are its long time process and poor flowing property of the mixture. Lyophillization/ freeze drying technique is considered as an alternative to solvent evaporation and involve molecular mixing of drug and carrier in a common solvent. |
| 5 | Co-precipitation technique | In this method, the guest solute and solid carrier solvent are dissolved in the volatile solvent such as alcohol. The liquid solvent is removed by evaporation under reduced pressure or freeze drying which produces amorphous precipitation of guest in crystalline carrier. This method is suitable for thermolabile substances but has a number of disadvantages like high cost of |

| | | |
|---|---|---|
| | | processing, used of large quantity of solvent, difficulty in complete removal of solvent. |
| 6 | Neutralization precipitation method. | In this technique the inclusion complex is formed by precipitation methods by dissolving the drug into the alkaline solution like sodium/ ammonium hydroxide and mixing it to the aqueous solution of cyclodextrins. This resultant solution is then neutralized using hydrochloric acid solution under constant till it reaches to its equivalent point. |
| 7 | Milling / Co-grinding technique | In this method, the drug and the cyclodextrin is mixed physically and then milling is performed using oscillatory mill for a required time. Even ball mill can be used. Then the milled blend is sieved from the appropriate sieve. |
| 8 | Atomization/ Spray drying method | It is the most common technique to obtain a dry powder from a liquid solution. By this technique the mixture can be stored for a long time as the water present in it is eliminated. The efficient interaction takes place between drug and the cyclodextrin. |
| 9 | Microwave irradiation method | In this technique microwave radiations are passed through the drug and the complexing agent using microwave oven. In this process the drug and the cyclodextrins are mixed in the mixture of water and organic solvent and are heated in oven for 2-3 minutes at 60˚C. After the completion of this procedure, a suitable solvent is added to the mixture to remove uncomplexed drug - cyclodextrins complex. The precipitates so formed are filtered through the whatman filter paper and dried in vacuum oven at 40oC for 48 hours. The major disadvantage is that the thermosensitive drugs can-not be used. But it requires less time to process and produces high yield. |
| 10 | Supercritical anti -solvent technique | Here carbon dioxide is used as an anti-solvent for the solute while it acts as an solvent for organic solvents. Low critical temperature and pressure helps heat labile drug process easily. This technique is non-toxic, inflammable, inexpensive, and easy. |

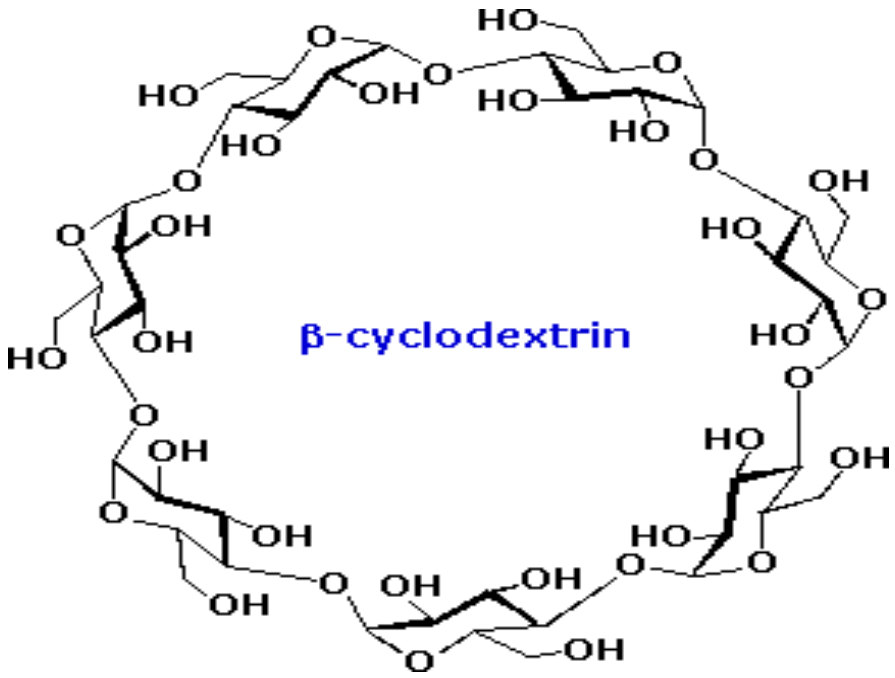
## 2.11 INTRODUCTION TO EXCIPIENTS:[12]

### 2.11.1 β Cyclodextrins:

Nonproprietary name: Betadex

Synonyms: Beta-dextrin, Kleptose

Molecular weight: 1135 g/mol




Functional Category:

- Solubilizing agents.
- Stabilizing agents.
- Taste masker.

Description:

It has 7 glucose units. It occurs as white, practically odourless, fine crystalline powder, having slight sweet taste.

Melting point: 255-265˚C

Solubility:1 in 200 parts of propylene glycol.

- 1 in 50 of water at 20˚C
- 1 in 20 of water at 50˚C

- Practically insoluble in acetone, ethanol and methylene chloride.

Regulatory status: It is included in the FDA inactive ingredients guide (IM, IV and other parenteral preparations).It is included in the Canadian list of acceptable Non-medical ingredients. It is used in oral and rectal pharmaceutical formulations licensed in Europe, Japan and the USA.

### 2.11.2 Hypromellose:

Non-proprietary name: Hydroxy propyl Methyl cellulose.

Synonyms: Benecel

Molecular weight: 10,000-1500000

Functional Category: Coating agents

Film-former

Stabilizing agents

Suspending agents

Tablet binder

Viscosity-increasing agents

Description: It is odorless and tasteless, white or creamy white fibrous or granular powder.

Melting points: Browns at 190-200˚C

Chars at 225-230˚C

Solubility: Soluble in cold water.

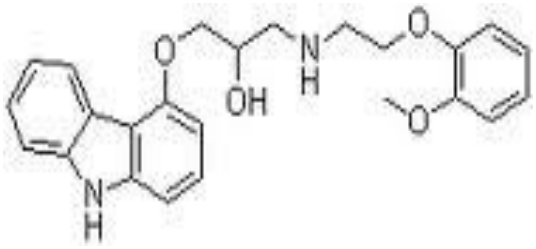
Soluble in mixture of ethanol and dichloromethane.

Practically insoluble in chloroform.

## 2.12 DRUG PROFILE OF CARVEDILOL:[11]

Carvedilol is both a non-selective beta adrenergic receptor blocker and an alpha adrenergic receptor blocker for the treatment of mild to moderate congestive heart failure (CHF). It blocks beta-1 and beta-2 adrenergic receptors as well as the alpha-1 adrenergic receptors. It is a BCS Class II Drug (insoluble in water), resulting in a low bioavailability of 42%.

- **Generic name:** Carvedilol
- **Synonyms:** Carvedilolum
- **Chemicalname:** 1-(9H-carbazol-4-yloxy)-3-{2-(2-methoxyphenoxy) ethyl amino} propan2-ol
- **Chemical structure:**




- **Chemical formula:** $C_{26}H_{26}N_2O_4$
- **Melting point**: 114-115°*c*
- **Molecular weight**: 406.474
- **Category**: Anti -hypertensive, anti- angina, Congestive heart failure, antioxidant.
- **Description**: White or almost white, crystalline powder.
- **Solubility**: Practically insoluble in water (0.01mg/ml)
  It is slightly soluble in ethanol (22.7mg/ml)
  Practically insoluble in dilute acids.
- **Heavy metals**: Maximum 10ppm
- **Sulphated ash**: Maximum 0.1% determined on 1 gm.
- **Loss on drying:** Maximum 0.5% determined on 1gm by drying in an oven at 100-105°*c*

- **Mechanism of action**:

Carvedilol is both a non -selective beta adrenergic receptor blocker.Carvedilol reversibly binds to β adrenergic receptor on cardiac myocytes. Inhibition of these receptor prevents a response to sympathetic nervous system leading to decrease heart rate and contractility.This action is beneficial in heart failure patients where sympathetic nervous system is activated as a compensatory mechanism. α1,β1, β2, Adrenergic receptor blockade properties.Carvedilol has been shown to have organ protective effect.Carvedilol is a potent anti-oxidant and a scavenger of reactive oxygen radical. Carvedilol is racemic and both R (+) and S (-) enantiomers have the same alpha adrenergic receptor blocking properties and anti-oxidant properties. Carvedilol has anti-proliferative effects on human vascular smooth muscles cells. Carvedilol reduces the peripheral vascular resistance via selective blocker adrenoceptor.Carvedilol attenuates the increase in blood pressure. Carvedilol has no adverse effect on lipid profile. A normal ratio of lipo-protein to low density lipoprotein is maintained.

**2.12.1 Pharmacokinetics:**[9]

a**) Absorption**:

Carvedilol get absorbed orally on oral administration. In healthy volunteers the maximum serum concentration is reached after approximately 1 hour. The absolute bio-availability of carvedilol in human is approximately 25%.

b**)Distribution:**

Carvedilol is highly lipophilic compound, approximately 98% to 99% bound to plasma proteins. The distribution volume is approximately 2L/KG.

c**) Metabolism**:

In human carvedilol is metabolized rapidly and get eliminated via bile.The first pass metabolism after oral administration reaches to about 60-75%

d**) Elimination**:

The average elimination half-life of carvedilol is approximately 6 hours.

### 2.12.2 Indication and usage

**a) Hypertension:**

Carvedilol is indicated for the management of essential hypertension. It can be used alone or in combination with other antihypertensive agents (eg. Calcium channel blocker, diuretics)

**b)Treatment of Angina Pectoris**:

Carvedilol is efficacious in the treatment of chronic stable angina and unstable angina.

a) **Chronic heart failure**:

Carvedilol is indicated for the treatment of symptomatic patients with stable, mild, moderate and severe chronic heart failure of ischaemic or non- ischaemic etiology. In combination with ACE inhibitors, diuretics and optional digitalis (standard therapy).Carvedilol reduces morbidity (cardiovascular hospitalization and patient wellbeing) and mortality as well as delaying progression of the disease.

**b) Post myocardial infarction:**

Carvedilol is indicated for long term treatment following post myocardial infarction complicated by left ventricular dysfunction(left ventricular ejection fraction =40% or wall motion index=1.3) including well controlled heart failure, in combination with ACE inhibitors and other treatment recommended in the management of myocardial infraction.

### 2.12.3 Dosage and Administration:

**Essential Hypertension:**

The recommended dose for initiation therapy is 12.5 mg once a day for the first two days. Thereafter the recommended doses is 25mg once a day.

**Angina Pectoris:**

The required doses for initation of therapy is 12.5mg twice a day for the first two days and the required doses is 25 mg twice a day.

**Symptomatic Stable Chronic Heart failure**:

The required doses for initation of therapy is 3.125 mg twice daily for two times. If this doses is tolerated, the doses may thereafter increase, at

intervals of not less than two weeks to 6.25mg, 12.5 mg and 25mg twice daily.

**2.12.4 INTERACTIONS**

**PHARMACOKINETIC INTERACTIONS:**

**Digoxin:**

Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly

**Insulin or oral hypoglycaemics:**

Agents with β-blocking properties may enhance the blood-sugar-reducing effect of insulin and oral hypoglycaemics**.**

**Cyclosporin:**

Modest increases in mean through cyclosporins concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patient suffer from chronic vascular injection.

**2.12.5. Pharmacodynamic interactions:**

**Clonidine:**

Concomitant administration of clonidine with $\beta$-blocking properties may potentiate BP and heart rate lowering effects.

**Calcium channel blockers:**

Isolated cases of conduction disturbance have been observed when carvedilol administered with diltiazem**.**

**2.12.6. SIDE EFFECTS:**

- Dizziness
- Drowsiness
- Diarrhoea
- Vision problem
- Dry eyes
- Swelling
- Dizziness
- Trouble breathing

### 2.12.7. Contraindication of the Carvedilol:

1.Chronic heart failure.

2.Diabetes

3.Peripheral vascular disease

4.Hypersensitivity

5.Pregnancy

6.Lactation

7.Bradycardia.

8.Psoriasis

9.Renal function

### 2.12.8. Marketed product of Carvedilol:

| **S.no** | **Brand name** | **Manufacturer name** |
|---|---|---|
| 1. | Carca | Intas Pharmaceutical Ltd. |
| 2. | Cardivas | Sun pharmaceutical Ltd. |
| 3. | Carloc | Cipla Medpro |
| 4. | Cavipress | Cipla Generics Pharmaceutical Ltd. |
| 5. | Carvedil | Alkem labarotory |
| **6.** | Carvel-P | Taurus Labaratory |
| **7.** | Carvel-F | Taurus Labaratory |
| **8.** | Oricar | Nicholas Piramal Ltd**.** |

# CHAPTER-3

# LITERATURE REVIEW

## 3.1 Literature Review on Inclusion Complex:

**1.** T.E.G.K Murthy et al performed experiment using hydroxy propyl β – cyclodextrins and carvedilol preparing inclusion complex by kneading methods and solvent evaporation technique. Three different ratios of Drug: Complexing agents were selected 1:1, 1:2, 1:3 and stastical analysis was performed from the results of dissolution. From these data kneading method having 1:2 drug: complexing agent ratio was found to be best.[9]

**2.** Thorsteinn Loftson and Marcus E .Brewster performed CDs as functional excipients methods to enhance Complexation efficiency. These cyclodextrins have gained useful solubilizing excipients with an ever increasing list of beneficial property and function. Increasing ability of cyclodextrins to complex with drugs through manipulation of complexation efficiency.[5]

**3.** Xianhong Wen and Zhijun Jing performed experiment on inclusion complex by using microwave irradiation methods. Phase solubility study indicates the ability of β-CD to complex with carvedilol and increases the drug solubility. These experiment performed the existence of 1:2 inclusion complex of carvedilol with β-CD and perform the formation of constant of complex by using fluorescence methods. In this carvedilol interacts with β cyclodextrin and form complexes and interaction increases the solubility.[11]

**4.** Gita Chaurasia, performed the formulation and evaluation of cyclodextrins based carvedilol solid inclusion complex by lyophilization methods.Phase solubility of drug indicated formation of 1:1 molar and 1:2 molar ratio inclusion complex in solution with β-CD and 2 HP-β-CD.Solid inclusion complex were prepared by lyophilization methods and characterized by SEM, DSC, FTIR,UV-spectrometry.[12]

**5.** Jessie Sofia Pamudji, Rachmat Mauludin, Visi Anisa Lestari reported improvement of carvedilol dissolution rate through formation of inclusion complex through β cyclodextrin.Preparations of the inclusion complex were performed by kneading, co-precipitation, and freeze drying methods. The variations of molar ratio of 1:1, 1:2, and 1:3 between carvedilol and β-

cyclodextrin were carried out. The amount of carvedilol included in β-cyclodextrin was calculated based on the amount of included carvedilol in binary system and free carvedilol in solution. Evaluations of the inclusion complex were performed by infrared spectroscopy, X-ray diffractometry (XRD) and Scanning Electron Microscopy (SEM).[13]

6. Rehab N. Shamma and Mona Basha reported Soluplus: A novel polymeric solubilizer for optimization of carvedilol solid dispersions formation design effect and effect of methods of preparations. Solid dispersion were prepared by 3 techniques: solvent evaporation, freeze drying, spray drying in different carvedilol: soluplus ratios using $3^2$ full factorial design. Carvedilol solid dispersions using freeze drying methods at ratio of 1:10 shows highest saturation solubility .Solid state characterization was evaluated by DSC, XRD, SEM, FTIR analysis indicated the complete transformation of carvedilol in solid dispersions from crystalline to amorphous state[14]

7. Saravana Kumar K. et al presented a review article on dissolution enhancement of poorly water soluble drugs using inclusion complexation techniques. Major focus was made on the use of cyclodextrins as the carrier material for inclusion complex. It is a comprehensive literature survey of utilizing cyclodextrins as complexing agents, solubility enhancers, permeability enhancers, etc. Brief introduction of different techniques like physical blending, kneading technique, co-precipitation, solvent evaporation, neutralization, co-grinding, spray drying, microwave irradiation, supercritical antisolvent and freeze drying techniques were given. Few examples of poorly water soluble drugs and different forms of cyclodextrins are given.[15]

8. Patil J.S. et al presented a review article on inclusion complex for improving the solubility and bioavailability of poor soluble drugs. They gave brief introduction for all the techniques of inclusion complex and the carriers used in inclusion complex .As the cyclodextrins have high aqueous solubility, they become capable to enhance the dissolution rate and bioavailability of poorly soluble drugs.[16]

9. K.Yuvaraja and Jasmina khanam presented a review article on enhancement of carvedilol solubility by solid dispersion technique using cyclodextrins, water soluble polymers and hydroxyl acid. Different products of carvedilol solid dispersion has been used in different pH condition to check the enhancement of the solubility and dissolution rate of carvedilol. In this the crystalline state of drugs has been converted into amorphous state.Solid dispersions using ionization process HPβCD and tartaric acid as a carrier system was found appropriate to improve the solubility and dissolution rate of carvedilol.[17]

10 Subhashis Chakraborty, Dali Shukla, Achint Jain, Bramheswar Mishra,Sanjay Singh presented a review article on assessment of solubilization characteristics of different surfactants for carvedilol phosphate as a function of pH. Use of anionic surfactants minimized the pH dependent variation of the drug solubility.Cationic and non-ionic surfactants were found to suitable for enhancing the solubility of Carvedilol phosphate can be employed for maintaining the in vitro sink condition in the basic dissolution medium.[18]

11.E.M. Martin Del Valle presented a review article on cyclodextrin properties and their uses. Cyclodextrin are of three types α,β,γ cyclodextrin referred to as first generation or parent cyclodextrin.α, β and γ cyclodextrin consists of 6,7 & 8 α 1,4 linked glucosyl unit.β cyclodextrin is most accessible lowest price and most useful.Cyclodextrin mainly uses in the cosmetic,personal care, toiletry, food and flavour, pharmaceuticals, agricultural, chemical industries, adhesive ,coatings.[19]

12 Thorsteinn Loftson and Pekka Jaro presented a review article on cyclodextrin in drug delivery. Cyclodextrin consists of hydrophilic outer surface and lipophilic central cavity. Cyclodextrins are able to increase their physical and chemical stability of the drugs in various formulation and reduced the local drug irritation .These are used in oral drug delivery, sublingual drug delivery, pulmonary drug delivery, nasal drug delivery, injectable drug delivery, ophthalmic drug delivery.[4]

13. P.J Salustio,G feio, J.F Pinto, H.M Carbel Marques presented a review article on influence of the preparation methods on inclusion of model drugs in a β-cyclodextrin complexes.The formation of inclusion complex obtained from

different methods related to interaction in aqueous solution and solid state suggested a mechanism of the complexation by inclusion of the drug in a β-cyclodextrin cavity.The kneading process shows the best yield and has less time consuming and shows effective drug release.[20]

14. Varsha Pokharkar et al performed ternary inclusion complex using drug, beta-cyclodextrin and citric acid in the molar ratio 1:2:2. Inclusion complex was prepared by techniques – kneading method and spray drying method. Results of spray dried complex showed better results with significant improvement of solubility compared to other techniques. Stability study was also performed for further 3 months at accelerated conditions resulting in stable complex. They performed phase solubility study and found $A_N$ type of graph resulting to 1:2 inclusion complex. They also performed inclusion efficiency which showed that complexation was much more in spray dried product as compared to others. They concluded that there was no significant change in complexation when tested after 3 months. [21]

# CHAPTER-4

# EXPERIMENTAL WORK

### 4.1 List of Chemials Used:

| Materials | Use | Supplier |
|---|---|---|
| Drugs | Cardiovascular agents | Torrent Pharma Pvt. Ltd, Ahemdabad |
| Beta-cyclodextrins | Complexing agents | Zydus Cadilla Pvt. Ltd, Ahemdabad Industry |
| Avicel PH 102 | Diluent | Sun Pharmaceutics,Baroda |
| Magnesium stearate | Lubricants | Triveni Industry, New Delhi |
| Talc | Glidants | Central drug house. |
| Methanol | Solvent | Central Drug House, |

### 4.2 List of Equipment and Company name:

| Equipments | Company name |
|---|---|
| UV/VIS Double beam spectrophotometer | **S**himadzu Co- orporation |
| FTIR | Jasco FT/IR-6100 |
| Digital pH meter | Analab Scientific Instrument Pvt. Ltd. |
| Tablet dissolution tester(USP) | Electrolab |
| Rotary tablet machine | Rimek Mini Press-1 |
| Weighing balance | Texas Exports Ahemdebad, India |
| Hardness tester | Campbell Electronics |

## 4.3. IDENTIFICATION OF DRUG:

### 4.3.1. MELTING POINT STUDY:

Melting point is the temperature at which the pure liquid and solid exist in the equilibrium. The capillary method of melting point determination was used in the present study. The melting point of carvedilol was found to be 111-112°C.The reported standard range of melting point of carvedilol is 114-115°C.The observed value is very closed to the standard value. This indicates the identity and purity of procured drug sample.

| | |
|---|---|
| Actual melting point | 114-115˚C |
| Observed melting point | 111-112˚C |

**Result:** The melting point of carvedilol was found to be 111-112˚C

**Conclusion**: The melting point determined was within the range of standard value, hence it was concluded that the drug sample having intimate physical property as standard drug.

### 4.3.2. Determination of λmax by UV Spectroscopy:

Drug is official in IP, BP and USP. Determination of λmax of drug was done by UVspectrophotometer using 1.45 pH buffer solution.

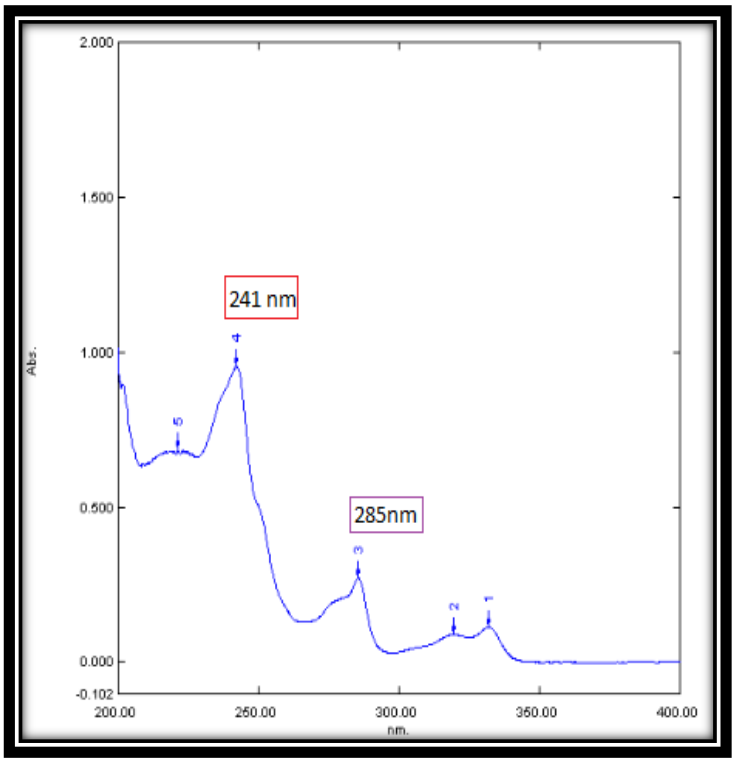



**Fig: 4.1 UV-Spectrum of drugs.**

The above UV Spectrum of Carvedilol showed the maximum wave length at 241 nm.and 284 nm which matches with the reported value.

### 4.3.3. Determination by FTIR Spectroscopy:

IR spectra of drug in KBR pellets was done using FTIR(at moderate scanning speed between 4000-400 $cm^{-1}$). The wave number ($cm^{-1}$) and the possibility of presence of functional groups are shown in figure 4.2 and 4.3

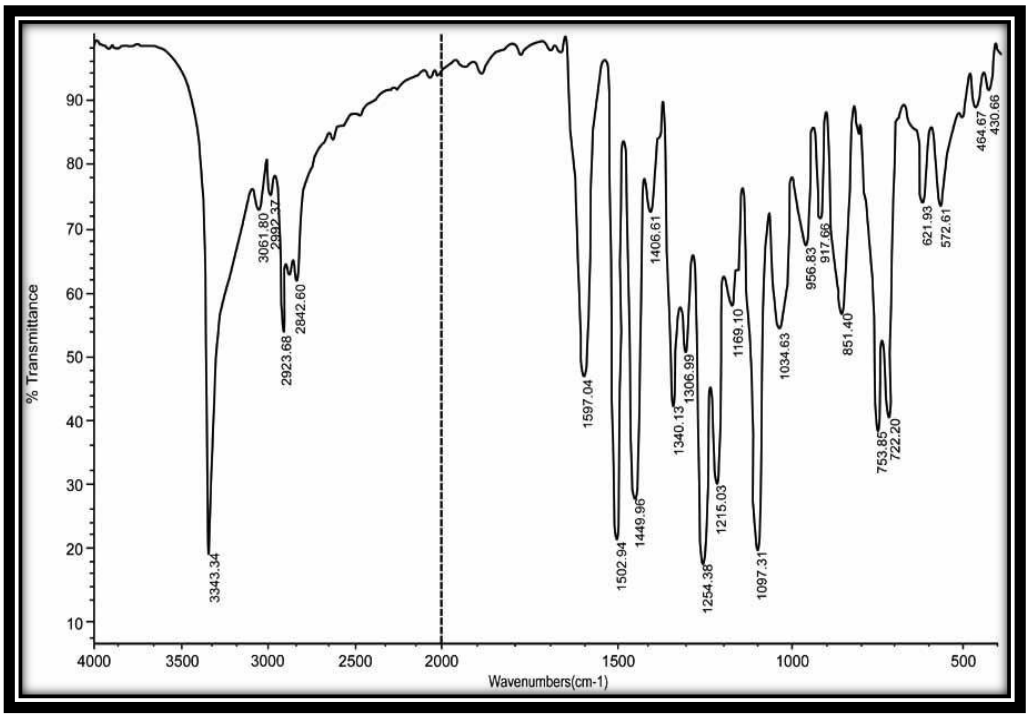



**Figure 4.2.INFRARED SPECTRA OF STANDARD DRUG**

Fig.4.3 Infrared Spectra of pure drugs

**Fig 4.3: IR Peaks of Sample**

| Functional group | Observed Wave number |
|---|---|
| N-H stretching | 3344.93, 1590.99 |
| C-H stretching | 2842.56, 2922.59 |
| O-H stretching | 1504.2 |
| C=O stretching | 1217.83, 1100.19 |

**Result:** The peak values represent wave numbers. The FTIR spectrum of the drug was compared with that of reference spectrum. Both the spectra were found to be almost identical. Thus the drug sample was found to be the Carvedilol.

### 4.3.4. PREPARATION OF STANDARD CURVE:

Weight accurately 10mg of drug and then dissolved in 10ml of 1.45 buffer solution(1000µg/ml).From stock solution different dilutions were prepared from 5-50µg/ml

### 4.3.5 Standard Calibration Curve of Carvedilol at pH 1.45

| Concentration(µg/ml) | Absorbance-I | Absorbance-II | Average |
|---|---|---|---|
| 5 | 0.038 | 0.039 | 0.038 |
| 10 | 0.082 | 0.083 | 0.082 |
| 15 | 0.13 | 0.14 | 0.13 |
| 20 | 0.168 | 0.169 | 0.168 |
| 25 | 0.227 | 0.228 | 0.227 |
| 30 | 0.263 | 0.264 | 0.263 |
| 35 | 0.343 | 0.344 | 0.343 |
| 40 | 0.348 | 0.349 | 0.348 |
| 45 | 0.45 | 0.35 | 0.35 |
| 50 | 0.442 | 0.443 | 0.442 |

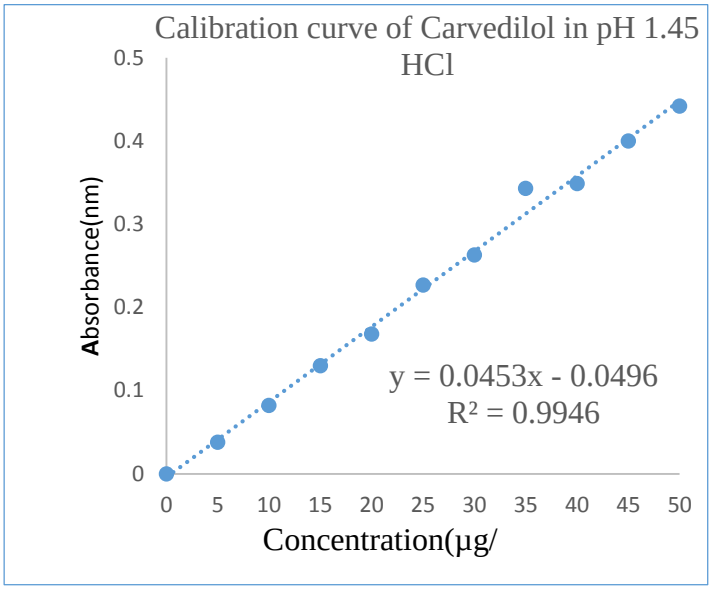



**fig 4.4 :Calibration curve at pH 1.45 buffer solution**

**Regression Analysis: Regression analysis for standard calibration curve of carvedilol phosphate in 1.45 pH buffer solution.**

| **Regression parameter** | **Values** |
|---|---|
| **Correlation coefficient** | **0.9946** |
| **Slope** | **0.0453** |
| **Intercept** | **-0.0496** |

### 4.3.6 Standard Calibration curve of Carvedilol in methanol:

| Concentration (µg/ml) | Absorbance- 1 | Absorbance-2 | Avg. |
|---|---|---|---|
| 5 | 0.085 | 0.086 | 0.085 |
| 10 | 0.153 | 0.154 | 0.153 |
| 15 | 0.273 | 0.274 | 0.274 |
| 20 | 0.389 | 0.388 | 0.388 |
| 25 | 0.425 | 0.426 | 0.425 |
| 30 | 0.579 | 0.578 | 0.578 |
| 35 | 0.663 | 0.664 | 0.663 |
| 40 | 0.72 | 0.73 | 0.73 |
| 45 | 0.881 | 0.882 | 0.882 |
| 50 | 0.915 | 0.916 | 0.915 |

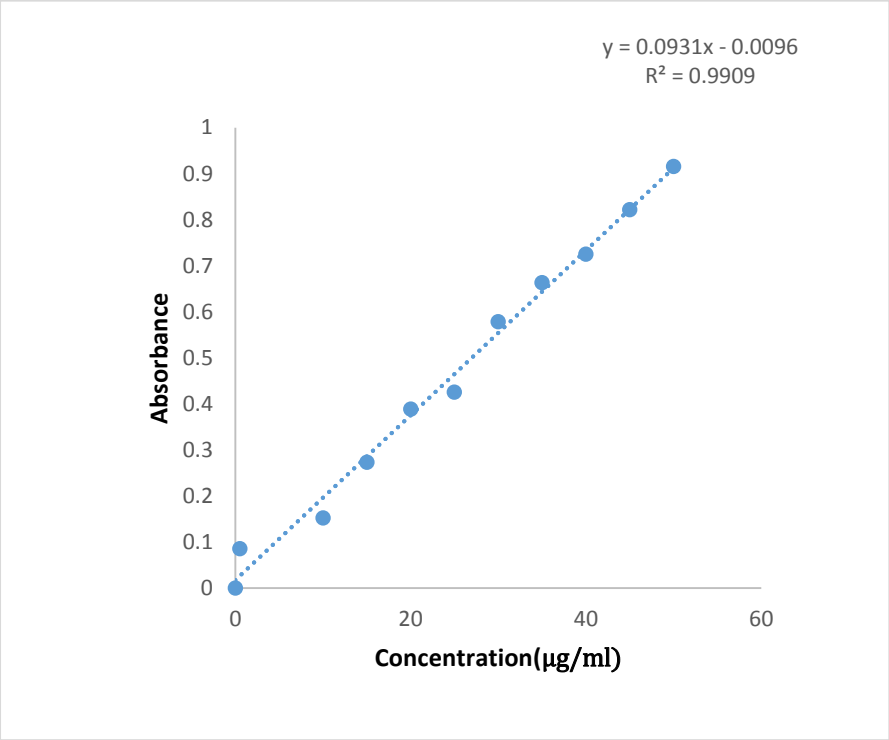



**Fig.4.5 Calibration curve in methanol**

**Regression Analysis:** Regression analysis for std. curve of carvedilol phosphate in methanol.

| **Regression parameter** | **Values** |
|---|---|
| Correlation coefficient | 0.9909 |
| Slope | 0.0931 |
| Intercept | -0.0096 |

## 4.4 Phase Solubility Study:

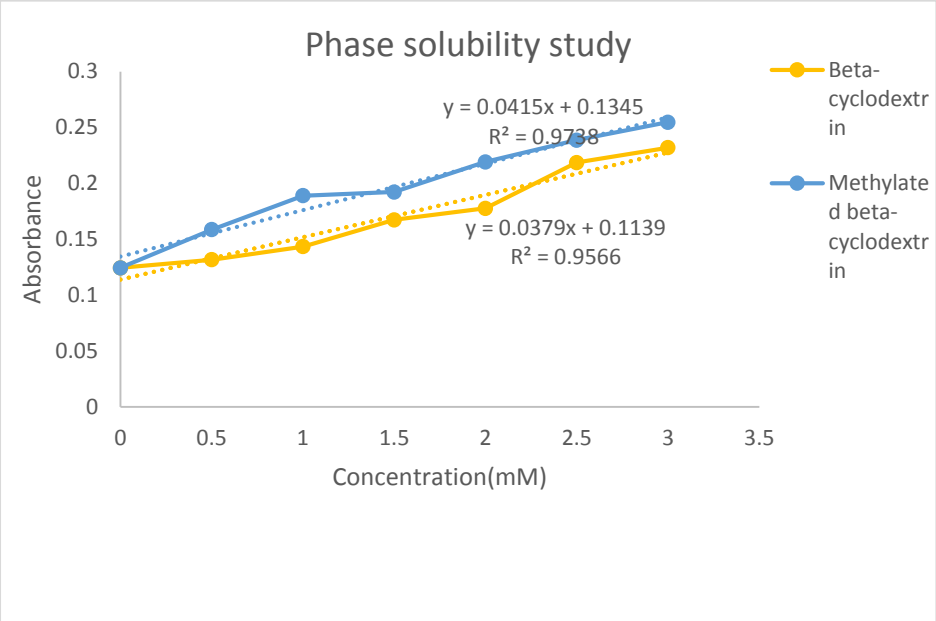
1. Prepare 0-3mMol concentration of β- cyclodextrin in distilled water.
2. Add excess amount of drug in each of the test tubes.
3. Shake these tubes for several hour.
4. Analyze the samples at 284nm using UV spectrophotometer.

### 4.4.1 For Beta- cyclodextrins:

| Concentration(mM) | Absorbance | Concentration of drug | Amount in mg. | Conc.in m Mol /ltr |
|---|---|---|---|---|
| 0 | 0.521 | 10.406 | 50 | 0.1241 |
| 0.5 | 0.535 | 10.715 | 53.576 | 0.1308 |
| 1 | 0.578 | 11.664 | 58.322 | 0.1434 |
| 1.5 | 0.666 | 13.607 | 68.0359 | 0.1670 |
| 2 | 0.794 | 16.432 | 72.257 | 0.2029 |
| 2.5 | 0.855 | 17.779 | 88.894 | 0.2183 |
| 3 | 0.904 | 18.860 | 94.306 | 0.2329 |

### 4.4.2 For methylated Beta-cyclodextrin:

| Concentration (mM) | Absorbance | Concentration of Drug | Amount in mg. | Concentration in mMol/ltr |
|---|---|---|---|---|
| 0 | 0.508 | 10.119 | 50.596 | 0.124 |
| 0.5 | 0.634 | 12.900 | 64.503 | 0.158 |
| 1 | 0.746 | 15.373 | 76.865 | 0.189 |
| 1.5 | 0.758 | 15.637 | 78.189 | 0.192 |
| 2 | 0.857 | 17.823 | 89.116 | 0.219 |
| 2.5 | 0.929 | 19.412 | 97.064 | 0.238 |
| 3 | 0.988 | 20.715 | 103.57 | 0.254 |




According to Higuchi Connor's Equation:

$$K_C = \text{slope}/S_o(1- \text{slope})$$

- **For Beta-CD:**

Slope=0.0379

$S_O$=0.00129

$\mathbf{K_c}$ =Slope/$S_O$(1- Slope)

=0.037/0.00129(1- 0.0379)

=0.037/0.001242

=29.784 $M^{-1}$

- **For methylated Beta-Cyclodextrin**:

Slope=0.0421

$K_c$= Slope/$S_o$(1-Slope)

=0.0421/0.00129(1-0.0421)

=34.06 $M^{-}$

**Result of $K_c$ Value**:

| Complexation | Standard value | Observed value | Result |
|---|---|---|---|
| **1:1** | **50-2000 $M^{-1}$** | **29.784 & 34.06 $M^{-1}$** | **The drug:Beta cyclodextrin complex obeys 1:2 complexation.** |
| **1:2** | **0-50 $M^{-1}$** | | |

**Conclusion**:According to Higuchi and Connor's classification,the phase solubility diagram for the drug and Beta-cyclodextrin inclusion complex can be classified under $A_p$ types phase solubility.

**4.5.Preparation of Inclusion complex by Physical mixing methods:**

**Procedure:**

Wt. accurately drug ,beta-cyclodextrin in ratio of 1:1,1:2 and mix it well in mortar and pestle.

**CALCULATION:**

| | (**Physical mixing(1:1)** | **Physical mixing(1:2)** |
|---|---|---|
| **Drug** | 40.65 | 40.65 |
| **Beta-CD** | 113.4 | 226.8 |

**I)**.**In 1:1 ratio(fig.1)**

154.05mg contains 40.65mg drug

25mg contains 154.05× 25/ 40.65

=94.74mg

II).**In 1:2 ratio(fig.2)**

267.45mg contains 40.65mg

25mg contains 267.45×25/40.65

=164.48mg

## 4.6 Preparation of Inclusion Complex by kneading methods:

### 4.6.1 Procedure:

1. Weight accurately drug and Beta-cyclodextrins in their respective ratio 1:1, 1:2

2. Mix it well in mortar and pestle and moistened with small volume of methanol and water (15:85v/v)

3. Then the mixture was kneaded like paste by addition of little amount of solvent.

4. Paste was dried at room temperature overnight.

5 .Dried mass was carried out for dissolution study.

### 4.6.2 In vitro dissolution profile:

Dissolution study were performed according to the USP paddle methods. For 1:1 molar ratio 94.74 mg of powder and for 1:2 molar ratio 164.74mg of powder were introduced into 900 ml of a dissolution medium having pH 1.45 and maintained at 37± 0.5˚C.The revolution speed of paddle were was kept constant at 50rpm.The aliquot of 5ml sample was withdrawn at 10, 20, 30,45,60,90,120min.and filtered through 0.45 membrane filters. The concentration of carvedilol was determined spectrophotometrically at λmax 284nm and analyzed by using UV-Spectrophotometer.

### 4.6.3. Procedure for preparation of buffer solution:

Dissolve 0.7% (7ml/L) of conc. HCL acid adjusted with 50%w/w of NaoH to a pH of 1.45±0.2

## 4.7. Dissolution study:

### 4.7.1 In-Vitro dissolution study of the pure drugs:

**A. Weight of the pure drugs: 25mg**

**B. Dissolution profile:**

The in-vitro drug dissolution were generated using following conditions:

1. Dissolution apparatus: USP Type II (Paddle types)

2. Medium: 1.45 p H HCL

3. Volume of buffer: 900 ml

4. Rotation: 50 RPM

4. Temperature: 37±0.2˚C

5. Sampling time: 10, 20, 30,45,60,90,120 min.

6. Volume of Sample with drawn: 5ml

7. Sink condition: Maintained

8. λ max: 284 nm

**C. Procedure for preparation of buffer solution:**

Dissolve 0.7% (7ml/L) of HCL acid, adjusted with 50% w/w NaoH to a pH of 1.45± 0.2

**D. % drug release:** Drug release of pure drug is tested in p H 1.45 HCL

| Time (min) | Abs.1 | Abs.2 | Avg | Concn (mcg/ml) | Concn(mg/ml) | Amount in 900ml | % drug release |
|---|---|---|---|---|---|---|---|
| 10 | 0.129 | 0.130 | 0.129 | 3.743 | 0.003 | 3.369 | 13.47 |
| 20 | 0.188 | 0.189 | 0.188 | 3.600 | 0.003 | 3.240 | 12.96 |
| 30 | 0.199 | 0.198 | 0.198 | 4.790 | 0.004 | 4.311 | 17.24 |
| 45 | 0.26 | 0.27 | 0.26 | 5.012 | 0.005 | 4.510 | 18.04 |
| 60 | 0.33 | 0.34 | 0.33 | 6.241 | 0.006 | 5.617 | 22.47 |
| 90 | 0.38 | 0.39 | 0.38 | 7.653 | 0.006 | 6.887 | 22.55 |

**Table:4.7.1**

**Result and discussion:**

The drug release pattern showed that the only 22% of drug was released at 90 minutes.Thus, to enhance the drug release physical mixing was studied at different ratio.

### 4.7.2 In-Vitro dissolution study of the Physical mixture(1:1) A1:

**A. Formulation:**

40.65mg drugs contains- 154.05mg

25mg contains :154.05/40.65×25 = 94.74mg

| Ingredients | Weight (mg) |
|---|---|
| Drugs | 40.65 |
| Beta- cyclodextrins | 113.4 |
| **Total mixture:** | 154.05 |

**B. In-vitro drug dissolution profile:**

| Time | Absorbance | Concn. (µg/ml) | Concn(mg/m | Amount in 900ml | % drug release |
|---|---|---|---|---|---|
| 10 | 0.496 | 9.854 | 0.009 | 8.868 | 35.47 |
| 20 | 0.486 | 9.633 | 0.0096 | 8.670 | 34.68 |
| 30 | 0.442 | 8.662 | 0.0086 | 7.796 | 31.18 |
| 45 | 0.453 | 8.905 | 0.0089 | 8.014 | 32.05 |
| 60 | 0.456 | 8.971 | 0.0089 | 8.074 | 32.29 |
| 90 | 0.48 | 9.501 | 0.0095 | 8.550 | 34.20 |

**Table:4.7.2**

**Result and discussion**: The drug release pattern shows that only 34% of drug was released within 90 minutes.

**4.7.3 In-vitro dissolution study of physical mixture (1:1) A2:**

**A. Formulation: Same as above 4.10.2**

**B. In-vitro dissolution profile:**

| Time | Absorbance | Concn (µg/ml) | Concn (mg/ml) | Amount in 900ml | % drug release |
|---|---|---|---|---|---|
| 10 | 0.263 | 4.7108 | 0.0047 | 4.239 | 16.958 |
| 20 | 0.257 | 4.578 | 0.0045 | 4.120 | 16.482 |
| 30 | 0.326 | 6.101 | 0.0061 | 5.491 | 21.965 |
| 45 | 0.385 | 7.403 | 0.0074 | 6.663 | 26.654 |
| 60 | 0.439 | 8.596 | 0.0085 | 7.736 | 30.945 |
| 90 | 0.508 | 10.119 | 0.0101 | 9.107 | 36.429 |

**Result and discussion:**

The drug release pattern showed that the only 36% of drug was released within 1.5 hrs.

### 4.7.4. In-Vitro dissolution study of physical mixture( 1:2 )A3

**A. Formulation:**

| Ingredients | Weight (mg) |
|---|---|
| Drug | 40.65 |
| Beta- cyclodextrins | 226.8 |
| **Total mixture:** | 267.45 |

**B. In-vitro dissolution profile:**

| **Tim** | **Absorbance** | **Concn. (mcg/ml)** | **Concn (mg/ml)** | **Amount in 900ml** | **% drug release** |
|---|---|---|---|---|---|
| 10 | 0.366 | 6.984 | 0.006 | 6.286 | 25.144 |
| 20 | 0.555 | 11.156 | 0.011 | 10.041 | 40.164 |
| 30 | 0.561 | 11.289 | 0.0112 | 10.160 | 40.641 |
| 45 | 0.588 | 11.885 | 0.0118 | 10.696 | 42.786 |
| 60 | 0.592 | 11.973 | 0.0119 | 10.776 | 43.104 |
| 90 | 0.598 | 12.105 | 0.0121 | 10.895 | 43.581 |

**Table:4.7.4**

**Result and Discussion:**

The drug released pattern showed that by physical mixing ratio only 43.58% of drugs was released.

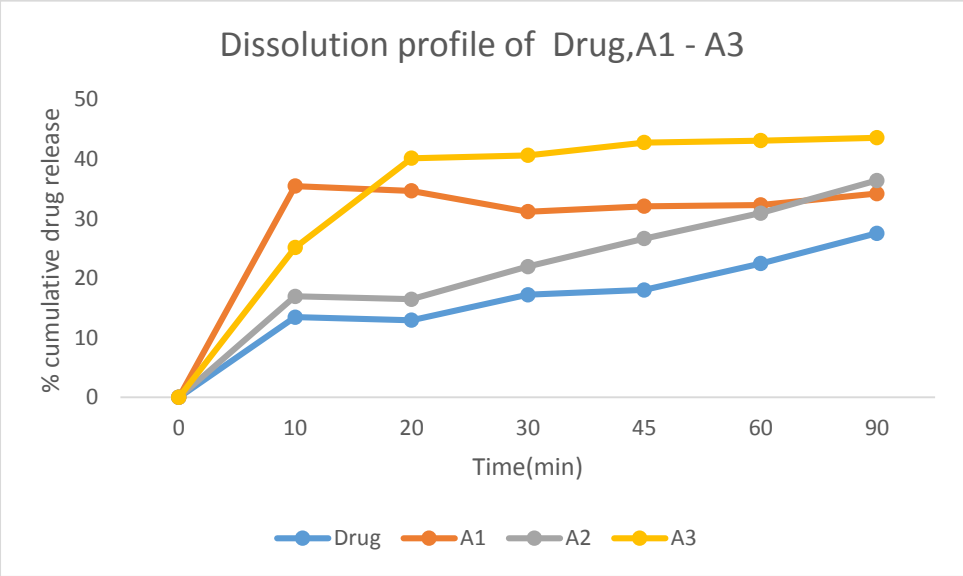



**Fig.4.7 In-vitro drug release of batches drug, A1, A2, A3**

**Conclusion:**

From the above batches of inclusion complex prepared by the physical mixing the % cumulative drug release and inclusion complex. shows good results in A3 as compared to that of pure drug, A1, A2.

## 4.8 Preparation of Inclusion Complex by kneading method:

### 4.8.1 Procedure:

1. Weight accurately drug and Beta-cyclodextrins as per requirements.

2. Mix it well in mortar and pestle and moistened with small volume of ethanol and water (15:85v/v)

3. Then the mixture was kneaded like paste by addition of little amount of the paste.

4. Paste was dried at room temperature for 24 hours.

5. Dried mass was evaluated by dissolution study.

**In-vitro dissolution study**:

The in-vitro drug dissolution profile were generated using following conditions:

1. Dissolution apparatus: USP Type II

2. Medium: 1.45 pH HCL

3. Volume of buffer: 900 ml

4. Temperature: 37±0.2˚C

5. Sampling time: 10, 20, 30, 45, 60, 90 min

6. Volume of Sample with drawn: 5 ml

7. Sink condition: Maintained

8.λ max: 284 nm

9.Rotation: 50 RPM

## 4.9. Comparison of physical mixing with the kneading methods:

### 4.9.1 Physical mixing (1:1)-S1

**A .Formulation:**

| | |
|---|---|
| **Drugs** | **40.65** |
| **Beta-cyclodextrin** | **113.4** |
| **Total:** | **154.05** |

**B. In-Vitro drugs dissolution study:**

| Time | Absorbance | Concentration(mcg/ml) | Concentration (mg/ml) | Amount in 900ml | % Drug release |
|---|---|---|---|---|---|
| 10 | 0.366 | 6.984 | 0.006 | 6.286 | 25.144 |
| 20 | 0.555 | 11.156 | 0.0111 | 10.041 | 40.164 |
| 30 | 0.561 | 11.289 | 0.01128 | 10.160 | 40.641 |
| 45 | 0.588 | 11.885 | 0.0118 | 10.696 | 42.786 |
| 60 | 0.592 | 11.973 | 0.011 | 10.776 | 43.104 |
| 90 | 0.598 | 12.105 | 0.012 | 10.895 | 43.581 |

**Result and Discussion:**

The drug released pattern showed that by physical mixing ratio only 43.58% of drugs was released.

### 4.9.2. Physical mixing (1:2)-S2

**A. Formulation: Same**

**B. In-Vitro drug dissolution study:**

| Time | Absorbanc | Concn(mcg/ml) | Conc (mg/ml) | Amount in 900ml | %drug release |
|---|---|---|---|---|---|
| 10 | 0.595 | 12.039 | 0.0120 | 10.835 | 43.343 |
| 20 | 0.606 | 12.282 | 0.0122 | 11.054 | 44.217 |
| 30 | 0.617 | 12.525 | 0.012 | 11.272 | 45.091 |
| 45 | 0.623 | 12.657 | 0.012 | 11.392 | 45.568 |
| 60 | 0.628 | 12.768 | 0.0127 | 11.491 | 45.965 |
| 90 | 0.643 | 13.099 | 0.0130 | 11.789 | 47.157 |

**Result and Discussion:**

The drug released pattern showed that by physical mixing ratio 1:2only 47.58% of drugs was released.

### 4.9.3. Kneading methods (1:2)-S3

**A. Formulation: Same**

**B. In-vitro drug dissolution study:**

| Time | Absorbance | Conc (mcg/ml) | Conc (mg/ml) | Amount in 900ml | %drug release |
|---|---|---|---|---|---|
| 10 | 0.588 | 11.885 | 0.0118 | 10.696 | 42.786 |
| 20 | 0.619 | 12.569 | 0.0125 | 11.312 | 45.250 |
| 30 | 0.618 | 12.547 | 0.01254 | 11.292 | 45.170 |
| 45 | 0.629 | 12.790 | 0.0127 | 11.511 | 46.045 |
| 60 | 0.659 | 13.452 | 0.0134 | 12.107 | 48.429 |
| 90 | 0.695 | 14.247 | 0.0142 | 12.8225 | 51.290 |

**Result and Discussion:**

The drug released pattern showed that by Kneading methods in ratio of 1:2only 51.290 % of drugs was released

### 4.9.4 Kneading method(1:2)-S4

**A. Formulation: Same**

**B. In-vitro drug dissolution study:**

| Time | Absorbance | Conc (mcg/ml) | Conc (mg/ml) | Amount in 900ml | % drug release |
|---|---|---|---|---|---|
| 10 | 0.778 | 16.079 | 0.0160 | 14.4718 | 57.88 |
| 20 | 0.818 | 16.962 | 0.0162 | 15.267 | 61.064 |
| 30 | 0.819 | 16.984 | 0.0167 | 15.282 | 61.144 |
| 45 | 0.84 | 17.448 | 0.0174 | 15.706 | 62.813 |
| 60 | 0.839 | 17.426 | 0.0174 | 15.6831 | 62.738 |
| 90 | 0.84 | 17.448 | 0.0174 | 15.7036 | 62.813 |

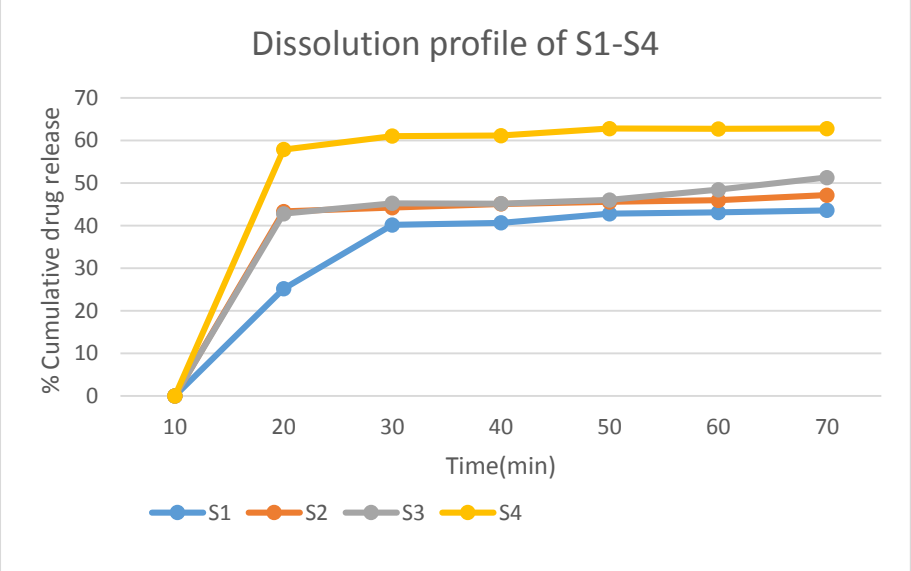



**Fig.4.8 In-vitro drug release of batches S1, S2, S3, S4**

**Conclusion:**

From the comparative in-vitro dissolution profile of inclusion complexes it was concluded that:

1. Complexation with beta CD increases drug dissolution.
2. Kneading method is better than physical mixing.
3. 1:2 drug to β- CD ratio is require for solubility enhancement
4. S3 and S4 by kneading methods in ratio of 1:2 shows higher dissolution profile.

### 4.10. Effect of kneading time:

### 4.10.1. Kneading time (5min)-B1

### A. Formulation: Same as 1:2 ratio

### B. In-vitro Dissolution profile:

| Time | Abs.1 | Abs.2 | Avg | Conc(mcg/ml) | Conc(mg/ml) | Amount in 900ml | % drug release |
|---|---|---|---|---|---|---|---|
| 10 | 0.33 | 0.37 | 0.35 | 6.63 | 0.006 | 5.968 | 23.87 |
| 20 | 0.38 | 0.39 | 0.39 | 7.51 | 0.007 | 6.76 | 27.05 |
| 30 | 0.44 | 0.49 | 0.46 | 9.05 | 0.009 | 8.15 | 32.61 |
| 45 | 0.55 | 0.58 | 0.56 | 11.26 | 0.011 | 10.14 | 40.56 |
| 60 | 0.58 | 0.59 | 0.59 | 11.92 | 0.011 | 10.73 | 42.94 |
| 90 | 0.62 | 0.64 | 0.63 | 12.81 | 0.012 | 11.53 | 46.12 |

**Table:4.7.1**

**Result and Discussion:**

The drug released pattern showed that by Kneading time of 5 min.only 46.3% of drugs was released

### 4.10.2. Kneading time (10min)- B2

**A .Formulation: Same as 1:2 ratio**

**B. In-vitro Dissolution profile:**

| Time | Absorbance | Concn. (µg/ml) | Concn. (mg/ml) | Amount in 900ml | %drug release |
|---|---|---|---|---|---|
| 10 | 0.366 | 9.174 | 0.0091 | 8.256 | 33.02 |
| 20 | 0.478 | 11.6468 | 0.01164 | 10.482 | 41.92 |
| 30 | 0.558 | 13.4128 | 0.01341 | 12.071 | 48.28 |
| 45 | 0.574 | 13.766 | 0.01376 | 12.389 | 49.55 |
| 60 | 0.589 | 14.097 | 0.01409 | 12.687 | 50.74 |
| *90* | *0.596* | *14.251* | *0.014* | *12.82* | 51.30 |

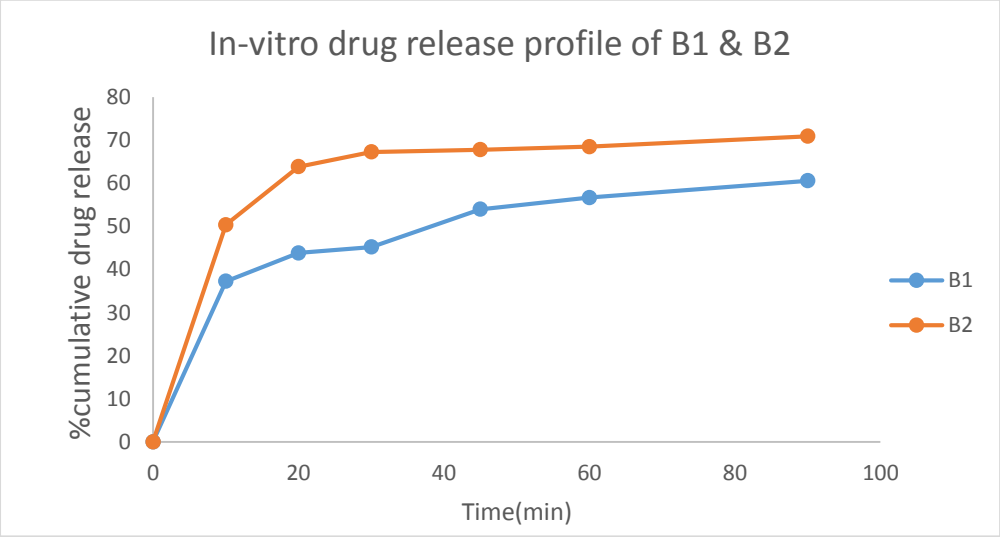



**Fig:4.9 In-vitro drug release profile of B1 and B2**

**Conclusion:** It was concluded that 10 mins kneading is require for better inclusion complexation formation

## .4.11. Effect of solvent for kneading:

### 4.11.1. Effect of solvent as Water (A5)

| | |
|---|---|
| Kneading time: | 10 Minutes |

**A.Formulation(1:2)**

| Ingredients | Weight |
|---|---|
| Drugs | 40.65 mg |
| Beta- cyclodextrins | 226.8 mg |
| Water | 2ml |
| Total | 267.8 mg |

**B. In-vitro Dissolution Profile:**

| Time | Absorbance | Conc(µg/ml) | Conc(mg/ml) | Amount in 900ml | % drug release |
|---|---|---|---|---|---|
| 10 | 0.672 | 13.759 | 0.013 | 12.383 | 49.533 |
| 20 | 0.675 | 13.821 | 0.138 | 12.439 | 49.756 |
| 30 | 0.672 | 13.739 | 0.013 | 12.365 | 49.462 |
| 45 | 0.675 | 13.814 | 0.013 | 12.433 | 49.732 |
| 60 | 0.676 | 13.830 | 0.013 | 12.447 | 49.788 |
| 90 | 0.676 | 13.843 | 0.0138 | 12.458 | 49.835 |

**Table:4.11.1**

**Result and Discussion:**

The drug released pattern showed that by effect of water only 49.83% of drugs was released

### 4.11.2. Effect of solvent as methanol (A6)

A. **Formulation:**

| **Ingredients** | **Weight** |
|---|---|
| Drugs | 40.65 mg |
| Beta- cyclodextrins | 226.8 mg |
| Methanol | 2ml |
| Total | 267.8 mg |

**B.% Drug release**:

| Time | Absorbance | Conc(µg/ml) | Conc(mg/ml) | Amount in 900ml | %drug release |
|---|---|---|---|---|---|
| 10 | 0.4195 | 8.165 | 0.0081 | 7.349 | 29.39 |
| 20 | 0.502 | 9.986 | 0.0099 | 8.98 | 35.95 |
| 30 | 0.519 | 10.373 | 0.0103 | 9.33 | 37.34 |
| 45 | 0.63 | 12.812 | 0.0128 | 11.53 | 46.12 |
| 60 | 0.664 | 13.573 | 0.0135 | 12.21 | 48.86 |
| 90 | 0.7135 | 14.655 | 0.0146 | 13.190 | 52.76 |

**Table:4.11.2**

**Result and Discussion:**

The drug released pattern showed that in effect of solvent as methanol only 52.76% of drug was released.

### 4.11.3. Effect of solvent water: methanol as ratio 85:15(A7)

| | |
|---|---|
| **Kneading time** | **10 minutes** |

**A. Formulation:**

**B. Dissolution medium: Same**

| Ingredients | Weight |
|---|---|
| Drugs | 40.65 mg |
| Beta- cyclodextrins | 226.8 mg |
| Water: Methanol | 85:15 ratio- 1ml |
| Total | 267.8mg |

**C. % drug release:**

| Time | Absorbance | Conc(mcg/ml) | Conc(mg/ml) | Amount in 900ml | % drug release |
|---|---|---|---|---|---|
| 10 | 0.778 | 16.079 | 0.0160 | 14.471 | 57.8860 |
| 20 | 0.818 | 16.962 | 0.0169 | 15.266 | 61.064 |
| 30 | 0.819 | 16.984 | 0.0169 | 15.286 | 61.144 |
| 45 | 0.84 | 17.448 | 0.0174 | 15.703 | 62.813 |
| 60 | 0.839 | 17.426 | 0.0174 | 15.683 | 62.733 |
| 90 | 0.86 | 17.889 | 0.0174 | 15.703 | 64.813 |

**Table:4.11.3**

**Result and Discussion:**

The drug released pattern showed that in effect of solvent water:methanol shows only 64.813% of drug was released

### 4.11.4. Effect of solvent water: methanol as ratio 85:15(A8)

| | |
|---|---|
| Kneading time: | 10 minutes |

**A.Formulation:**

| | |
|---|---|
| Drugs | 40.65 mg |
| Beta- cyclodextrins | 226.8 mg |
| Water: Methanol | (85:15) -2ml |
| Total | 267.8mg |

**B.In-vitro Drug release:**

| Time | Abs.1 | Concn.(mcg/ml) | Concn(mg/ml) | Amount in 900ml | % drug Release |
|---|---|---|---|---|---|
| 10 | 0.641 | 13.055 | 0.0130 | 11.749 | 46.998 |
| 20 | 0.744 | 15.328 | 0.0153 | 13.796 | 55.181 |
| 30 | 0.756 | 15.593 | 0.0155 | 14.034 | 56.137 |
| 45 | 0.76 | 15.682 | 0.0156 | 14.113 | 56.455 |
| 60 | 0.76 | 15.682 | 0.0156 | 14.1139 | 56.455 |
| 90 | 0.89 | 18.551 | 0.01852 | 16.6966 | 66.786 |

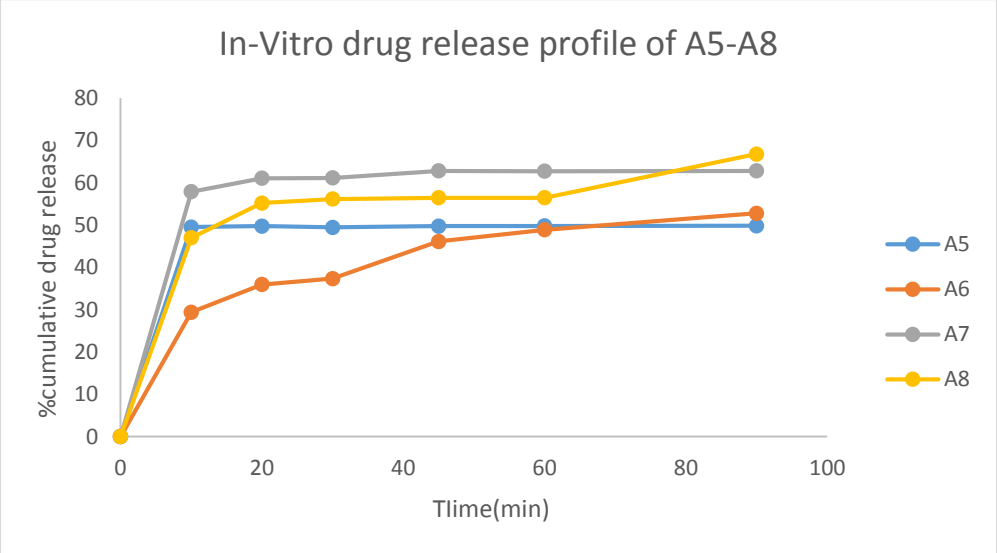



**Fig: 4.10 In-vitro drug release profile of batches A5-A8**

**Conclusion:**

From the comparative in-vitro dissolution profile of inclusion complexes it was concluded that batch A7&A8 showed higher drug release and hence water: methanol (85:15) was selected as solvent.

### 4.12. Effect of ethanol as organic solvents:

### 412.1. Effect of solvent water: methanol as ratio 85:15(A7)

| | |
|---|---|
| Kneading time | 10 minutes |

**Formulation:**

| **Ingredients** | **Weight** |
|---|---|
| Drugs | 40.65 |
| Beta- cyclodextrins | 226.8 |
| Water: Methanol | (85:15)-1ml |
| Total | 267.8 |

**B. In-vitro dissolution profile:**

| **Time** | **Absorbance** | **Conc(mcg/ml)** | **Conc(mg/ml)** | **Amount in 900ml** | **%drug release** |
|---|---|---|---|---|---|
| 10 | 0.778 | 16.079 | 0.0160 | 14.471 | 57.886 |
| 20 | 0.818 | 16.962 | 0.0169 | 15.266 | 61.0649 |
| 30 | 0.819 | 16.984 | 0.0169 | 15.286 | 61.144 |
| 45 | 0.84 | 17.448 | 0.0174 | 15.703 | 61.813 |
| 60 | 0.839 | 17.4260 | 0.0174 | 15.683 | 62.733 |
| 90 | 0.84 | 17.448 | 0.0174 | 15.703 | 64.813 |

**Table:4.12.1**

**Result and Discussion:**

The drug released pattern showed that in effect of solvent water:methanol in 1ml shows only 64.813% of drug was released.

### 4.12.2Effect of solvent water: methanol as ratio 85:15(A8)

**A. Formulation:**

| **Ingredients** | **Weight** |
|---|---|
| Drugs | 40.65 |
| Beta- cyclodextrins | 226.8 |
| Water: Methanol | (85:15)-2ml |
| Total | 267.48 |

**B.In-vitro dissolution profile:**

| time | Abs.1 | Concn(mcg/ml) | Conc(mg/ml) | Amount in 900ml | % drug release |
|---|---|---|---|---|---|
| 10 | 0.641 | 13.055 | 0.0130 | 11.749 | 46.99 |
| 20 | 0.744 | 15.328 | 0.0153 | 13.796 | 55.18 |
| 30 | 0.756 | 15.593 | 0.015 | 14.034 | 56.13 |
| 45 | 0.76 | 15.682 | 0.015 | 14.113 | 56.45 |
| 60 | 0.76 | 15.68 | 0.015 | 14.11 | 56.45 |
| 90 | 0.89 | 18.55 | 0.018 | 16.69 | 66.78 |

**Table:4.12.2**

**Result and Discussion:**

The drug released pattern showed that in effect of solvent water:methanol at 75:15 in 2ml shows only 66.78% of drug was released.

### 4.12.3 Effect of solvent water: ethanol as ratio 75:15(A9)

**A. Formulation**:

| **Ingredients** | **Weight** |
|---|---|
| Drugs | 40.65 |
| Beta- cyclodextrins | 226.8 |
| Water: ethanol | (75:15)-2ml |
| Total | 267.8 |

**B.In-vitro dissolution profile**

| Time | Abs.1 | Conc.(mcg/ml) | Conc(mg/ml) | Amount in 900ml | % drug release |
|---|---|---|---|---|---|
| 10 | 0.527 | 10.538 | 0.010 | 9.484 | 37.93 |
| 20 | 0.662 | 13.518 | 0.0135 | 12.166 | 48.667 |
| 30 | 0.635 | 12.922 | 0.012 | 11.630 | 46.52 |
| 45 | 0.59 | 11.929 | 0.0119 | 10.73 | 42.94 |
| 60 | 0.71 | 14.578 | 0.014 | 13.120 | 52.48 |
| 90 | 0.72 | 14.799 | 0.0147 | 13.319 | 53.276 |

**Result and Discussion:**

The drug released pattern showed that in effect of solvent water:ethanol at 75:15 shows only 66.78% of drug was released

### 4.12.4 Effect of solvent water: ethanol as ratio 85:15 (A10)

| | |
|---|---|
| Kneading time | 10 minutes |

**A.Formulation:**

| **INGREDIENTS** | **QTY** |
|---|---|
| Drugs | 40.65 |
| Beta- cyclodextrins | 226.8 |
| Water:ethanol | (85:15)-2ml |
| Total | 267.48 |

**B.In-vitro dissolution profile:**

| Time | Abs. | Conc(mcg/ml) | Conc(mg/ml) | Amount in900ml | % release |
|---|---|---|---|---|---|
| 10 | 0.499 | 9.920 | 0.0099 | 8.928 | 35.713 |
| 20 | 0.588 | 11.885 | 0.0118 | 10.69 | 42.786 |
| 30 | 0.589 | 11.907 | 0.0119 | 10.716 | 42.866 |
| 45 | 0.686 | 14.048 | 0.0140 | 12.643 | 50.574 |
| 60 | 0.718 | 14.754 | 0.0147 | 13.279 | 53.117 |
| 90 | 0.798 | 16.520 | 0.0165 | 14.868 | 59.475 |

Table:4.12.4

**Result and Discussion:**

The drug released pattern showed that in effect of solvent water:ethanol at 85:15 shows only 59.46 % of drug was released

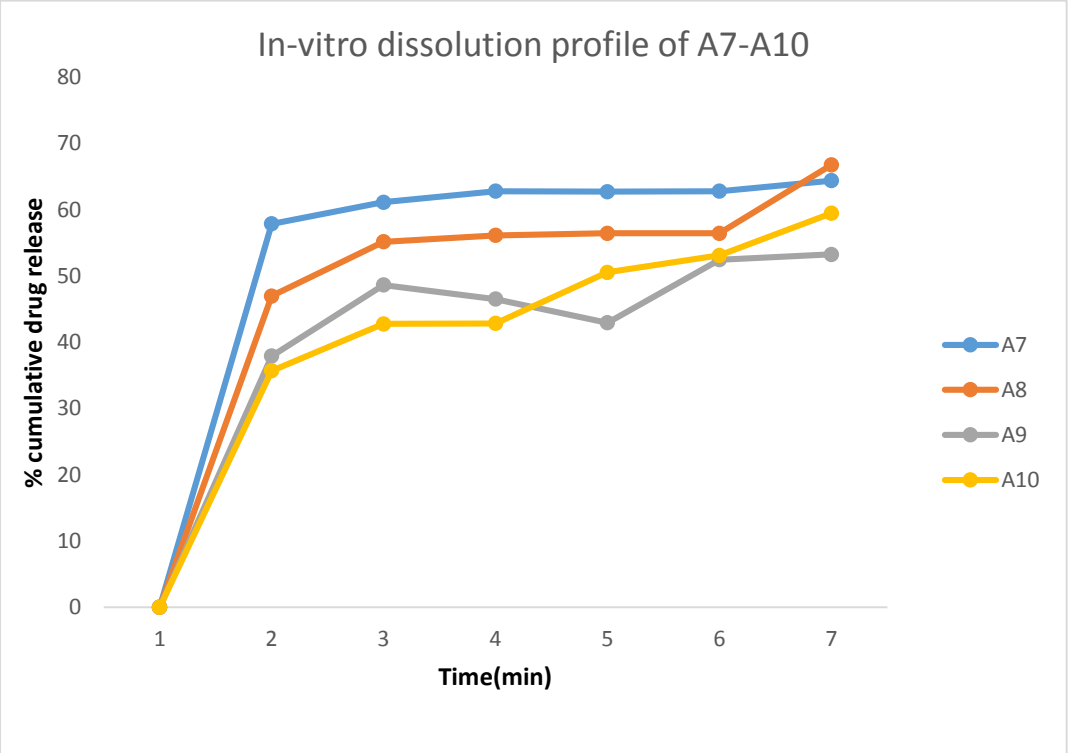



**Fig4.11: In-vitro drug release profile of batches A7-A10**

Conclusion:

It was observed that batch A7and A8prepared using (water: methanol) in ratio of 85:15 showed higher drug dissolution hence water: methanol was selected as solvent.

## 4.13 Volume of Solvent:

### 4.13.1Effect of volume of the solvent-1ml (A11)

| | |
|---|---|
| Kneading time | 10 min |

**A. Formulation:**

| | |
|---|---|
| Drug | 40.65 |
| Beta-cyclodextrin | 226.8 |
| Water: Methanol | (75:25)-1ml |
| Total | 267.48 |

**B.In-vitro dissolution profile:**

| Time | Abs.1 | Abs.2 | Avg. | Conc(µg/ml) | Conc(mg/ml) | Amount in 900ml | % drug release |
|---|---|---|---|---|---|---|---|
| 10 | 0.59 | 0.56 | 0.575 | 11.59 | 0.011 | 10.43 | 41.75 |
| 20 | 0.63 | 0.611 | 0.620 | 12.60 | 0.012 | 11.342 | 45.36 |
| 30 | 0.653 | 0.688 | 0.670 | 13.70 | 0.013 | 12.335 | 49.34 |
| 45 | 0.667 | 0.677 | 0.672 | 13.73 | 0.013 | 12.365 | 49.46 |
| 60 | 0.689 | 0.679 | 0.684 | 14.004 | 0.0140 | 12.603 | 50.415 |
| 90 | 0.679 | 0.699 | 0.689 | 14.114 | 0.014 | 12.703 | 50.81 |

**Result and Discussion:**

The drug released pattern showed that in effect of volume of solvent 1ml shows only 50.81% of drug was released

### 4.13.2. Effect of volume of solvent 2ml-(A12)

**Kneading time-10 min**

**A. Formulation:**

| Ingredients | Wt.(mg) |
|---|---|
| Drugs | 40.65 |
| Beta- cyclodextrins | 226.8 |
| Water: Methanol | (85:15)-2ml |
| Total | 267.8 |

**B.In-vitro dissolution profile:**

| Time | Abs.1 | Abs.2 | Avg. | Conc.(µg/ml) | Conc.(mg/ml) | Amount in 900ml | %drug release |
|---|---|---|---|---|---|---|---|
| 10 | 0.569 | 0.567 | 0.568 | 11.443 | 0.011 | 10.299 | 41.19 |
| 20 | 0.63 | 0.64 | 0.635 | 12.922 | 0.012 | 11.630 | 46.52 |
| 30 | 0.653 | 0.655 | 0.654 | 13.341 | 0.013 | 12.007 | 48.03 |
| 45 | 0.667 | 0.769 | 0.718 | 14.754 | 0.014 | 13.279 | 53.11 |
| 60 | 0.789 | 0.799 | 0.794 | 16.432 | 0.016 | 14.789 | 59.15 |
| 90 | 0.789 | 0.7884 | 0.7891 | 16.324 | 0.016 | 14.692 | 58.76 |

**Table:4.13.2**

**Result and Discussion:**

The drug released pattern showed that in effect of volume of solvent 2ml shows only 58.81% of drug was released

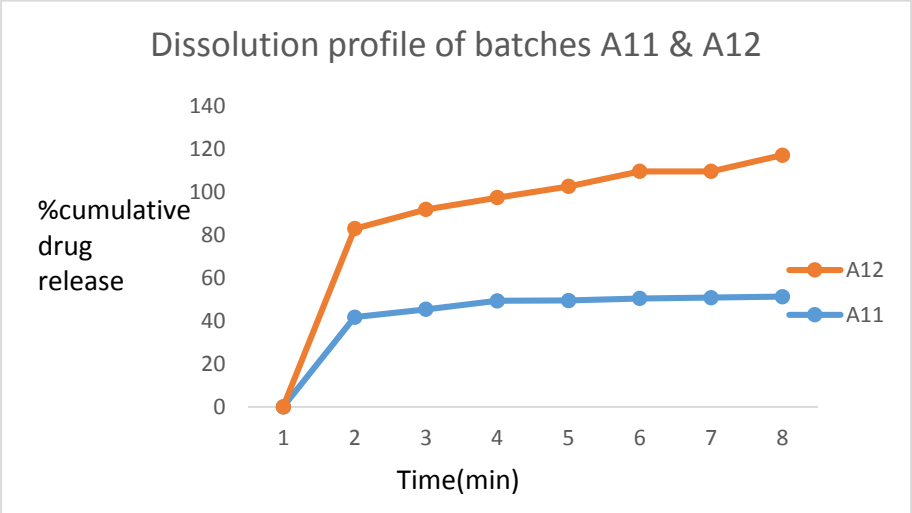



**Fig.4.12: In-vitro drug release profile of batches A11 and A12**

**Conclusion:**

From the comparative in-vitro dissolution profile of inclusion complexes it was concluded that the drug release profile of batches A12 was higher compared to that of A11 and hence 2 mL volume was finalized for kneading.

## 4.14. Solvent addition:

### 4.14.1 EFFECT OF SOLVENT ADDITION:

**(DRUG+METHANOL+WATER+BETA-CD) - A13**

**Kneading time: 10 min.**

**A. Formulation:**

| Ingredients | Weigh |
|---|---|
| Drugs | 40.65 |
| Beta- cyclodextrins | 226.8 |
| Water: methanol | (15:85)-2 ml |
| Total | 267.45 |

**Procedure:**

In this batches all the ingredients was mixed directly in the mortar and pestle. It was kneaded for 10 min with the addition of solvent.

**B. Dissolution media: same as above**

**C.In-vitro dissolution release:**

| Tim | Abs1 | Abs.2 | Avg | Con. (mcg/ml) | Conc.(mg/ml) | Amount in 900ml | %release |
|---|---|---|---|---|---|---|---|
| 10 | 0.43 | 0.47 | 0.453 | 11.105 | 0.0159 | 9.995 | 39.981 |
| 20 | 0.538 | 0.59 | 0.56 | 13.638 | 0.0136 | 12.270 | 49.080 |
| 30 | 0.644 | 0.69 | 0.671 | 15.913 | 0.0159 | 14.326 | 57.305 |
| 45 | 0.71 | 0.78 | 0.75 | 17.681 | 0.0176 | 15.915 | 63.663 |
| 60 | 0.78 | 0.79 | 0.79 | 18.589 | 0.0185 | 16.730 | 66.921 |
| 90 | 0.72 | 0.74 | 0.73 | 17.275 | 0.0172 | 15.54 | 67.193 |

**Result and Discussion:**

The drug released pattern showed that in effect of solvent addition directly shows only 67.193% of drug was released

**4.14.2Effect of solvent was added in to drug and then Beta-cyclodextrins was added: (A14)**

A.**Formulation:**

| **INGREDIENTS** | **QTY.** |
|---|---|
| Drugs | 40.65 mg |
| Beta- cyclodextrins | 226.8 mg |
| Water: methanol | (15:85)-2 ml |

Procedure:

In this batches drugs was added in the mortar pestle and then Beta-cyclodextrin was added in a little amount with a addition of small amount of solvent and kneaded for 10 minutes. Again the complete beta-cyclodextrin was added by trituration in mortar and pestle**.**

**B.% drug release:**

| Time | Abs.1 | Abs.2 | Avg | conc.(mcg/ml) | conc.(mg/ml) | Amount in*900ml | % release |
|---|---|---|---|---|---|---|---|
| 10 | 0.728 | 0.639 | 0.639 | 13.011 | 0.0139 | 12.594 | 50.376 |
| 20 | 0.72 | 0.85 | 0.85 | 17.668 | 0.0176 | 15.901 | 63.887 |
| 30 | 0.726 | 0.888 | 0.888 | 18.507 | 0.0185 | 16.656 | 67.277 |
| 45 | 0.728 | 0.89 | 0.89 | 18.55 | 0.0185 | 16.696 | 67.807 |
| 60 | 0.73 | 0.894 | 0.894 | 18.640 | 0.0186 | 16.776 | 68.498 |
| 90 | 0.729 | 0.92 | 0.92 | 19.214 | 0.0192 | 17.292 | 70.949 |

**Fig:4.14.2**

## Result and Discussion:

The drug released pattern showed that when these ingredients added indirectly shows only 70.93% of drug was released

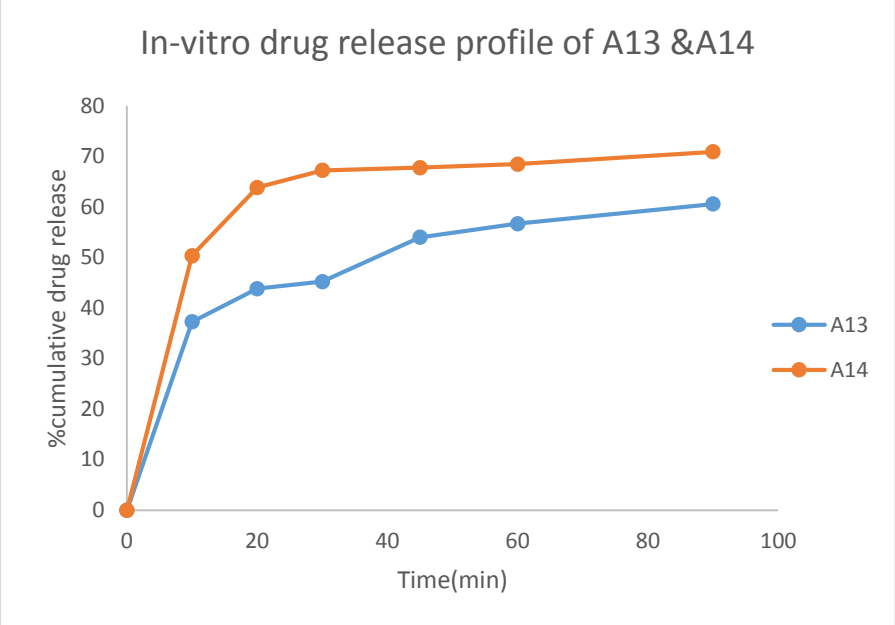



**Fig: 4.13 In-vitro drug release profile of batches A13 and A14**

**Conclusion:**

It was observed that order of addition plays an important role. When solvent was added into drug, it dissolves drug well and hence better inclusion occurs.

### 4.15. Effect of HPMC

### 4.15.1. Effect of HPMC by indirect methods: A17

**A. Formulation:**

| INGREDIENTS | QTY |
|---|---|
| Drugs | 40.65 mg |
| Beta- cyclodextrins | 226.8 mg |
| Water: methanol | (15:85 )-2 ml |
| HPMC | 40.65 mg |

**Procedure:** In this the drug was added and then beta-cyclodextrin in a small amount in the mortar and pestle with addition of solvent and kneaded for 10 minutes.

**B.In-vitro dissolution profile:**

| Time | Abs-1 (without dilution) | Abs-1 with dilution) | Avg. | mcg/ml (without dilution) | mcg/ml (with dilution) | Conc(mg/ml) | Amount in 900ml | % drug release |
|---|---|---|---|---|---|---|---|---|
| 10 | 0.896 | 0 | 0.896 | 18.684 | - | 0.018 | 16.815 | 67.26 |
| 20 | 0.925 | 0 | 0.925 | 19.32 | - | 0.019 | 17.392 | 69.568 |
| 30 | 0.986 | 0 | 0.986 | 20.67 | - | 0.020 | 18.603 | 74.415 |
| 45 | 0.995 | 0 | 0.995 | 20.86 | - | 0.020 | 18.782 | 75.131 |
| 60 | 0.51 | 2 | 0.51 | 10.16 | 20.326 | 0.020 | 18.294 | 78.176 |
| 90 | 0.59 | 2 | 0.59 | 11.92 | 23.858 | 0.0238 | 21.472 | 85.891 |

**Fig.4.15.2**

## Result and Discussion:

The drug released pattern showed that when these ingredients added indirectly shows only 85.83% of drug was released

**4.15.2. Effect of HPMC by direct methods**:-A 18

**A. Formulation**:

| Ingredients | Weight |
|---|---|
| Drugs | 40.65 mg |
| Beta- cyclodextrins | 226.8 mg |
| Water: methanol | (15:85)-2 ml |
| HPMC | 40.65 mg |

**Procedure:**

In this all the ingredients was added in the mortar and pestle with addition of solvent and kneaded for 10 minutes.

**B. In-vitro Dissolution profile:**

| Time | Abs 1 | Avg | Conc.(mcg/ml) | Concn(mg/ml) | Amount in 900ml | % release |
|---|---|---|---|---|---|---|
| 10 | 0.85 | 0.85 | 17.668 | 0.0176 | 15.901 | 63.607 |
| 20 | 0.867 | 0.867 | 18.044 | 0.0180 | 16.2397 | 64.958 |
| 30 | 0.881 | 0.881 | 18.353 | 0.0183 | 16.517 | 66.0715 |
| 45 | 0.898 | 0.898 | 18.728 | 0.0187 | 16.854 | 67.422 |
| 60 | 0.927 | 0.927 | 19.368 | 0.0193 | 17.431 | 69.727 |
| 90 | 0.958 | 0.958 | 20.052 | 0.0200 | 18.047 | 72.190 |

Fig:4.15.2

## Result and Discussion:

The drug released pattern showed that when these ingredients added directly shows only 72.190% of drug was released

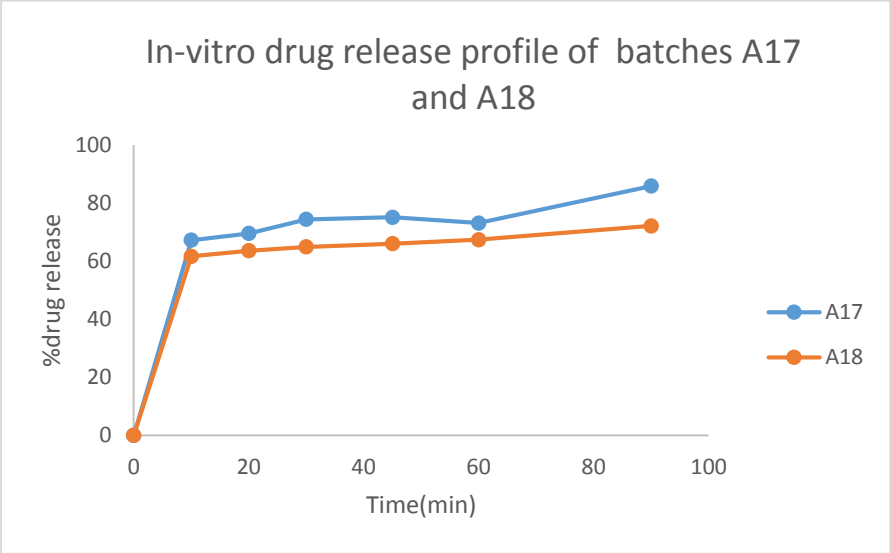



**Fig:4.14 In-vitro drug release profile of batches A17 and A18**

**Conclusion**:

From the complete in-vitro dissolution profile it was concluded that the A17 has higher drug release profile than A18.

## 4.16.Effect of HPMC and PVP K-30:

## 4.16.1..Effect of HPMC By direct mixing(A19)

**A. Formulation** (1:2:1.5)

| **Ingredients** | **QTY** |
|---|---|
| Drugs | 40.65 mg |
| Beta- cyclodextrins | 226.8 mg |
| Water: methanol | (15:85 )-2 ml |
| HPMC | 60.97 mg |

**Procedure:**

In this all the ingredients was added in the mortar and pestle with addition of solvent and kneaded for 10 minutes.

**B. % Drug release:**

| **Time** | **Abs 1** | **Avg** | **mcg/ml** | **mg/ml** | **Amount in 900ml** | **% drug release** |
|---|---|---|---|---|---|---|
| 10 | 0.84 | 0.85 | 17.66 | 0.0176 | 15.901 | 63.60 |
| 20 | 0.86 | 0.867 | 18.044 | 0.018 | 16.23 | 64.95 |
| 30 | 0.88 | 0.881 | 18.35 | 0.018 | 16.51 | 66.07 |
| 45 | 0.89 | 0.898 | 18.72 | 0.018 | 16.85 | 67.42 |
| 60 | 0.92 | 0.927 | 19.36 | 0.019 | 17.43 | 69.72 |
| 90 | 0.95 | 0.958 | 20.05 | 0.02 | 18.04 | 71.190 |

## Result and Discussion:

The drug released pattern showed that when HPMC added directly shows only 71.190% of drug was released

## 4.16.2. Effect of PVP K-30 by direct mixing(A20)

**I .Formulation**(1:2:1.5)

| **Ingredients** | **QTY** |
|---|---|
| Drugs | 40.65 mg |
| Beta- cyclodextrins | 226.8 mg |
| Water: methanol | (15:85) -2 ml |
| PVP K30 | 60.97 mg |

Procedure:

In this all the ingredients was added in the mortar and pestle with addition of solvent and kneaded for 10 minutes.

**II.% DRUG RELEASE:**

| **Time** | **Abs.1** | **Conc.(mcg/ml** | **Conc.(mg/ml** | **Amount in 900ml** | **%release** |
|---|---|---|---|---|---|
| 10 | 0.641 | 13.05 | 0.013 | 11.74967 | 46.99 |
| 20 | 0.744 | 15.32 | 0.015 | 13.79603 | 55.18 |
| 30 | 0.756 | 15.59 | 0.015 | 14.03444 | 56.13 |
| 45 | 0.76 | 15.68 | 0.015 | 14.11 | 56.45 |
| 60 | 0.76 | 15.68 | 0.015 | 14.11 | 56.45 |
| 90 | 0.89 | 18.55 | 0.018 | 16.69 | 60.78 |

## Result and Discussion:

The drug released pattern showed that when PVP K-30 added directly shows only 60.78% of drug was released

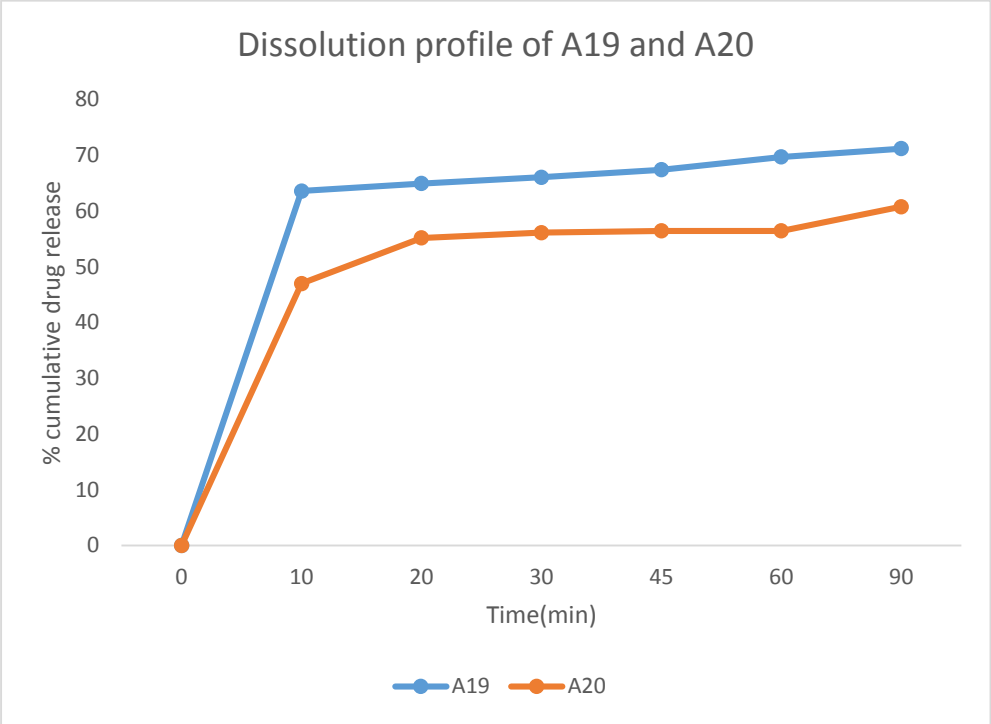



Fig:4.15 In-vitro drug release profile of batches A19 and A20

Conclusion:

Hence,drug release profile of A19 has higher drug release than A20.Hence, HPMC is selected for the drug release profile.

## 4.17.Effect of HPMC by direct mixing for tablets(A21):

### A.Formulation:

| INGREDIENTS | QTY |
|---|---|
| Drugs | 40.65 mg |
| Beta- cyclodextrins | 226.8 mg |
| Water: methanol | 15:85 -2 ml |
| HPMC | 40.65 mg |

### B.Procedure:

In this all the ingredients was added in the mortar and pestle with addition of solvent and kneaded for 10 minutes.

C . % Drug release:

| Time | Abs.1 | Abs.2 | Avg. | Conc(mcg/ml) | Conc(mg/ml) | Amount in 900ml | % drug release |
|---|---|---|---|---|---|---|---|
| 10 | 0.36 | 0.327 | 0.3435 | 6.487 | 0.0064 | 5.83 | 23.35 |
| 20 | 0.551 | 0.538 | 0.5445 | 10.924 | 0.010 | 9.83 | 39.32 |
| 30 | 0.66 | 0.69 | 0.675 | 13.805 | 0.013 | 12.42 | 49.700 |
| 45 | 0.72 | 0.79 | 0.755 | 15.57 | 0.015 | 14.01 | 56.05 |
| 60 | 0.81 | 0.86 | 0.835 | 17.33 | 0.017 | 15.60 | 62.41 |
| 90 | 0.83 | 0.89 | 0.86 | 17.88 | 0.0178 | 16.10 | 64.40 |

Table.4.17.

## 4.18.Comparison of the marketed with the prepared tablets:

### 4.18.1.In-vitro Dissolution of the tablets(A22):

A.Formulation:

| S.No | Formulation | Qty in mg. | For6 tablets |
|---|---|---|---|
| 1. | Complex | 164.48mg | 987mg |
| 2. | MCC(Avicel) | 126.52mg | 760mg |
| 3. | Talc | 6mg | 36mg |
| 4. | Magnesium stearate | 3mg | 18mg |
| | TOTAL | 300mg | 1800mg |

B.Procedure:

All the ingredients were mixed together and the tablets were manufactured in a rotary tablet machine.

C.In-vitro dissolution profile:

| Time | ABS.1 | ABS.2 | Avg | Conc.(mcg/ml) | Conc.(mg/ml) | Amount in 900ml | % drug release |
|---|---|---|---|---|---|---|---|
| 10 | 0.27 | 0.29 | 0.28 | 5.08 | 0.0050 | 4.577 | 18.309 |
| 20 | 0.42 | 0.43 | 0.425 | 8.28 | 0.0086 | 7.458 | 29.833 |
| 30 | 0.51 | 0.56 | 0.535 | 10.71 | 0.0107 | 9.64 | 38.574 |
| 45 | 0.58 | 0.52 | 0.55 | 11.04 | 0.0110 | 9.941 | 39.769 |
| 60 | 0.61 | 0.65 | 0.63 | 12.81 | 0.0128 | 11.531 | 46.125 |
| 90 | 0.89 | 0.87 | 0.88 | 18.33 | 0.0186 | 16.49 | 65.992 |

Table:4.18.1

## 4.18.2.**Marketed Products of the tablets(A23)-**

A.In-vitro dissolution of the marketed products

| **Time** | **Abs** | **Abs** | **Avg.** | **Conc. (mcg/ml)** | **Conc (mg/ml)** | **Amount in 900ml** | **% drug release** |
|---|---|---|---|---|---|---|---|
| 10 | 0.41 | 0.46 | 0.44 | 8.66 | 0.008 | 7.796 | 31.18 |
| 20 | 0.61 | 0.64 | 0.63 | 12.83 | 0.012 | 11.55 | 46.20 |
| 30 | 0.80 | 0.74 | 0.77 | 16.02 | 0.016 | 14.42 | 57.68 |
| 45 | 0.80 | 0.77 | 0.78 | 16.28 | 0.016 | 14.66 | 58.64 |
| 60 | 0.8 | 0.79 | 0.79 | 16.53 | 0.016 | 14.87 | 59.51 |
| 90 | 0.82 | 0.80 | 0.81 | 16.87 | 0.016 | 15.18 | 60.74 |

Result and Discussion:

In-vitro drug release profile of the prepared tablets was compared with the marketed products.Hence, it was concluded that the prepared tablets has higher drug release profile than the marketed products.

Comparison of the marketed products with the prepared tablets:

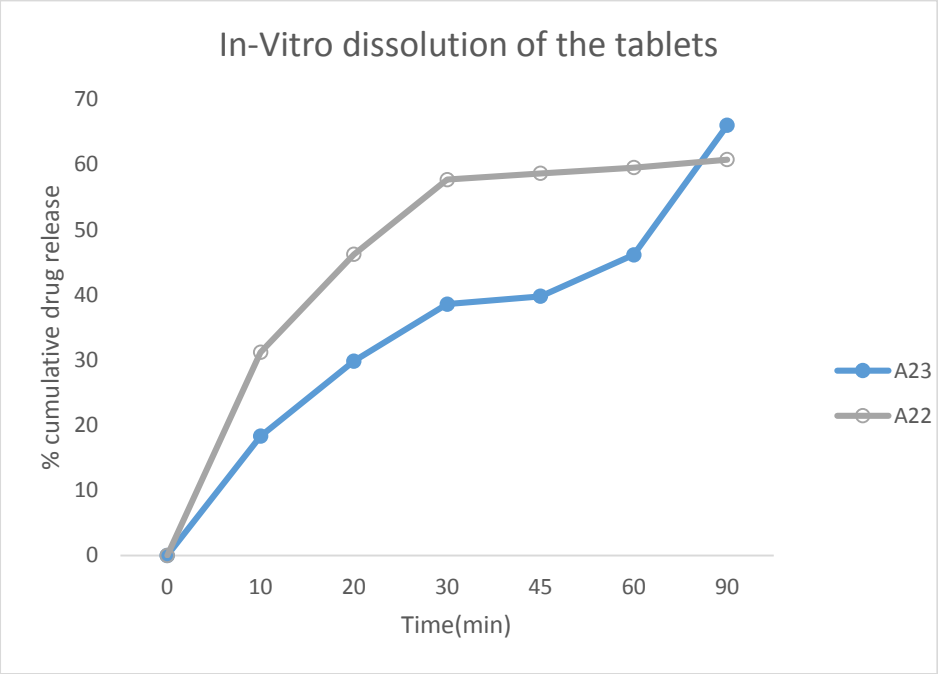



**Fig: 4.16 Comparison of marketed products with prepared tablets.**

Result and Discussion:

Hence, from in-vitro dissolution of the tablets it was found that the prepared tablets has higher drug release than the marketed products of the tablets. Therefore, A22 has higher drug release profile than A23.

## 4.19.Tablet properties:

The prepared tablets were evaluated for hardness, thickness and friability test.

- **HARDNESS:**

The crushing strength of the tablets was measured using Pfizer Hardness tester.

- **Friability:**

Friability was measured using Roche friabilator (Electrolab).Five pre-weighed tablets were rotated at 100 rpm.The tablets were then re-weighed and the percentage of weight loss was calculated.

| **Properties** | **I** | **II** | **Avg.** |
|---|---|---|---|
| 1.Hardness | 21.24kg/cm$^2$ | 29.29kg/cm$^2$ | 25.29kg/cm$^2$ |
| 2.Diameter | 6.48mm | 6.34mm | 6.31mm |
| 3.Thickness | 4.13mm | 3.99mm | 4.07mm |

Table:4.19

## 4.20 Evaluation of the Best batches:

### I).Infrared Spectroscopy(FTIR):

Infrared absorption spectra was obtained on KBR disks , under static air using an FTIR spectrophotometer. The final batches of 1:2:1 ratio of drug, Beta-cyclodextrin and HPMC.

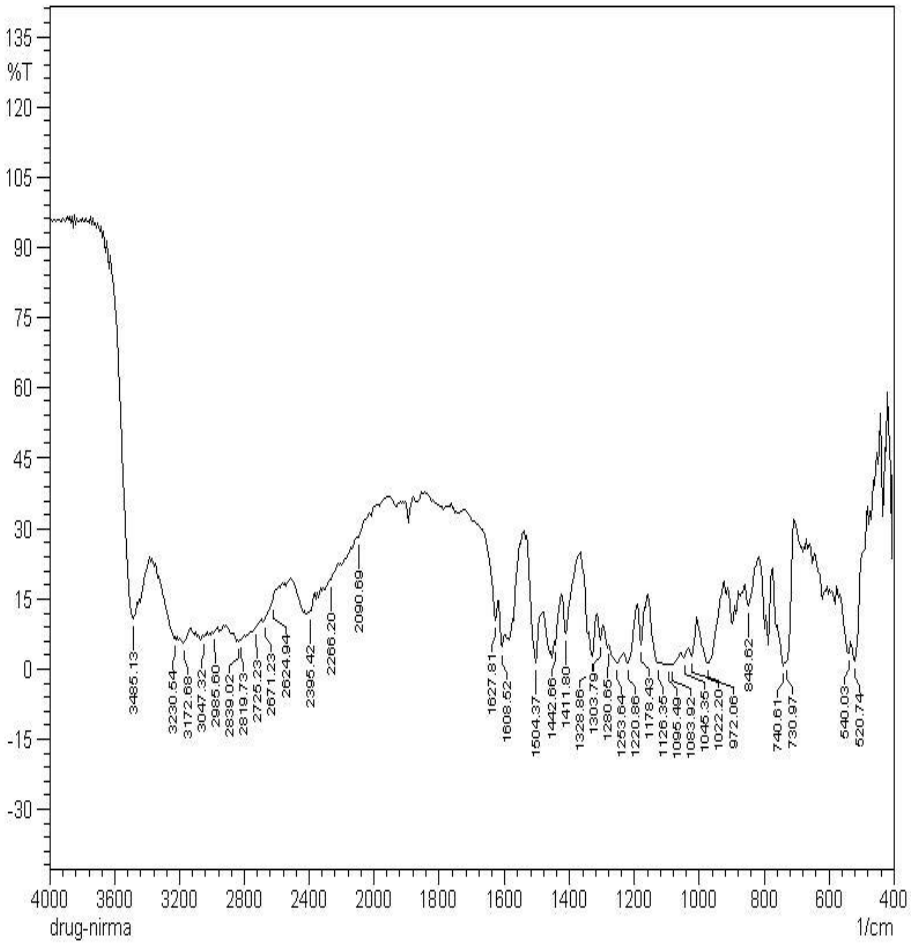



**Fig.4.17 FTIR SAMPLE OF STANDARD DRUG.**

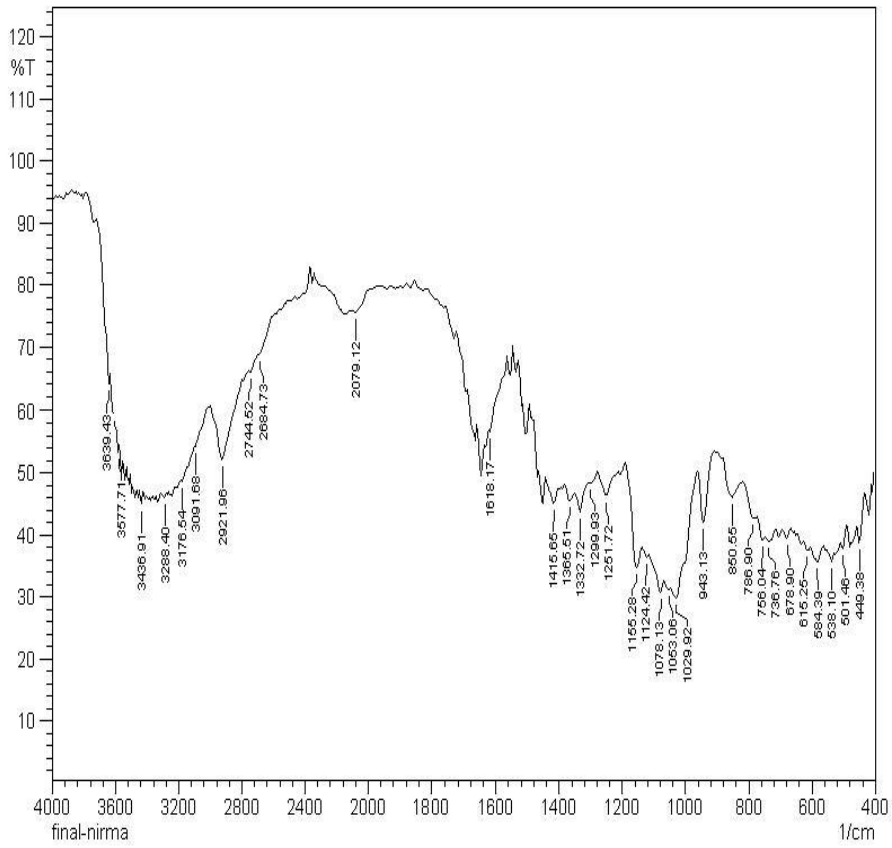



**Fig.4.18 FTIR Sample of final batches ratio of 1:2:1**

**Result:**

The peak values represent wave numbers. The FTIR spectrum of the drug was compared with that of final product of drug-Beta-cyclodextrin-HPMC. Both the spectra were not found to be almost at same wavelength. Thus, the final product of ratio 1:2:1 proves that the complexation has occurred.

## ii).DSC (DIFFRACTION SCANNING COLORIMETRY):

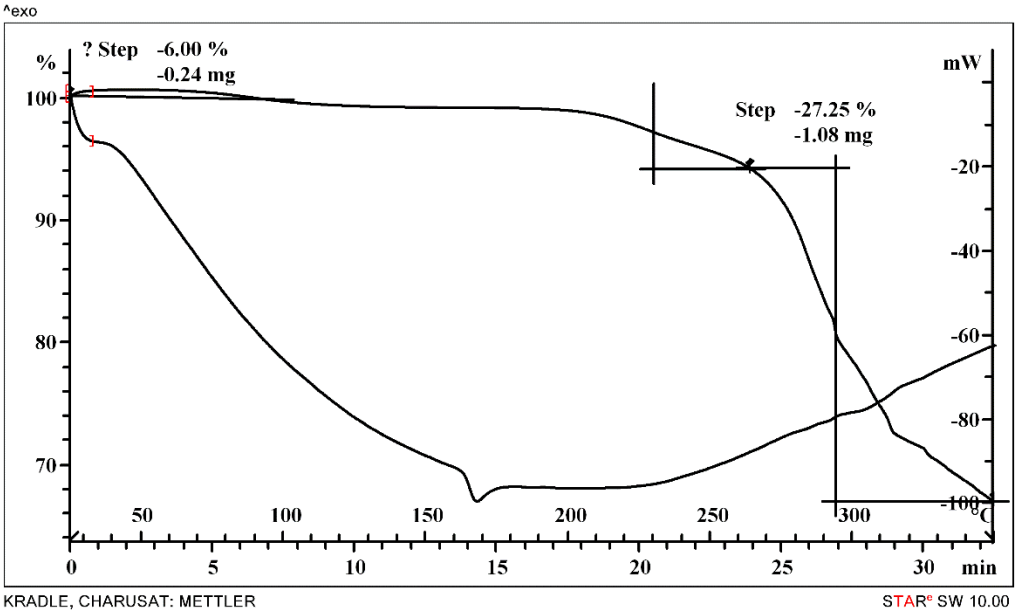



**Fig4.19 DSC OF THE PURE DRUG**

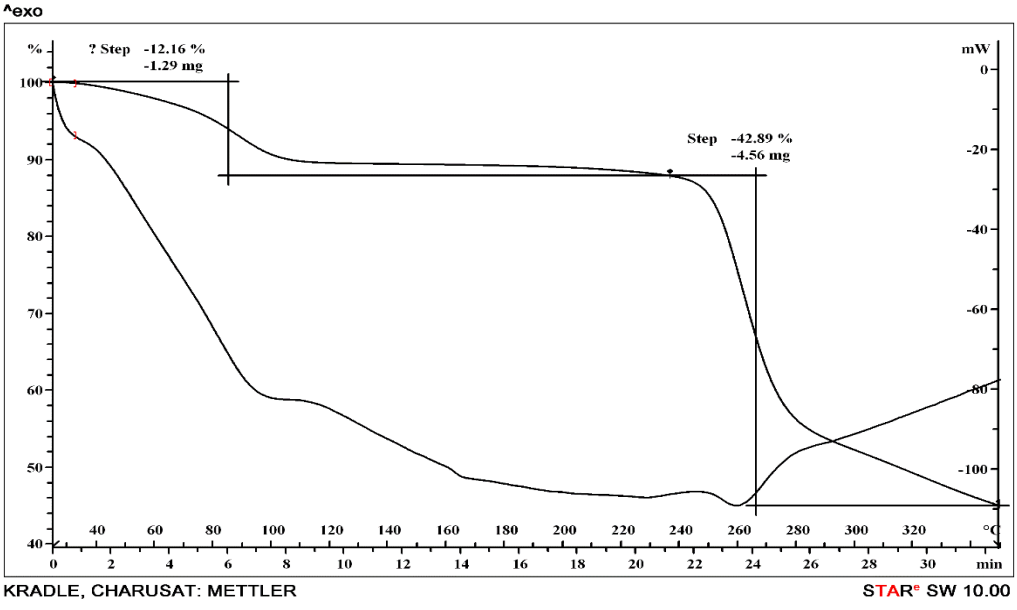



**Fig.4.20 DSC OF THE FINAL BATCHES OF RATIO 1:2:1**

**Conclusion:**

From the DSC results it is concluded that as the characteristic melting point peak is seen in between 150-200˚C in the pure drugs but it is not seen in the fig.4.20 which indicates that the crystalline form of drug might be changed to amorphous form which might enhance the solubility.

## III)XRD (X-RAY Diffraction)

# Chapter-5

# SUMMARY

## SUMMARY:

Carvedilol is an anti-hypertensive drugs which is multiple action adrenergic receptor blocker with alpha-1, Beta-1, Beta-2, Adrenergic receptor blockade properties. When it is given orally it is rapidly absorbed and it is extensively metabolized in liver, half-life of carvedilol is 7-10 hrs. Carvedilol is a BCS Class-II drugs having low bio-availability of 40-42% .It has a p H dependent solubility in range of 4-6 which results in poor bio-availability after oral administration.Thus, to overcome the issue of solubility various solubility enhancement techniques are used.

Different solubility enhancement techniques were used such as physical mixing, kneading methods According to Higuchi and Connor's equation for phase solubility study Ap type of graph was obtained and based on calculation equilibrium constant 1:2 was resulted. .Kneading methods were best as compared to physical mixing methods.The variable change in the kneading methods was the effect of the solvent addition, effect of kneading time, effect of types of solvent, effect of volume of liquids, effect of addition of other hydrophilic materials.Evaluation parameter was in-vitro dissolution profile. From the results it was concluded that 1:2:1 ratio with kneading time 10 minutes, inclusion batch was found to be optimum as it showed highest inclusion efficiency and % drug release. In this ratio of drug, β-cycodextrin, HPMC in ratio of 1:2:1 were used. In this the highest dissolution profile of 85% were obtained by indirect mixing methods i.e. drugs, Beta-cyclodextrin, HPMC. Then, the tablets were manufactured in ratio of 1:2:1 and in-vitro dissolution profile was compared with the marketed products. Tablets showed acceptation parameters and improve dissolution rate when compared to marketed product and pure drug. Thus, it can be concluded that complexation can successfully be used for solubility enhancement of hydrophobic drugs.

# CHAPTER-6

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