AN ATTEMPT TO ENHANCE SOLUBILITY OF METOCLOPROMIDE BASE DRUG BY SOLID DISPERSION TECHNIQUE AND ITS USE OF THESE SOLID DISPERSION IN THE PREPERATION OF TRANSDERMAL FILM.

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NONDITA GHOSH

Roll No. 001411402001

Registration No. 129101 of 2014-15

DEPARTMENT OF PHARMACEUTICAL TECHNOLOGY

FACULTY OF ENGINEERING AND TECHNOLOGY

JADAVPUR UNIVERSITY

KOLKATA - 700032

INDIA.

JADAVPUR UNIVERSITY

KOLKATA-700032

Title of the thesis

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Name, Designation & institution of the supervisor:

Dr. (Mrs.) Jasmina Khanam

Professor

Department of Pharmaceutical Technology

Jadavpur University

Kolkata-700 032, India.

DEPARTMENT OF PHARMACETICAL TECHNOLOGY
FACULTY OF ENGINEERING AND TECHNOLOGY
JADAVPUR UNIVERSITY

CERTIFICATE OF APPROVAL

This is to certify that the thesis entitled ''**An attempt to enhance solubility of Metoclopromide base drug by solid dispersion technique and its use of these solid dispersion in the preparation of transdermal film**'' Submitted by **Nondita Ghosh**, of Jadavpur University is absolutely based upon her own work under the supervision of **Dr. Jasmina Khanam**, Professor, Department of Pharmaceutical Technology, Jadavpur University, Kolkata and that neither her thesis nor any part of the thesis has been submitted for any degree/diploma or any other academic award anywhere before.

(Signature of Project Guide)

Prof. (Dr.) Jasmina Khanam

Department of Pharmaceutical Technology,

Jadavpur University, Kolkata – 700 032.

(Signature of Head of the Department)

Prof. (Dr.) Biswajit Mukherjee

Department of Pharmaceutical Technology

Jadavpur University, Kolkata-700 032.

(Signature of Dean)

Prof. Sivaji Bandyopadhyay

Faculty of Engineering and Technology

Jadavpur University, Kolkata- 700 032.

DECLARATION BY THE CANDIDATE

I do hereby declare that the work incorporated in the thesis entitled ‘‘An attempt to enhance solubility of Metoclopromide base drug by solid dispersion technique and its use of these solid dispersion in the preparation of transdermal film**.**’’ has been carried out by me in the Department of Pharmaceutical Technology, Jadavpur University under the supervision of **Dr. Jasmina Khanam, Professor**, Department of Pharmaceutical Technology, Jadavpur University, Kolkata – 700032. Neither the thesis nor any part therefore has been submitted for any other degree.

Date: Signature of the candidate

Place: Kolkata, India **(NONDITA GHOSH)**

Dedicated to My Family and My Guide

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Date: NONDITA GHOSH

PREFACE

The present thesis work entitled ‘‘An attempt to enhance solubility of Metoclopromide base drug by solid dispersion technique and its use of these solid dispersion in the preparation of transdermal film.’’ deals with the development of controlled release dosage form (transdermal film) of poorly water soluble drugs in order to improve bioavailability and to control drug release for a longer period. Solid Dispersion Method was used to improvement of poorly water soluble drug Metoclopromide base.

The introduction part of the thesis (Chapter 1) describes important features of solubility enhancement by solid dispersion technique, the concept of transdermal drug delivery systems. Chapter 2 represents a careful selection and presentation of recent published works related to the present topic of work. The aims and objectives of this work are laid sequentially and logically in Chapter 3. Chapter 4 consists of the modification of Metoclopramaide HCl to Metoclopramaide base form, preparation of solid dispersion by various hydrophilic carriers, experimental analysis of physicochemical properties of drug and its solid dispersions, formulation of transderml film by pure drug and its solid dispersion and ex-vivo study of the patches. The conclusions drawn from the entire work are detailed in Chapter 5. Chapter 6 gives a comprehensive list of references cited in the text.

List of Abbreviations

MET	Metoclopromide
HPβCD	Hydroxypropyl Beta cyclodextrin
PVP	Polyvinyl pyrrolidone
PLX	Poloxamer
SD	Solid dispersion
PM	Physical mixture
FTIR	Fourier Transform Infrared Spectroscopy
DSC	Differential Scanning Calorimetry
SS	Stirring speed
HLB	Hydrophilic-Lipophilic Balance
Std. Dev	Standard deviation
C.V.	Coefficient of variation
Rpm	Revolution per minute
Rel	Release
Equiv	Equivalent
K_c	Complexation constant
ΔG	Gibbs free energy change
ΔH	Enthalpy change
ΔS	Entropy change
ρ	Density of liquid
η	Viscosity of liquid

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Chapter 1

INTRODUCTION

INTRODUCTION

For many decenniums, various medicinal dosage forms like tablets, capsules, liquids, injectables, ointments, creams, suppositories, aerosols are used for the treatment of acute and chronic diseases. Drugs are rarely administered as pure chemical substances alone and are almost always given as formulated preparations or medicines. These can vary from relatively simple solutions to complex drug delivery systems through the use of appropriate additives or excipients in the formulations. The excipients provide varied and specialized pharmaceutical functions. The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large-scale manufacture with reproducible product quality. To ensure product quality, numerous features are required: chemical and physical stability, with suitable preservation against microbial contamination if appropriate, uniformity of dose of drug, acceptability to users, including both prescriber and patient, as well as suitable packaging and labeling. Ideally, dosage forms should also be independent of patient-to-patient variation. Dosage forms can be designed for administration by alternative delivery routes to maximize therapeutic response. The absorption pattern of drugs varies considerably between individual drug substances as well as between the different administration routes. Dosage forms are designed to provide the drug in a suitable form for absorption from each selected route of administration. In figure 1.1 and figure 1.2 are shown the route of administration and the pathway of drug to reach systemic circulation to the respective dosage forms.

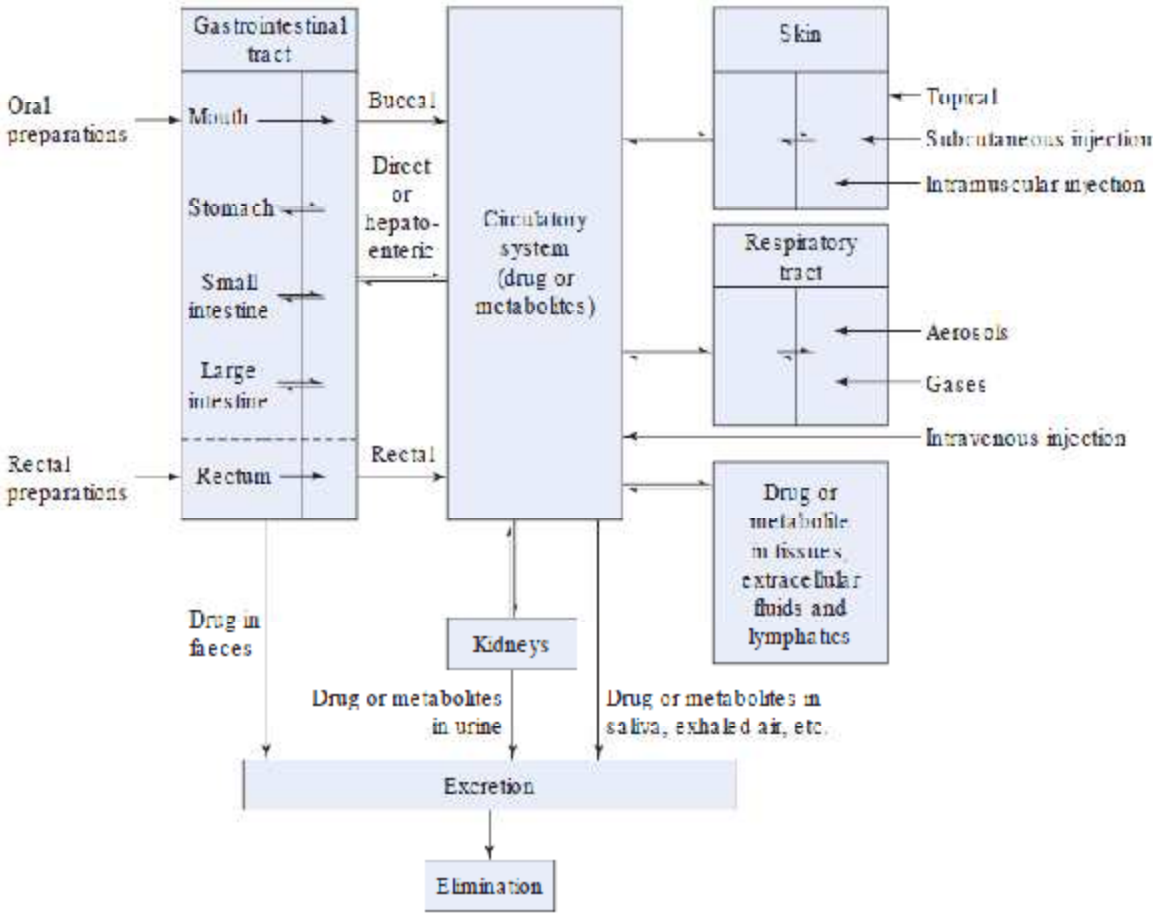


Figure:1.1. Pathways a drug may take following the administration of a dosage form by different routes

Dosage forms can thus be listed in order of time of onset of therapeutic effect (Table 1.2). However, all drugs irrespective of their delivery route remain foreign substances to the human body and distribution, metabolic and elimination processes commence immediately following drug absorption until the drug is eliminated from the body via the urine, feces, saliva, skin or lungs in unchanged or metabolized form. (Aulton, fourth edition).

Administration route	Dosage forms
Oral	Solutions, syrups, suspensions, emulsions, gels, powders, granules, capsules, tablets
Rectal	Suppositories, ointments, creams, powders, solutions
Topical	Ointments, creams, pastes, lotions, gels, solutions, topical aerosols, foams, transdermal patches
Parenteral	Injections (solution, suspension, emulsion forms), implants, irrigation and dialysis solutions
Respiratory	Aerosols (solution, suspension, emulsion, powder forms), inhalations, sprays, gases
Nasal	Solutions, inhalations
Eye	Solutions, ointments, creams
Ear	Solutions, suspensions, ointments, creams

Fig:1.2. dosage forms available for different administration route.

Transdermal Drug Delivery System (TDDS)

Transdermal drug delivery systems are defined as self-contained, discrete dosage forms which applied to the skin and deliver the drug, through the skin, at controlled rate to the systemic circulation at a sufficient concentration to ensure the therapeutic efficacy. These are suitable for drugs that need to be administered for diseases those are chronic in nature (N. K. Jain, 1st edition). The trans-dermal Drug Delivery System (TDDS) is one of the dosage systems which use the skin as the port of drug administration and bypass the hepatic first-pass metabolism to maintain a constant and prolonged therapeutic blood level of drug in the body. Skin is an important site of drug application for both local and systemic effects. The idea of transdermal drug delivery system (delivering drugs through skin) is old, as the use of it is reported back in16th century B.C. The first transdermal patch was approved by FDA in

1979.Topical and transdermal products remain key formulations for delivering drugs not only to the skin, but also through it for systemic action. (Michael E. Aulton, 4th edition). When aim is to deliver through skin in a predetermined controlled fashion the result is transdermal drug delivery. (J. Ali, R.K. Khar. 2nd edition 2004-2005)

Advantages

1. Avoidance of risks and inconveniences of I.V. therapy.
2. By pass hepatic first pass and gastrointestinal incompatibility.
3. Reduce side effects due to optimization of the blood concentration time profile.
4. Provide predictable and extended duration of activity.
5. Greater patient compliance due to elimination of multiple dosing intervals.
6. Reduce frequency of dosage.
7. Reversibility of drug delivery which would allow the removal of drug source.
8. Enhance therapeutic efficiency.
9. Minimize inter and intra patient variations.
10. Self administration

There are huge advantages of TDDS, although have some limitations also. These includes: (N. K. Jain, 1st edition)

1. The barrier function of the skin changes from one site to another on the same person or person to person and with age.
2. Drugs that require high blood levels cannot be administered.
3. Drug or drug formulation may cause skin irritation or sensitization.
4. Uncomfortable to wear.
5. May not economical.

Ideal properties of drug, which are preferable for transdermal patches. (Chandrasekar and Shobha, 2008)

1. Dose should be less than 20mg/day.
2. Half life ($t_{1/2}$) of drug less than 10 in hour.

3. Molecular weight should be less than 400 Dalton.
4. Melting point of drug should be less than 300˚C.
5. Partition coefficient (log P) should be between -1.0 to 4.
6. Skin permeability coefficient more than 0.5×10^{-3} cm/h
7. Skin reaction must be non-irritating and non-sensitizing.
8. Therapeutic index must be low.
9. First pass metabolism should be extensive.

Skin structure

The skin completely covers the body and is continuous with the membranes lining the body orifices. It:

- protects the underlying structures from injury and from invasion by microbes.
- contains sensory *(somatic)* nerve endings of pain, temperature and touch.
- is involved in the regulation of body temperature.

The skin has a surface area of about 1.5 to 2 m2 in adults and it contains glands, hair and nails. There are two main layers:

- epidermis
- dermis.

Between the skin and underlying structures there is a layer of subcutaneous fat. Human skin is a highly complex multilayered organ designed to keep the outside out and the insides in. It is the largest organ of the body, comprising around 10% of the body mass and covers an area of approximately 1.8 m2 in a typical adult. As a self-repairing barrier, skin permits terrestrial life by preventing the ingress of microorganisms and chemicals whilst regulating heat and water loss from the body (Aulton, 4th edition).

In terms of drug delivery, human skin can be considered as a series of layers which potentially provide a series of barriers to a molecule traversing the tissue.

- **The subcutaneous layer:** The inner subcutaneous fatty layer is typically several millimeters thick, except for some areas such as the eyelids where it is mostly absent. This subcutaneous layer of adipose tissue provides mechanical protection against physical shock, insulates the body, provides a store of high-energy molecules and carries the principal blood vessels and nerves to the skin. The subcutaneous layer is seldom an important barrier to transdermal and topical drug delivery.
- **The dermis**: Overlying the fatty layer is the dermis, a layer typically 3–5 mm thick that is the major component of human skin. The dermis is composed of a network of mainly collagen and elastin in a mucopolysaccharide gel; essentially this combination provides an aqueous environment similar to a hydrogel. The dermis has several structures embedded within it, termed appendages, in particular nerve endings, pilosebaceous units (hair follicles and sebaceous glands) and eccrine and apocrine sweat glands The dermis is metabolically active and requires extensive vasculature for this, as well as for regulating body temperature, for wound repair, to deliver oxygen and nutrients to the tissue and to remove waste products.
- **The epidermis:** The epidermis overlies the dermis and is itself a multiple layer containing various cell types, including keratinocytes, melanocytes and Langerhans cells. Keratinocytes in the basal layer (stratum basale) undergo division and then differentiate as they migrate outwards, forming the stratum spinosum, then the stratum granulosum and nally the stratum corneum. Differentiation is complex and essentially changes the metabolically active basal cells that contain typical organelles, such as mitochondria and ribosomes, into stratum corneum that comprises anucleate attened corneocytes packed into multiple lipid bilayers.
- **The stratum corneum:** This outer skin layer is predominantly responsible for the barrier properties of human skin and limits drug delivery into and across the skin. The stratum corneum typically comprises only 10 to 15 cell layers and is around 10 μm thick when dry (although it can swell to several times this when wet). The stratum corneum is thinnest on the lips and eyelids and thickest on the load-bearing areas of the body such as the soles of the feet and palms of the hands. The lipid bilayers in which the keratin filled cells are embedded are uniquely different to other lipid bilayers in the body since they are comprised largely of ceramides, fatty acids,

triglycerides and cholesterol/ cholesterol sulphate, whilst phospholipids are largely absent.

Sectional view of skin showed in figure.1.3. (Tortora, 12th edition)

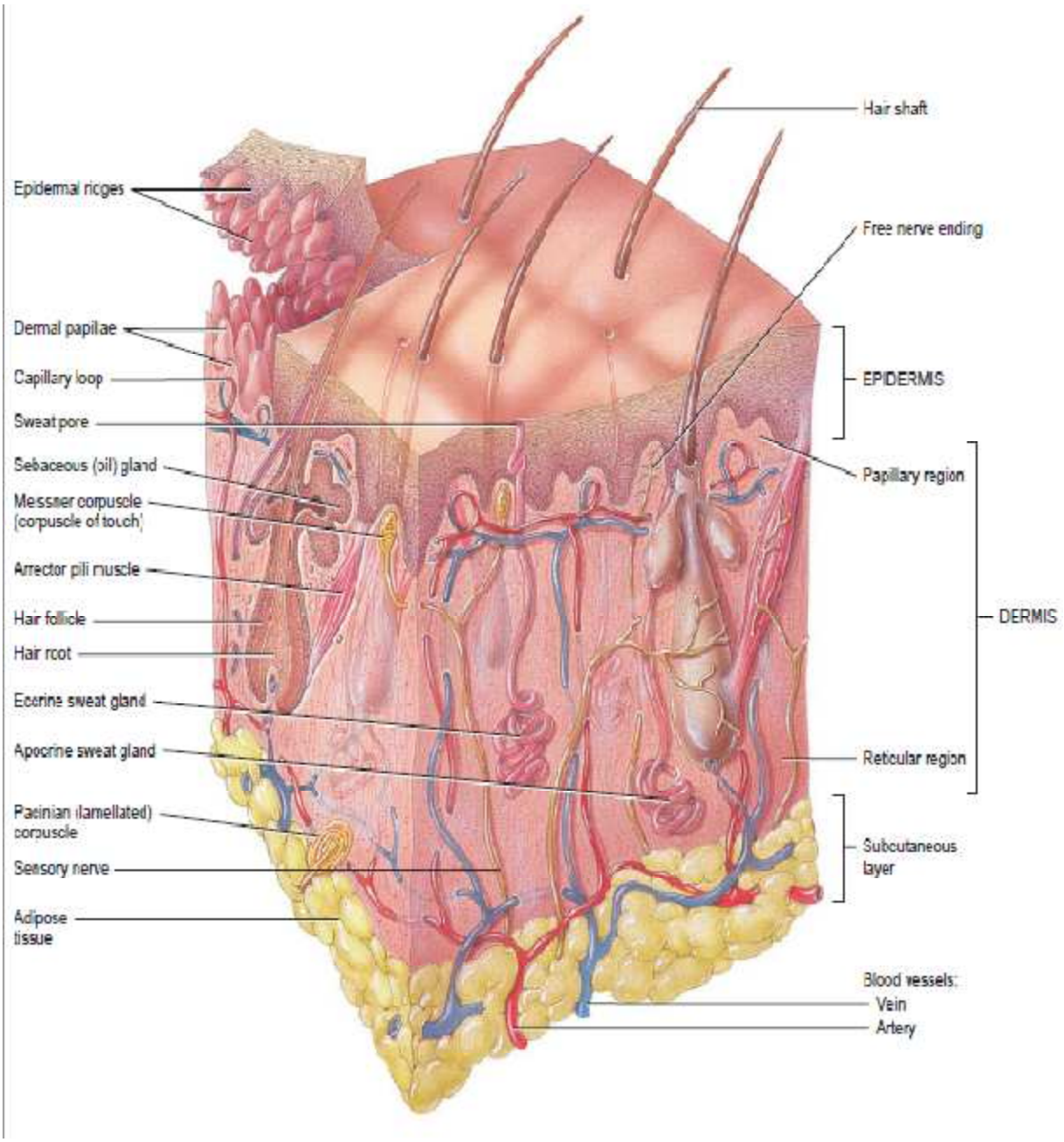


Figure: 1.3. Sectional view of skin and subcutaneous layer

Transport through the skin

From the above discussion on the structure of skin it is clear that delivery of drug molecules from a topically applied formulation into the systemic circulation is complex, with numerous processes occurring and several routes of transport in operation, as illustrated in Figure 1.4. Initially, drug molecules must be presented to the skin surface. Consequently, if the formulation contains solid drug, then dissolution and diffusion through the formulation is the initial step in delivery. If the formulation contains dissolved drug, then as the molecules nearest to the skin surface enter the tissue these must be replaced by other molecules diffusing within the formulation towards the skin surface. Once at the outer layer of the stratum corneum, the drug molecule has three potential routes to cross the skin. Firstly it can pass via the shunt routes as described above. In this case molecules will partition into sweat or sebum before diffusing against the outflow from the glands.

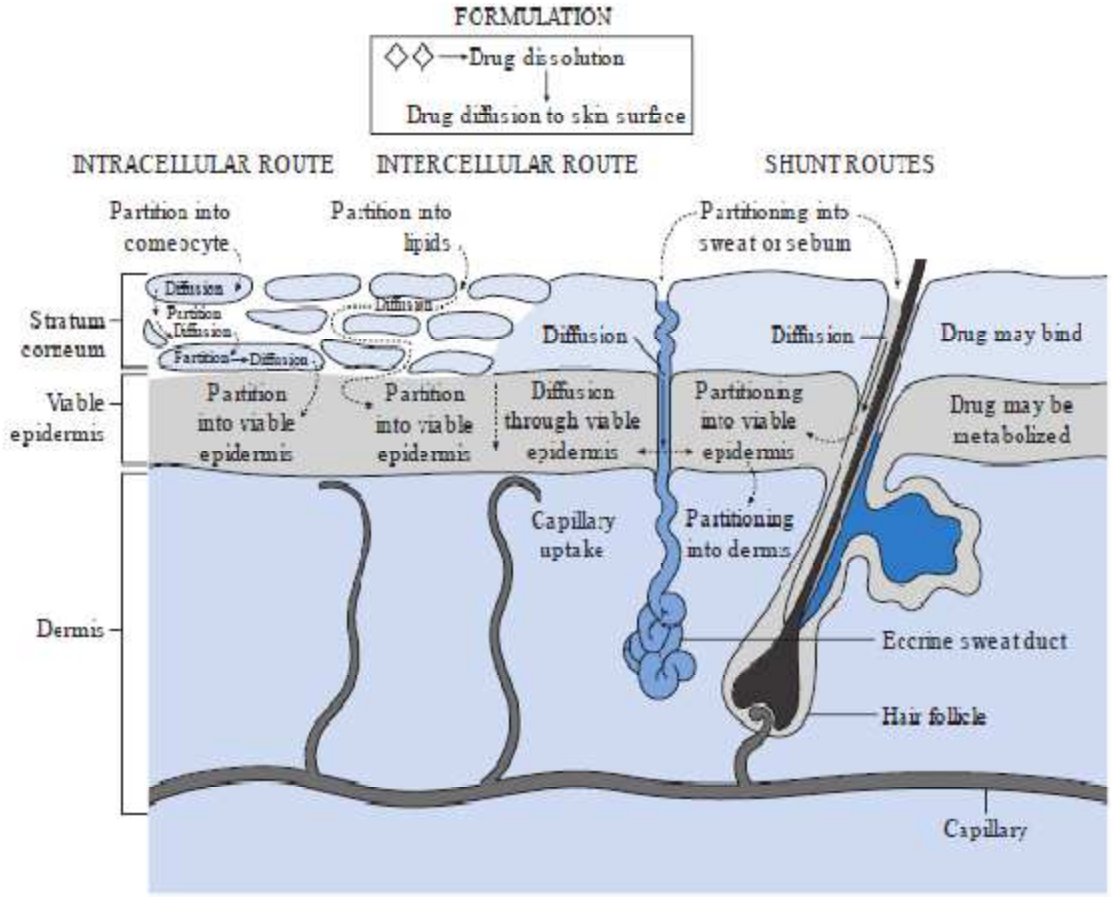


Figure 1.4. Some of the process occurring during transdermal drug delivery system (suspension form)

Comparison of human skin with pig ear skin: (Mayer et al 2007)

Parameters	Human skin	Pig ear skin
Thickness of stratum corneum	14.9 – 21.5 mm	15.1 – 18.9 mm
Viable epidermis	70 mm	66 -72 mm
Content of SC	Lipid, ceramide	same
Hair per cm^2	14 - 32	20
Hair follicle	Into dermis	same

Table: 1.1. Comparison between human skin and pig ear skin

Drug Solubility:

Now-a-days, in drug discovery has been to produce more and more compounds that exhibit high lipophilicity and poor water solubility. Such physicochemical characteristics lead to problematic biopharmaceutical properties, which in turn diminish the likelihood of success in the clinic. Many approaches have been developed to improve solubility and to enhance the dissolution rate of poorly soluble drugs, including both modifications to the drug substance itself and the creation of specific formulations. Physical modifications often aim to increase the surface area, solubility and wettability of the powder particles and therefore typically focus on particle size reduction or generation of amorphous states. Drug solubility enhancement is one of the most important challenges in the field of pharmaceutics. Among the five key physicochemical parameters in early compound screening viz. dissociation constant, solubility, permeability, stability and lipophilicity, poor solubility tops the list of critical compound properties. Advances in combinatorial chemistry and high throughput screening have led to the development of large number of molecules with requisite pharmacological activity. However these immobilized receptor techniques lead to the selection of compounds with undesirable physicochemical attributes like high lipophilicity, poor aqueous solubility and high molecular weights. The biopharmaceutical classification system (BCS) is the scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. It is a drug development tool that allows

estimation of the contributions of three major factors, dissolution, solubility and intestinal permeability that affect oral absorption of drugs.

Classification of drug as per solubility and permeability:

The Biopharmaceutics Classification System is a system to differentiate the drugs on the basis of their solubility and permeability. It is a guide for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. The fundamental basis for the BCS was established by Gordon Amidon, who was presented with a Distinguished Science Award at the August 2006 International Pharmaceutical Federation (FIP) congress in Salvador, Brazil.

Purpose of the BCS Guidance:

- Expands the regulatory application of the BCS and recommends methods for classifying drugs.
- Explains when a waiver for in vivo bioavailability and bioequivalence studies may be requested based on the approach of BCS.

Goals of the BCS Guidance:

- To improve the efficiency of drug development and the review process by recommending a strategy for identifying expendable clinical bioequivalence tests.
- To recommend a class of immediate-release (IR) solid oral dosage forms for which bioequivalence may be assessed based on in vitro dissolution tests.
- To recommend methods for classification according to dosage form dissolution, along with the solubility and permeability characteristics of the drug substance.

The drugs are classified in BCS on the basis of following parameters:

- ❖ Solubility
- ❖ Permeability
- ❖ Dissolution

The class boundaries for these parameters are as follows:

a) **Solubility class boundaries-** It is based on the highest dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water.

b) **Permeability class boundaries**- It is based indirectly on the extent of absorption of a drug substance in humans and directly on the measurement of rates of mass transfer across human intestinal membrane. Alternatively non-human systems capable of predicting drug absorption in humans can be used (such as in-vitro culture methods). A drug substance is considered highly permeable when the extent of absorption in humans is determined to be 90% or more of the administered dose based on a mass-balance determination or in comparison to an intravenous dose.

c) **Dissolution class boundaries-** An immediate release product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 15 minutes using USP Dissolution Apparatus 1 at 100 RPM or Apparatus 2 at 50 RPM in a volume of 900ml or less in the following media: 0.1 N HCl or simulated gastric fluid or pH 4.5 buffer and pH 6.8 buffer or simulated intestinal fluid.

According to the Biopharmaceutics Classification System, drug substances are classified as follows.

i. **Class I - high permeability, high solubility**: Those compounds are well absorbed and their absorption rate is usually higher than excretion.

ii. **Class II - high permeability, low solubility:** The bioavailability of those products is limited by their solvation rate. A correlation between the in vivo bioavailability and the in vitro solvation can be found.

iii. **Class III - low permeability, high solubility:** The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then class I criteria can be applied.

iv. **Class IV - low permeability, low solubility:** Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected.

The process of solubilization involves breaking of inter-ionic or intermolecular bonds in the solute, separation of the molecules of the solvent to provide space in the solvent for the solute and physical interaction between the solvent and the solute molecule or ion.

Solid dispersion

A first practical approach was made to enhance drug dissolution and absorption of sulfathiazole with a physiologically inert and easily soluble carrier urea by size reduction. Another approach is to prepare the eutectic mixture by melting the physical mixture of drug and carrier followed by the rapid solidification process (Sekiguchi and obi, 1961). The faster dissolution of drug happens because of drug in microcrystalline state and/or be molecularly dispersed in the matrix, and thereby forming a solid solution (Chiou and Riegelman, 1971).

Enhancement of solubility of poorly water-soluble drug by solid dispersion technique may be attributed to particles modified characteristics such as, particle size reduction, improved wettability and dispersibility, higher porosity, decreased lattice energy, amorphous state (Craig, 2002).

Though this is a simple technique to prepare solid dispersion (SD) of drug, but some problems are often encountered, for example maintenance of physicochemical stability of drugs and vehicle, making suitable formulation of solid dispersion into dosage forms, and scale-up of process.

Types of Solid dispersion

Solid dispersion can be typified into simple eutectic mixtures, solid solutions, and physical mixtures of microcrystalline drug dispersed in carriers that are completely miscible in the liquid state but only to a limited extent in the solid state. A eutectic mixture of a sparingly water soluble drug and a highly water-soluble polymer or carrier may be regarded as well

blended physical mixture of its two crystalline components which are assumed to crystallize simultaneously in microcrystalline sizes and thus it increases the rate of dissolution of a poorly water-soluble drug. In solid solution, particle size is reduced to molecular level. Solid solutions can be further classified further based on their miscibility (continuous versus discontinuous solid solutions) and distribution of drug molecules within carrier molecules (substitutional, interstitial or amorphous). In a continuous solid solution, the components are miscible in all proportions in both solid and liquid state as the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. In case of 'substitutional solid solutions' the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules. In 'interstitial solid solutions' the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. In an 'amorphous solid solution', the solute molecules are dispersed molecularly but irregularly within the amorphous carrier.

Complexation is a technique of preparing solid dispersion. Drug is bound to a carrier because of weak Vander Waals force and it is released from the bound state at suitable chemical environment. It is an approach to facilitate amorphization of drug and to enhance its solubility.

Complex Formation

In this kind of solid mixture, a guest molecule forms complex with an inert soluble carrier (host molecule) in the solid state. One of the most frequently used complex carriers is within the class of the cyclodextrins. Cyclodextrins are a family of cyclic oligosaccharides composed of α-(1, 4) linked glucopyranose subunits (Figure 1.5). It is composed of interior hydrophobic cavity, whereas the exterior is highly hydrophilic. The lipophilic cavity of cyclodextrin molecules provides a microenvironment into which appropriately sized non-polar moieties can enter to form inclusion complex (Valle, 2004). Complex formation between cyclodextrin and a substrate is assessed by binding/stability constant which is determined by Phase solubility method. The theory of this method was first proposed by Higuchi and Connors (1965) and it is the most widely applied method among other numerous

methods, such as circulardichroism, HPLC, Nuclear Magnetic Resonance (NMR), XRPD, DSC and UV spectroscopy (Miller et al., 2007; Challa et al., 2005).

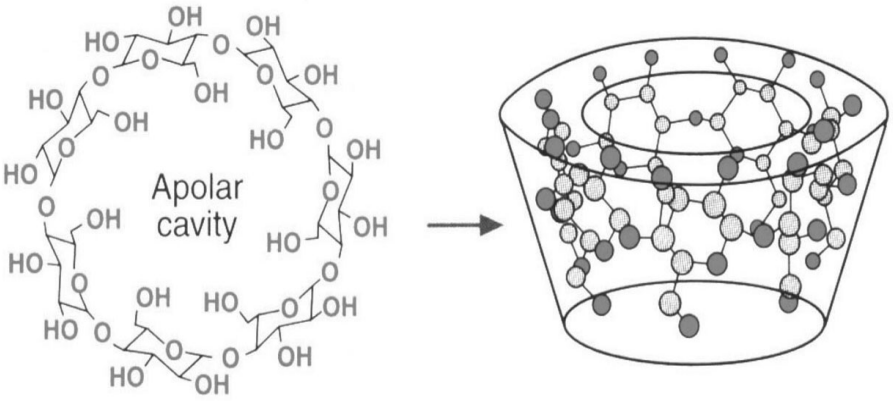


Figure 1.5. Chemical structure of Cyclodextrin

This experiment is performed by assessing solubility of drug after complex formation between drug and carrier. According to the solubility characteristics of drug in the complex formed, phase solubility profiles are broadly classified into type A and B (Figure 1.6). Type-A profile indicated the formation of inclusion complexes with higher solubility, while type-B profile indicates the formation of inclusion complexes with poor solubility. A B_S-type profile indicates complexes of limited solubility and B_I-curve is indicative of insoluble complexes. The A-curves are subdivided into A_L (linear increase of drug solubility as a function of cyclodextrin concentration), A_P (positively deviating isotherm) and A_N (negatively deviating isotherm) subtypes.

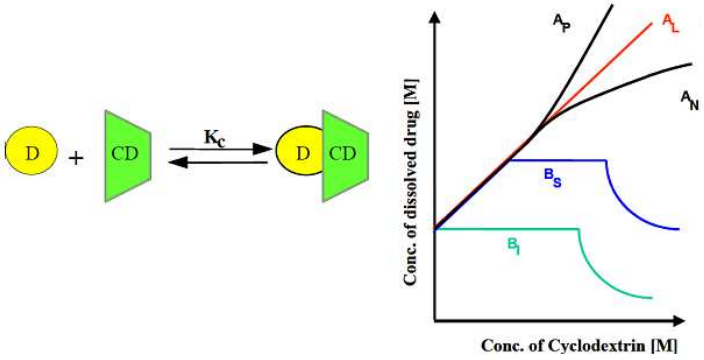


Figure 1.6. Phase solubility diagram

Solving algebraically the mass balance equations for guest molecule and host molecule following equation is obtained (Higuchi and Connors, 1965; Das et al., 2013)

$$S_T = S_O + KS_O\{[L_T]/(1 + KS_0)\} \quad (1)$$

Where $[S]_T$ is the total concentration of guest in solubilized state and S_O is that of the guest molecules (free) and $[L]_T$ is the total concentration of host molecule in the liquid.

Thus a plot of $[S]_T$ against $[L]_T$ is linear according to this expression, the stability constant is expressed as, $$K = \frac{\text{Slope}}{S_O(1-\text{Slope})} \quad (2)$$

Thermodynamic functions for the binding of guest and host molecules are related to overall stability constant, K_c by the following relationship: $\Delta G^0 = -2.303RT \log K$; where, ΔG^0 is the change of free energy at constant pressure (P) and absolute temperature (T) and R is the universal gas constant. The standard enthalpy change, ΔH, can be obtained from the slope of a profile by plotting log K versus 1/T as following the expression,

$$\log K = -\frac{\Delta H^0}{2.303RT} + \text{constant} \quad (3)$$

When, the values of K at two temperatures are known, the following equation can be used to determine ΔH:

$$\log(K_2/K_1) = \frac{\Delta H^0(T_2 - T_1)}{2.303\ R\ (T_1T_2)} \quad (4)$$

The standard entropy changes, ΔS^o, is obtained from the expression,

$$\Delta G^0 = \Delta H^0 - T\Delta S^o \quad (5)$$

ΔH^o generally becomes more negative as the stability constant for molecular complexation increases. Although large negative value of ΔS^o is not favorable for complexation, still large negative value of ΔH^o overcomes the unfavorable entropy contribution, leading to a negative ΔG^o (Martin, 1995).

Methods of preparation of solid dispersion

Various methods of preparation for solid dispersions had been reported in earlier literature (Chiou and Riegelman, 1971), such as Fusion method, Solvent evaporation method, Kneading method and use of surface active agents. In fusion method mixture of drug and carrier is melted followed by solidification and cooling at ambient temperature (Sekiguchi and Obi, 1961; Zerrouk et al., 2001and Boral et al., 1995).

Sekiguchi and Obi (1961) prepared simple eutectic mixtures by hot-melt method. Sulphathiazole and urea were melted together at a temperature above the eutectic temperature and immediately after fusion the sample was poured onto a metallic plate which was kept on ice bath. The solidification process is often effective on stainless-steel plates which facilitates rapid heat loss. Decomposition of chemicals should be avoided. Its efficacy depends on fusion time and rate of cooling (Zerrouk et al., 2001; Boral et al., 1995). The solvent evaporation method was first proposed by Tachibana and Nakamura (1965), in which they dissolved both the drug and the carrier in a common solvent, followed by the evaporation of solvent under vacuum and produced a solid solution. Solvent can be removed by slow heating at low temperature (Kearney et al., 1994; El-Zein et al., 1998), by freeze-drying **(**Betageri and Makarla, 1995) or by spray-drying (Chauhan et al., 2005). In kneading method, a mixture of drug and carrier substances is mixed with a liquid and the pasty mass is kneaded continuously for a period and dried and the solid mass is sifted. Surface active agents are also used often in formulation development to enhance solubility of active substance.

Solvent evaporation technique:

Solid dispersions prepared from hydrophilic polymers using the solvent evaporation technique were effective in improving drug dissolution. The process involves solubilizing an amphiphilic block copolymer in an appropriate volatile organic solvent, mixing it with an aqueous solution, and then evaporating the organic solvent under reduced. In this method, the capacity of the continuous phase is insufficient to dissolves the entire volume of disperse phase solvent. Thus, solvent evaporates from the surface of the dispersion to obtain hardened products. The advantages of this method are that the polymersome sizes can be readily and precisely tuned over a wide range; it is a robust method that can be applied to many different

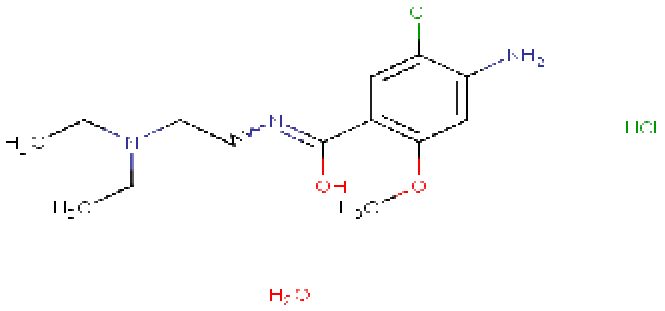
types of block copolymers; and finally it is very practical, as the process is complete in less than five minutes, uses standard laboratory equipment, and does not require high energy input.

Drug Candidate

Metoclopromaide Base:

Metoclopramide is chemically 4-amino-5-chloro-N-[2-(diethylamino) ethyl]-2 methoxybenzamide, an antiemetic and gastroprokinetic agent. It is commonly used to treat nausea and vomiting, to facilitate gastric emptying in people with gastroparesis, and as a treatment for gastric stasis often associated with migraine headaches. The antiemetic action of Metoclopramide is due to its antagonist activity at D2 receptors in the chemoreceptor trigger zone (CTZ) in the central nervous system (CNS)dthis action prevents nausea and vomiting triggered by most stimuli. At higher doses, 5-HT3 antagonist activity may also contribute to the antiemetic effect. The gastroprokinetic activity of Metoclopramide is mediated by muscarinic activity, D2 receptor antagonist activity and 5-HT4 receptor agonist activity. Metoclopramide is freely soluble in water and ethanol and practically insoluble in ether. The molecular formula is $C_{14}H_{22}ClN_3O_2$, which corresponds to a molecular weight of 299.8 and its melting point is 147˚C .

Structure of Metoclopramaide:



Mechanism of action of Metoclopromaide:

Metoclopramide inhibits gastric smooth muscle relaxation produced by dopamine, therefore increasing cholinergic response of the gastrointestinal smooth muscle. It accelerates intestinal transit and gastric emptying by preventing relaxation of gastric body and increasing the phasic activity of antrum. Simultaneously, this is accompanied by relaxation of the upper small intestine, resulting in an improved coordination between the body and antrum of the stomach and the upper intestine. Metoclopramide also decreases reflux into the esophagus by increasing the resting pressure of the lower esophageal sphincter and improves acid clearance from the esophagus by increasing amplitude of esophageal peristaltic contractions. Metoclopramide's dopamine antagonist action raises the threshold activity in the chemoreceptor trigger zone and decreases the input from afferent visceral nerves. Studies have also shown that high doses of metoclopramide antagonize 5hydroxytryptamine (5HT) receptors in the peripheral nervous system in animals.

Pharmacokinetics of Metoclopramide

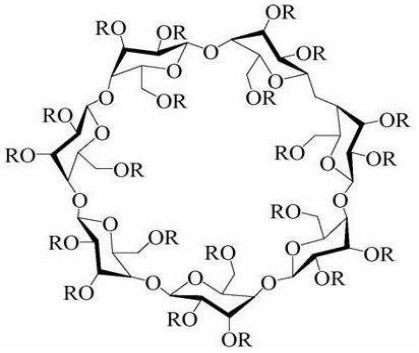
It is absorbed well after oral administration, but a significant first pass effect in some human patients may reduce systemic bioavailability to 30%. There apparently is a great deal of interpatient variation with this effect. Bioavailability after intramuscular administration has been measured to be 74-96%. After oral dosing, peak plasma levels generally occur within 2 hours. The drug is well distributed in the body and enters the CNS. Metoclopramide is only weakly bound to 13-22% of plasma proteins. The drug also crosses the placenta and enters the milk in concentrations approximately twice those of the plasma. Metoclopramide is primarily excreted in the urine in humans. Approximately 20-25% of the drug is excreted unchanged in the urine. The majority of the rest of the drug is metabolized to glucuronidated or sulfated conjugate forms and then excreted in the urine. Approximately 5% is excreted in the feces. The half life of metoclopramide in the dog has been reported to be approximately 90 minutes.

Carriers used to enhance solubility of drugs

Hydroxypropyl-β-cyclodextrin (HPβCD)

Hydroxypropyl-β-cyclodextrin (HPβCD) is produced from β-cyclodextrin (βCD) by the addition of propylene oxide to some of the hydroxyl groups of βCD. This modification results in greater solubility of HPβCD and complexation efficiency in comparison with that of βCD. Therefore, HPβCD is used when faster dissolution rates are needed. Other benefits obtained by complexation with the basic βCD, such as protection against chemical degradation and volatilization are retained by the HPβCD. Solutions may be stored for several weeks at room temperature. It is used in applications similar to β-CD, however, as it is not nephrotoxic, so it has been suggested for use in parenteral formulations too.

Structure



Molecular Weight: 1380

Molecular Formula: $(C_{42}H_{70-n}O_{35})(C_3H_7O)_n$

Where R – $CH_2CHOHCH_3$ or R-H

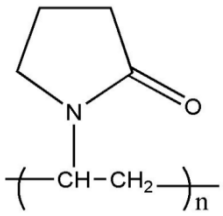
Appearance	White crystalline powder, odorless
Solubility in water at 25°C	50g/lit
Melting point	278°C
Degree of substitution	4-6

Table 1.2. Physicochemical Properties of HPβCD

Polyvinylpyrrolidone-K30 (PVP K30)

Polyvinylpyrrolidone (PVP K30), also commonly called Polyvidone or Povidone, is a water-soluble polymer made from the monomer *N*-vinylpyrrolidone. It is chemically 2-Pyrrolidinone, 1-ethenyl-, homopolymer. It is stored in tightly closed container, in a dry and cool place and away from direct sunlight. It has excellent wetting properties and readily forms films. This makes it good as a coating or an additive to coatings.

Structure



Average Molecular weight: 45,000

Molecular formula: $(C_6H_9NO)_n$

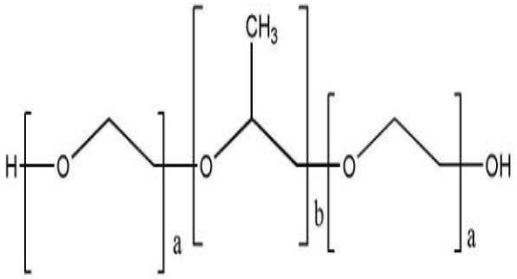
Solubility	Soluble in water, chloroform, alcohol, chlorinated hydrocarbons, amines, nitro paraffin's, lower weight fatty acids.
Melting point	150 - 180 °C (glass temperature)
Appearance	white to light yellow, hygroscopic, amorphous powder
Density	1.2 g/cm³

Table 1.3. Physicochemical Properties of PVP – K30

Poloxamer (188)

Poloxamer is a synthetic block copolymer of ethylene oxide and propylene oxide. It is a difunctional block copolymer surfactant terminating in primary hydroxyl groups. It is a nonionic surfactant that is 100% active and relatively nontoxic. It is stored in a tightly closed container and in dry state. It is to be protected against heat.

Structure



Molecular weight: 8,400

Molecular formula: $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$

Solubility in water at 23 °C	> 175 g/l
Melting point	52 – 57 °C
Appearance	Powder, coarse particle, waxy type, odorless, tasteless
Density	1.06 g/cm^3
HLB	29

Table 1.4. Physicochemical Properties of Poloxamer-188

Chapter- 2

LITERATURE SURVEY

(Jain P, et al. 2012) Transdermal drug delivery systems have been gaining increasing popularity among delivery systems on market. To screen crystallization inhibitors, perform accelerated stability testing and predict saturation solubility of levonorgestrel in drug-in-adhesive patches. Among the different designs of transdermal patches available on market, drug-inadhesive (DIA) systems are the most popular ones. The recent change of patch design from reservoir to drug inadhesive for Duragesic (fentanyl) patch can exemplify the benefits such as no leakage or dose dumping, which a DIA design offers. Here used polymer are Poloxamer and Copovidone, PVP (PVP 360), Backing membrane 9734 and Release liner 9744 (obtained as gift samples from 3M Scotchpak St. Paul, MN, USA), HPLC grade Acetonitrile and Propylene glycol etc. This work provides an insight to solutions for different problems of crystallization in drug-in-adhesive patches. Prediction of saturation solubility of a drug in adhesive via time lag experiment and accelerated stability testing with die cutting can help in saving a lot of time in the initial stages of patch development.

(R. Vijaya et, al 2012) Transdermal drug delivery system (TDDS) delivers the drug through topical route for systemic effect at a predetermined and controlled rate. The drug safety, therapeutic efficacy and patient compliance can be gained by reducing both the size and number of doses which can ultimately be achieved through TDDS. In this study, transdermal films of Amitriptyline HCl have been formulated by solvent evaporation technique. Matrix type of film was prepared using polymers of Eudragit E100, hydroxy propyl cellulose (HPC) and polyvinyl pyrolidone (PVP) in different compositions incorporating dibutyl phthalate as plasticizer. The films were evaluated for physicochemical properties, *in vitro* release, kinetics of drug release, skin permeation and skin irritation.

Yvaraja et al., (2014) prepared solid dispersion of carvedilol (cardiovascular drug which is poor water soluble) for enhancement of aqueous solubility. To increase solubility used polymers are Beta cyclodextrin, Hydroxypropyl-beta-cyclodextrin, Polyvinyl pyrrolidone, poloxamer-407, and Tartaric acid. Prepared products of carvedilol solid dispersions were evaluated by various experiments in different conditions (temperature,pH media) such as determination of saturation solubility, phase solubility studies, determination of a partition coefficient, determination of yield

(%), drug content (%) and saturation solubility , in-vitro dissolution studies. At finally decided that tartaric acid is useful in reducing bulk of primary carrier in the formulation of drug. Rajabalaya R et al, (2015) ROveractive bladder (OAB) is a common problem and anticholinergic drugs are first-line therapy, but they have side effects. Development of oxybutynin chloride (OC) transdermal gels and analyze its efficacy. To prepare proniosomal gels using various non-ionic surfactants, lipids, soy lecithin and isopropyl alcohol by phase separation coacervation method.

B. Anroop et al.,(2014), in this work studied that, co-administered of levodopa and carbidopa through skin using a drug in adhesive transdermal system and asses the formulation by the methods of in-vitro drug release, ex-vivo permeation, and in-vivo pharmacokinetics in rat model. The study encloses that the transdermal delivery route could be a feasible alternative to oral therapy for the successful delivery of levodopa in Parkinson's disorder. B. Anroop et al.,(2016), in this study, development of adhesive transdermal patches and compare with oral therapy of anti-diabetic drug vildagliptin. Here used 3M backing membrane and release liner and applicator thickness was 300µm. Used polymers are N-methyl-2-pyrrolidone, sodium lauryl sulphate, polyethylene glycol 400, menthol, ethyl acetate, acetonitrile, triethyl amine etc.

Domanska et al, (2011) scientists were investigate that guest-host complex formation of three drug derivatives of anthranilic acid, mefenamic acid, niflumic acid, and flufenamic acid with 2-hydroxypropyl-*β*-cyclodextrin (2HP-*β*-CD) in aqueous solutions was investigated using "Phase solubility study" with UV-vis spectrophotometry. Solubility of sparingly soluble drugs has been improved by addition of 2HP-*β*-CD at two temperatures 298.15 K and 310.15 K and two pH values 2 and 7. The influence of different 2HP-*β*-CD concentration on solubility of drugs at different pH and temperatures has been investigated. The 2HP-*β*-CD-drug complex stability constants (*K*), and dissociations constants (*K*), as well as the thermodynamic parameters of reaction, *i.e.*, the free energy change (Δ*G*), the enthalpy change (Δ*H*) and the entropy change (Δ*S*), were determined.

Madishetti et al, (2010), this team investigate that, domperidone bilayered matrix type transdermal therapeutic systems could be prepared with the required flux and suitable mechanical properties. Bilayered matrix type transdermal drug delivery systems (TDDS) of domperidone were prepared by film casting technique using hydroxypropyl methyl cellulose as primary and Eudragit RL 100 as secondary layers. Brij-35 was incorporated as a solubilizer, d-limonene and propylene glycol were employed as permeation enhancer and plasticizer respectively. The prepared TDDS were extensively evaluated for in vitro release, moisture absorption, moisture content, water vapor transmission, ex vivo permeation through rat abdominal skin, mechanical properties and stability studies.

Sadozai et al,. (2013) The objective of this study was to prepare and evaluate sustained release matrix tablets of domperidone using xanthan gum as a sustaining material in different drug to polymer ratios prepared by two different techniques by wet granulation and solvent evaporation and effect on release pattern by changing the preparation technique. Formulation prepared by wet granulation and solvent evaporation technique and showed that the sustaining effect of the xanthan gum was directly proportional to the concentration of the polymer used. It was observed that by changing the method of preparation from wet granulation to solvent evaporation the drug release becomes constant and no fluctuation was observed as compared to wet granulation technique the drug release profile shows little bit fluctuation due to uneven distribution of the drug and polymer. Different models for kinetic study were applied like zero order, first order, Higuchi, Hixson Crowell and Korsmeyer to study the release pattern and mechanism.

Ali M. M. eial,. (2014) in this study, to prepare a domperidone transdermal adhesive matrix patch to improve its therapeutic efficacy, patient compliance and to reduce the frequency of dosing and side effects, as well as to avoid its extensive first pass metabolism. And then evaluate the physicochemical and mechanical properties as well as in vitro release and rat skin permeation of domperidone. Different formulas of the patches were prepared by solvent/evaporation casting technique using Chitosan, Eudragit E100, Eudragit RS 100 and Eudragit L100 as polymers with many suitable plasticizer. The physicochemical parameters like drug content, thickness, and weight variation, mechanical parameters like elongation%, elastic modulus and strain as well as

drug release and permeation study were evaluated for the prepared patches. In the past two decades many researchers/formulators recognized the problem of insoluble property of medicinal agents in formulating a dosage form and had shown deep interest in modifying drugs solubility by various techniques and various agents. Among the solubilizing aids cyclodextrins were much exploited in the last two decades. These special molecules serve various purposes and are termed as molecular container (Das et al., 2013). In many cases, cyclodextrins form complexes with other chemicals and impart some special characteristics in the chemicals of interest.

The mouth-dissolving tablet formulated with ternary solid dispersion by spray drying technique was found to increase the solubility 110folds than that of pure drug and 100% of drug was released within five minutes. PVP K30 is known as a good solubilizing agent, Sharma and Jain (2010) used PVP K30 to prepare carvedilol solid dispersion by solvent evaporation method. They observed improved wettability and solubility of carvedilol in the presence of PVP K30, which was due to the formation of inter-molecular hydrogen bonding between the carbonyl group of PVP K30 and the hydrogen atom of the hydroxyl group of carvedilol.

Mehanna and his co workers (2010) investigated the dissolution enhancement of tadalafil (phosphate diesterase 5-inhibitor) solid dispersion employing various block copolymers (Pluronics-38, 68, 77, 108 and 127) by fusion technique. Among all the grades, Pluronic F-127caused higher dissolution rate of drug in solid dispersion productin comparison with that of pIn the year 2007, Thompson and his co researcher's investigated the effect of operating parameters on the preparation of ibuprofen loaded co polyesters microspheres by solvent evaporation technique. The operating parameters such as temperature, disperse phase volume and ratio of polymer and ibuprofen were varied during preparation. They reported that temperature had some effect on surface morphology, and they observed also that encapsulation efficiency was increased with the increase of polymer: drug and decrease of internal phase volume. Drug release from the batch of microspheres was dependent on the concentration and nature of polymer used.

Blend of cellulosic polymers (ethylcellulose & HPMC) as release retardant polymers had been widely used by many investigators. Jalil and his coworkers (2010) studied the effect of mixture of cellulosic polymers (ethylcellulose & HPMC) and polymethacrylic polymers on drug content

of Carbamazepine, encapsulation efficiency, particle morphology and release profiles from Carbamazepine sustained release dosage form. Cellulosic polymers form gel in aqueous medium which help in controlling release of drugure drug. In the year 2013, Koteshwara and his co workers prepared the floating microspheres of carvedilol using ethyl cellulose and hydroxypropyl methylcellulose as release retardant polymers. The new formulation sustained release (45.41 ± 0.13 %) upto 8 hours. Rao et al. in the year 2010. They investigated the effects of polymer ratio and drug concentration on drug encapsulation efficiency, release rate, size, and morphology of microspheres. The release study showed that release rate was controlled by addition of Eudragit L100 with cellulose acetate butyrate. In the year 2011, Mahale and Sreenivas investigated on nifedipine solid dispersion which was prepared with the carrier polyvinylpyrrolidone. Solid dispersion prepared with PVP K-90 (1:7) showed higher dissolution (96%, 1 hour) when compared with that of other formulations.

Chapter- 3

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

The main objective of this work is modification of metoclopromaide hydrochloride drug to metoclopromaide base drug and enhancement of solubility by solid dispersion technique and subsequent development of transdermal drug delivery system with these solid dispersion products. The purpose to develop solid dispersion formulation is to improve solubility of poorly water-soluble drug metoclopromide base. Insolubility of drug leads to poor bioavailability and adverse side effects in the body.

The aims and objectives of the present thesis work are laid systematically with following plans:

1. Modification of drug metoclopromaide hydrochloride into metoclopromide base.
2. Preparation of '**solid dispersions'** of modified metoclopromaide base drug which has poor water solubility.
3. Experimental analysis of metoclopromaide base drug and solid dispersion products with various carriers.
4. Preparation of transdermal patches containing solid dispersion of drug.
5. **Validations** of dosage forms by various studies: solid state characterizations, *in-vitro* studies.

Chapter 4

PREPARATION AND CHARACTERIZATION OF METOCLOPRAMAIDE SOLID DISPERSION.

Preparation and characterization of Metoclopramaide

Many of new API emerging out of high throughput and combinatorial screening tools are under great challenge owing to their poor aqueous solubility and dissolution rate like other existing poorly soluble drug molecules. As per BCS classification both solubility and permeability of a drug regulate extent of 'maximum absorbable dose'. Various approaches of solubility enhancement are being adopted to make it orally bioavailable and therapeutically effective**:** the most widely used easy approach is solid dispersion technique. The aim of present investigation is to prepare solid dispersion of metoclopramide (in base form, antiemetic, M.W. 299.8) with various carriers to enhance its aqueous solubility, and to compare solubility in various types of aqueous media. In this method, metoclopramide base and carrier (HPβCD, polaxamer 188, PVP K30) were dispersed in a mixture of ethanol and dichloromethane to produce a clear solution by stirring in a magnetic stirrer at room temperature, and subsequently, upon removal of solvent solid powder was obtained. The study includes determination of solubility of SD products and phase solubility study of binary systems with carriers to investigate cause of solubilization, and characterizations of various solid dispersion products.

Materials and methods:

Polymers used:

- Hydroxypropyl-β-cyclodextrin (HPβCD) [Tokyo Chemical Industries Co. Ltd.]
- Polyvinyl pyrolidone (PVP K-30) [Loba Chemie, Mumbai]
- Poloxamer-188 [Sigma Chemicals]
- Ethyl cellulose [Sigma Aldrich Chemicals]
- Hydroxypropyl methylcellulose or Hypromellose (HPMC) [Colorcon Asia Pvt. Ltd, GAO, India].

Properties of polymers:

- Hydroxypropyl-β-cyclodextrin: ~1375 g/mol (M.W), 267□C (M.P)
- PVP K-30: 40,000 Da (M.W), 150□C-180□C (M.P)

- Poloxamer: 102.1317 g/mol (M.W), 52□ C (M.P)
- Ethyl cellulose: 454.50 g/mol (M.W), 240□-255□C (M.P)
- HPMC: 1261.43872 g/mol (M.W), 190-230□C (M.P)

Drug used: Metoclopramide HCl (M.P-: 147□C, M.W-: 299.8 g/mol) [Yarrow chemical]

Reagents used are of analytical grade: Potassium dihydrogen phosphate (Merck specialities Pvt. Ltd., Mumbai), Sodium hydroxide (Merck specialities Pvt. Ltd., Mumbai), sodium chloride (Qualikems Fine Chemicals Pvt. Ltd. New Delhi).

Solvents used: Acetone (Quest Chemicals, Kolkata), Methanol (Spectrochem Pvt. Ltd. Mumbai), Dichloromethane (Merck specialities Pvt. Ltd., Mumbai), Ethanol (obtained from the departmental store of Pharm. Tech. Jadavpur University), Double distilled water (obtained from the lab of Pharmaceutical Engineering, dept. of Pharm. Tech. JU), phosphate buffer pH 7.4.

Plasticizer used: Dibutyl phthalate (Merck specialities Pvt. Ltd., Mumbai)

Backing layer : gifted by 3M Drug Delivery, U.S.A.

Apparatus:

- Franz diffusion cell was fabricated by Remco (local glass blower), height, internal diameter, outer diameter and volume of receptor cell are 11cm for both (receptor cell and donor cell), 2cm (internal diameter of donor cell), and of donor cell) 50 mL respectively. Both ends of donor cell (elongated tube) are open; diameter of external opening is 2.5 cm. Receptor cell is jacketed externally for water circulation.
- Metal applicator: stainless steel 316, length 9cm, breadth 2cm, height 11 cm. width of gap for film casting 150, 250, 350, 500 micron.

Instruments:

- UV-Visible spectrophotometer (ANALAB, UV-180).
- Water bath (Integrated electrolife system by SUNBIM)
- Magnetic stirrer (Trasons, multispins) and REMI (2MLH, magnetic stirrer).

Methods:

Conversion of metoclopramide hydrochloride to metoclopramide base form:

In the present work metoclopramide in base form is required and metoclopramide is available in hydrochloride form (aqueous soluble) in the market. Therefore, it is necessary to convert hydrochloride to **Metoclopramide.**

Required amount (4 gm) of metoclopramide hydrochloride was dispersed in sufficient double distilled water followed by stirring until the total amount of drug gets fully dissolved. The solution was neutralized by 1 M sodium hydroxide solution and gradually a precipitate was formed. The precipitate was collected by filtration (Whatman filter paper grade 1) and the precipitate thus obtained was washed several times with double distilled water to remove HCl which was produced during precipitation. The wet precipitate was dried in a hot air oven at 50˚C.Afterward the solid material was cooled upto room temperature (25˚C). Next, dried solid material was treated with acetone to make a saturated solution and stirred continuously at 50˚C. The solution was allowed to attain room temperature and thereafter it was kept in a refrigerator and crystal particles of **Metoclopramide** (base form) was formed and collected and dried at 50˚C in a hot air oven. The material was cooled at room temperature and it was weighed and its melting point was determined.

Preparation of calibration curve:

To construct a calibration curve of metoclopramide (base form) 10 mg of drug (metoclopramide base) was accurately weighed and dissolve in known volume of methanol (~3 ml) and finally the rest of volume was adjusted with aqueous phase (DDW, Phosphate buffer pH 7.4 as required) upto 100 mL. A series of dilutions were made from stock solution (2-20 μg/ml concentrations) for each buffers and assayed under UV- spectrophotometer (ANALAB and model of UV-180) at wave length of 272 nm. Average absorbance data of three observations were plotted against dilutions. The linear curve for phosphate buffer pH 7.4, DDW, phosphate buffer pH 6.8 and pH 5.5 buffer showed (R^2 = 0.999, Y= 0.049 +0.018), (R^2 = 0.999, Y= 0.049x+0.009), (R^2 = 0.999, Y=0.044+0.003) and (R^2 = 0.999, Y=0.047+0.003) respectively. Thus obtained was used to estimate unknown concentration of metoclopramide.

Determination of aqueous solubility of drug:

Aqueous solubility study was performed by taking excess amount of metoclopramide in an aqueous phase (phosphate buffer pH 7.4, DDW, phosphate buffer pH 6.8 and pH 5.5 buffer) and shaken at 37˚C, 40˚C, 45˚C respectively. After 24 hr absorbance was observed to obtain solubility.

Phase solubility study:

From data of aqueous solubility it was observed that metoclopramide has poor aqueous solubility. So, phase solubility study in various carriers (Hydroxypropyl beta cyclodextrin, PVP K30 and Poloxamer 188) was performed. Phase solubility studies were done by dissolving known amount of polymers with increasing amount to each of series of test tubes containing aqueous phase (phosphate buffer pH 7.4, DDW). Thereafter, excess amount of drug was added to each of the tube and shaken for 24 hr (12 hr +12 hr) at 25 37˚C, 40˚C and 45˚C respectively. After 24 hr very slight quantity of insoluble material (drug) was observed at the bottom of each test tube and then content of each test tube was filtered and filtrate was collected and its absorbance was recorded. Phase solubility curve was constructed and thermodynamic parameters and binding constants (Ka) were calculated.

Preparation of solid dispersion by solvent evaporation technique:

Solvent evaporation method was carried out by dispersing a physical mixture of drug and polymer at certain ratio in a common solvent and then it was evaporated until a transparent solvent free thin layer of mass was obtained. Then the film was dried till constant weight at 50˚C (Mogal S. A et al, 2012).

Determination of yield (%), drug content (%) of SD:

Prepared solid dispersion (drug-carrier complex/mixture) was collected and weighed accurately. Yield (%) of solid dispersion was calculated by the following Eq. (3).

$$\text{Yield}(\%) = \frac{\text{weight of solid dispersion}}{\text{Total weight of carrier and drug}} \times 100 \text{---------} (3)$$

A sample of 10 mg of metoclopramaide solid dispersions was weighed and dissolved in 5 ml of methanol and diluted up to 100 ml with double distilled water in a volumetric flask and then the necessary dilution was made. The content of drug was determined by a UV Spectrophotometer.

Characterization of solid dispersion formulation:

Characterization of solid dispersion was performed by instrumental analysis like Fourier Transform Infrared Spectroscopy (FTIR) analysis and Differential Scanning Calorimetry (DSC) analysis.

FTIR analysis:

FTIR analysis was done to observe the stability of drug and also to confirm drug- polymer interaction if any. Fourier transform infra red (FTIR) spectroscopy of solid dispersion samples was performed using Shimadzu Co., Kyoto; Japan combined with Quick Snap sampling modules by the KBr disc method over wave number range of 4000–400 cm−1. Individual polymers, drug (Metoclopramide base), and physical mixtures were run as controls. 10 mg of sample was used to study FTIR.

DSC analysis

DSC analysis was carried out for metoclopramide loaded solid dispersions, physical mixture and also for pure drug to analyze the crystallinity and amorphous nature of compounds. DSC analysis was carried out in (Pyri's diamond TG/DTA; P, Perkins Elmer Instruments) supported by a thermal analyzer. Under nitrogen flow of 150 mL/min, approximately 10mg of sample (Metoclopramide base, polymer substances and solid dispersions) was placed in a sealed aluminum pan and heated at a scanning rate of 10□C/min over the temperature range of 30□C to 300□C.

Aqueous solubility study:

Aqueous solubility study was performed by taking excess amount of solid dispersions in an aqueous phase (DDW, phosphate buffer pH 7.4, phosphate buffer pH 6.8 and pH 5.5 buffers) and shaken at 37˚C, 40˚C, 45˚C respectively. After 24 hr absorbance of each collected filtrate was observed and solubility was determined.

Dissolution study:

Release study of metoclopramide was performed in (Yarrow Chem. Products, phosphate buffer pH 7.4 with 0.9% NaCl, USP rotating paddle II type) dissolution apparatus under sink condition at 37±0.5˚C and 50 rpm. A sample of solid dispersion equivalent to 10 mg of metoclopramide was used in each test. Samples were withdrawn at distinct time intervals and absorbance was observed at λ_{max} of 272 nm using UV-visible spectrophotometer.

***Ex-vivo* permeation study:**

Ex-vivo permeation study was done by using excised ear part of pig followed by removal of external debris. After cleaning a part of ear it was mounted between donor and receptor compartment of Franz diffusion cell (glass apparatus). The receptor portion contains aqueous phase (phosphate buffer pH 7.4 with 0.9% NaCl). Permeation study was carried out using pure drug and solid dispersion formulations in the donor cell which is in contact with the dorsal part of ear skin. Suitable concentration (1mg/mL and 5mg/mL) of drug / solid dispersion was maintained with solvent (ethyl alcohol and phosphate buffer pH 7.4 with 0.9% NaCl) in donor cell .Samples of permeate was collected at intervals and replaced immediately by equal amount of fresh aqueous phase. The samples as collected are then spectrophotometrically analyzed at 272 nm.

Fabrication of transdermal patch:

Patch was fabricated with the prepared formulations containing polymers ethyl cellulose, HPMC, PVP K-30 at different compositions in addition with known amount of dibutyl phthalate as plasticizer and liquid blend was cast on the backing layer by a metal applicator.

***In vitro* diffusion study:**

In-vitro diffusion study was carried out by using Franz diffusion cell. The Franz diffusion cell has receptor compartment of approximately 50 ml and effective surface area of diffusion /permeation was 3.14 square centimeter. The study was conducted in two steps. (i) At first diffusion of drug from transdermal patch was studied. Patch was attached between donor and receptor cell and samples were withdrawn from liquid (phosphate buffer pH 7.4) of receptor cell

at intervals and drug amount present in the samples was determined by observing absorbance. (ii) Secondly, diffusion of drug and simultaneous permeation of drug through the porcine ear skin was studied .The ear portion of pig was duly excised and external debris was removed by treating with phosphate buffer pH 7.4 for half an hour. Then the excised skin was placed in between donor and receptor compartment and a weighed extent of transdermal patch was fixed on the dorsal side of the skin. The receptor cell was filled up with phosphate buffer pH 7.4 and its content was stirred by a magnetic bar placed inside the cell. Temperature of receptor compartment was maintained at 37±0.5˚C by circulating water through external jacketed path .Water was supplied by a constant temperature water bath. Franz diffusion cells were placed on a multicell magnetic stirrer. Samples were withdrawn at intervals and replaced by equal amount of fresh buffer. The samples as collected were analyzed in a spectrophotometer at wave length of 272 nm.

Determination drug content (%) of film:

Drug content analysis was evaluated by taking 2 ml of methanol followed by addition of 1 square centimeter of different patches and stirred with a magnetic stirrer .Then slowly added the DDW and diluted up to 100 ml in a volumetric flask. Filtered the solution and the content of drug was determined by a UV Spectrophotometer. Blank solution was made by the blank patch (patch made without drug).

Results and Discussions

λ_{max} of Metoclopromide base determined first by scanning solution of Metoclopromide in a UV spectrophotometer. λ_{max} of Metoclopromide was found to be 272nm as shown in Figure 4.1.

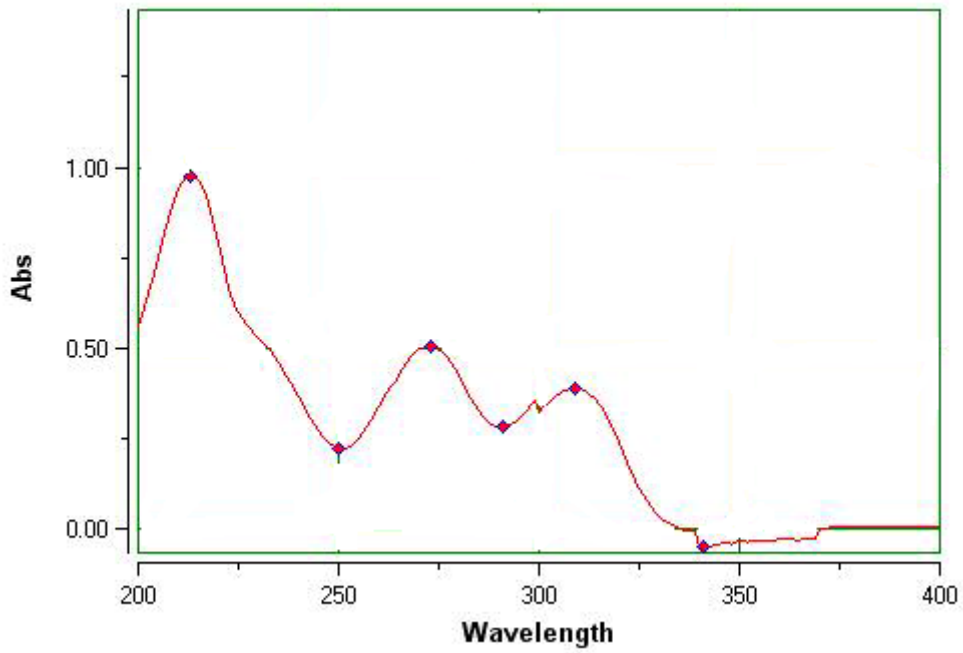


Figure 4.1. UV Scan of Metoclopromeide base solution at the concentration 10µgm/mL in the range of λ, 200 to 400nm

Preparation of calibration curve: The standard curve was pr 5epared by plotting absorbance against concentration of individual analysts. The calibration graph was found linear in the concentration range of 2 to 20µgm/mL in double distilled water (DDW), PH 7.4, PH 6.8, PH 5.5, PH 1.2 (Table :4.1,4. 2, 4.3, 4.4 and Figure :4.2, 4.3, 4.4, 4.5, 5.6).

Serial No.	Concentration (µgm/mL)	Absorbance at 272nm
1	2	0.113
2	4	0.2112
3	6	0.3056
4	8	0.411
5	10	0.5112
6	12	0.615
7	14	0.7142
8	16	0.8174
9	18	0.9032
10	20	0.9964

Table .4.1. Absorbance metoclopromide at 272nm for different concentrations in DDW

Serial No.	Concentration (µgm/mL)	Absorbance at 272nm
1	2	0.112
2	4	0.2138
3	6	0.3142
4	8	0.4016
5	10	0.525
6	12	0.6106
7	14	0.7078
8	16	0.7992
9	18	0.9014
10	20	0.995

Table .4.2. Absorbance metoclopromide at 272nm for different concentrations in PH 7.4

Serial No.	Concentration (µgm/mL)	Absorbance at 272nm
1	2	0.0924
2	4	0.185
3	6	0.2728
4	8	0.3638
5	10	0.4466
6	12	0.5462
7	14	0.635
8	16	0.7232
9	18	0.82144
10	20	0.8926

Table .4.3. Absorbance metoclopromide at 272nm for different concentrations in PH 6.8

Serial No.	Concentration (µgm/mL)	Absorbance at 272nm
1	2	0.1018
2	4	0.1972
3	6	0.2844
4	8	0.3866
5	10	0.4752
6	12	0.5826
7	14	0.6656
8	16	0.7668
9	18	0.859
10	20	0.9556

Table .4.4. Absorbance metoclopromide at 272nm for different concentrations in PH 5.5

Serial No.	Concentration (µgm/mL)	Absorbance at 272nm
1	2	0.0722
2	4	0.137
3	6	0.2066
4	8	0.265
5	10	0.3298
6	12	0.4006
7	14	0.4548
8	16	0.5236
9	18	0.593
10	20	0.6584

Table .4.5. Absorbance metoclopromide at 272nm for different concentrations in PH 1.2

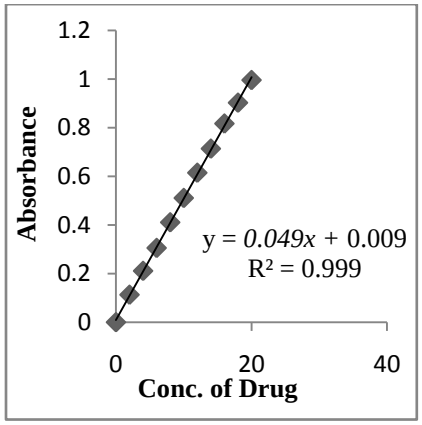


Fig.4.2.Standard curve in DDW

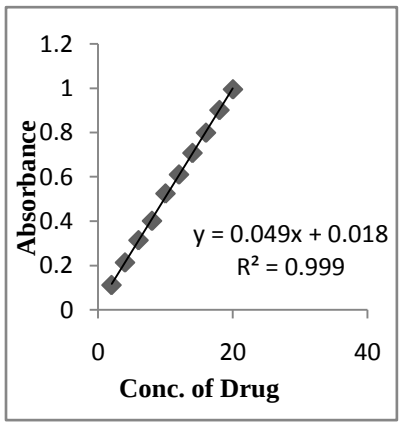


Fig.4.3.Standard curve in P^{H}7.4

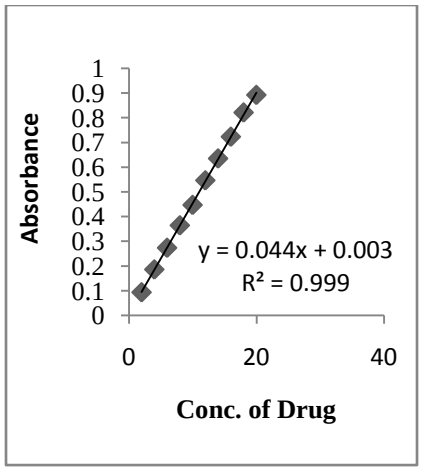


Fig.4.4.Standard curve in P^H6.8

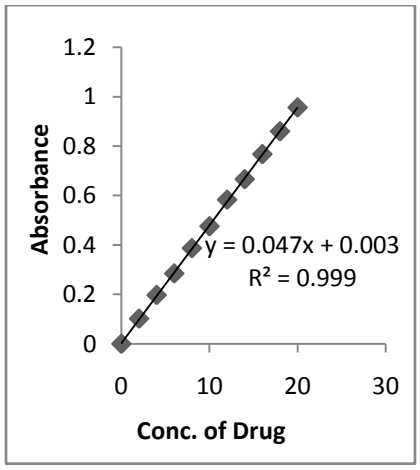


Fig.4.5.Standard curve in P^H5.5

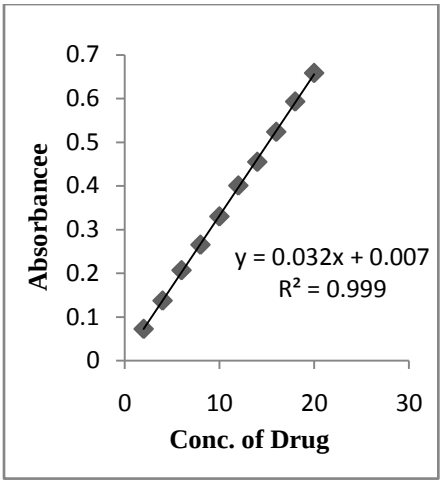


Fig.4.6.Standard curve in P^H5.5

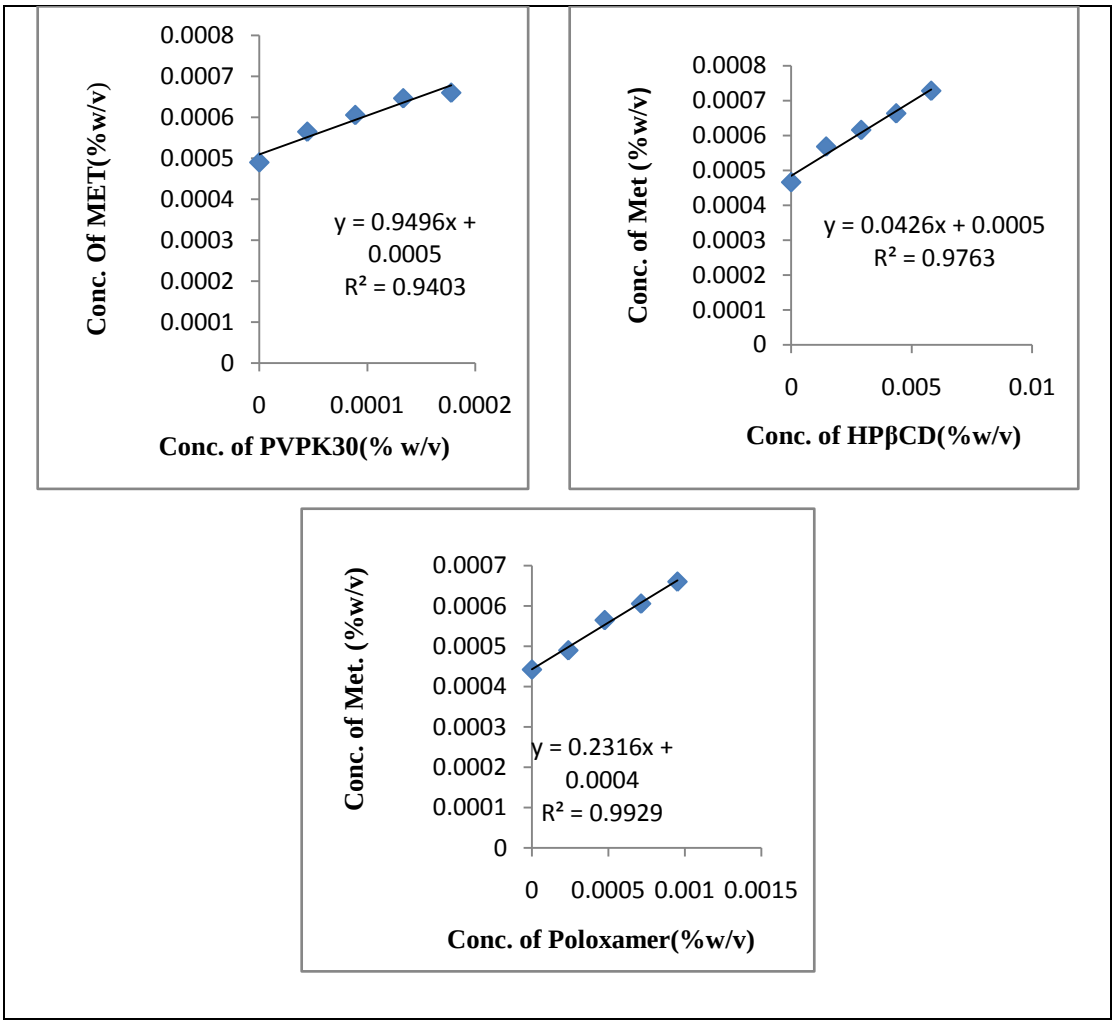


Figure.4.7. Phase solubility diagram of Metoclopromide base in water at 298K temperature in presence of different carriers.

The phase solubility study is carried out to determine binding/complexation constant (K_c) of polymer-drug complexes. These complexes effectively modify solubility characteristics of drug. Phase-solubility studies of binary systems (MET-HPβCD, MET-PVP K-30 and MET-PLX-188), were performed to see the effects of complexation ability of different carrier systems. The shapes of phase solubility profiles (Fig.4.7.) are A_L type of isotherms for PVP K-30, HPβCD, and PLX-188. A_L type linear profile illustrates, solubility enhancement of a guest molecule as a function of carrier's concentration. (Sharma and Jain, 2010).

The profiles showed different values of intercept and slope as temperature and pH of media were varied. Stability constant (K_c) was calculated by intercept and slope of linear part of profile. The apparent complexation constants, (K_c) and thermodynamic parameters (ΔG, ΔH & ΔS) of the phase solubility studies with three aqueous media (DD water pH 7.4 and pH 5.5) at different temperatures (298K, 310K, 313K and 318K) were displayed in Table 4.6.

Carrier		**Medium, DD water**		***Medium , pH 7.4***		**Medium, pH 5.5**	
	Temp. in Kelvin	**K_a (M-1)**	**ΔG,ΔH,ΔS (298 - 318) K**	***K_a (M-1)***	***ΔG,ΔH,ΔS (298 - 318) K***	**K_a (M-1)**	**ΔG,ΔH,ΔS (298 - 318) K**
PVP-K30	**298**	**95.71968**	**ΔG= -11.3013 ΔH= 26.60082 ΔS= 0.127188**				
	310	**145.0439**	**ΔG= -12.331 ΔH= 237.4796 ΔS= 0.83829**				
	313	**350.7873**	**ΔG= -14.519**				
HPβCD	**298**	**81.57048**	**ΔG= -10.905 ΔH= -10.3914 ΔS= 0.001723**	***73.9589***	***ΔG= -10.6623 ΔH= -12.196 ΔS= -0.00515***	**61.35846**	**ΔG= -10.1995 ΔH= -19.0854 ΔS= -0.02982**
	310	**69.34625**	**ΔG= -10.5027 ΔH= -7.88385 ΔS= 0.008788**	***61.1273***	***ΔG= -10.1902 ΔH= -5.89919 ΔS= 0.014399***	**45.53777**	**ΔG= -9.46071 ΔH= -9.85321 ΔS= -0.00132**
	313	**67.34263**	**ΔG= -10.4301 ΔH= -6.46247 ΔS= 0.013314**	***59.80089***	***ΔG= -10.1358 ΔH= -10.5123 ΔS= -0.00126***	**43.89936**	**ΔG= -9.36993**
	318	**64.76378**	**ΔG= -10.3333**	***56.12065***	***ΔG= -9.97483***	**41.68465**	
PLX-188	**298**	**444.9036**	**ΔG= -15.1079 ΔH= -5.35651 ΔS= 0.032723**				
	310	**409.185**	**ΔG= -14.9005 ΔH= -42.2772 ΔS= -0.09187**				
	313	**349.6546**	**ΔG= -14.511 ΔH= -77.5285 ΔS= -0.21147**				
	318	**218.8771**	**ΔG= -13.3504**				

*K_c= stability constant, * ΔG = change in Gibbs-free energy, *ΔH = change in enthalpy,*ΔS = change in entropy

Table.4.6. Binding constants and thermodynamic functions for the interaction of metoclopromide base with various carriers in different pH mediums at different temperatures.

Study of phase solubility was performed with three different carriers at different temperatures. In Fig.4.8, Fig.4.9, Fig.4.10, it had been clearly displayed that intercept and slope of solubility curve were used to calculate binding constants and thermodynamic parameters: change of free energy, change of enthalpy and change of entropy. Free energy change for these binary combinations was found negative which indicate spontaneous solubilization. Free energy change varies from ~ - 9 to -15 kJ/mol (Table 4.6.). It suggests that drug may bind with the carrier molecules which are held by weak physical forces like vander Waals force, hydrogen bonding and some hydrophobic forces.

Effect of temperature (298 – 318 K) on K_c in pH 5.5 was much prominent in each binding in comparison with that of pH 7.4 and DD water. With the rise of temperature mobility of ionic species of MET in acidic pH increases which in turn, possibly inhibits complex formation with the carriers. At higher temperature, the intrinsic solubility of drug increased while the stability constants were found low. Stability constant was lowered with the decrease of pH (pH 7.4 > pH 5.5) in each system. Degree of dissociation of MET increases with the decrease of pH. This fact may not favor hydrophobic binding, so K_c value decreases in acidic pH (Domanska et al., 2011) (Table 4.6). This is due to less interaction between ligand and guest molecule.

Complexation is of exothermic (-ΔH) type, entropy change (ΔS) was found negative in pH 5.5 and positive in higher pH. ΔG is favored by negative ΔH and positive ΔS, and spontaneity in complex formation is ensured by negative ΔG. Negative entropy change and lower K_c values in acidic pH 5.5 may be explained as ligand molecules are more ionized at pH 5.5 and water molecules are comparatively more ordered.

Higher K_c values for the MET-PVP K-30 and CV-PLX-407 systems were observed in comparison with that of the systems with MET-HPβCD. If ΔG values are highly negative and change of entropy is positive, it suggested that complexation is favored in higher pH in comparison with that of lower pH (5.5). MET-PVP-K30 and MET-PLX-188 system showed low solubility than that of other carriers, because of the influence of high stability constant (K_c). If stability constant is too high, it may form a more stable complex, so drug may not be released out to a greater extent from the complexed state (Yubaraj).

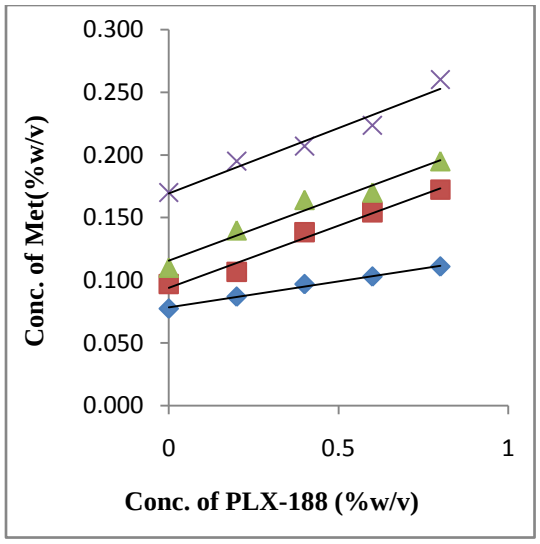


Figure.4.8: Phase solubility diagram of PLX-188 in DDW at different temperature.

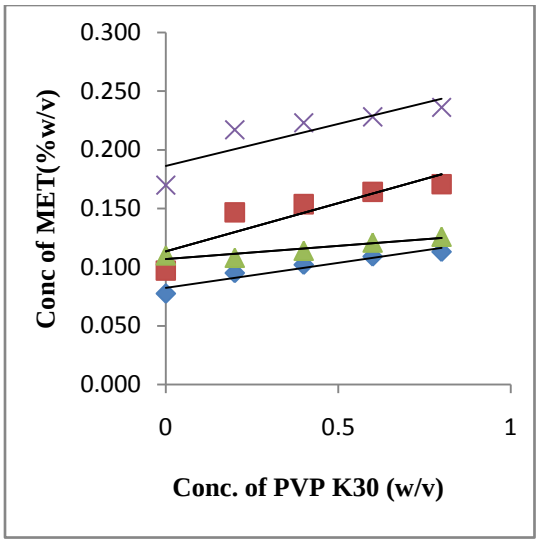


Figure4.9.: Phase solubility diagram of PVP K30 in DDW at different temperature

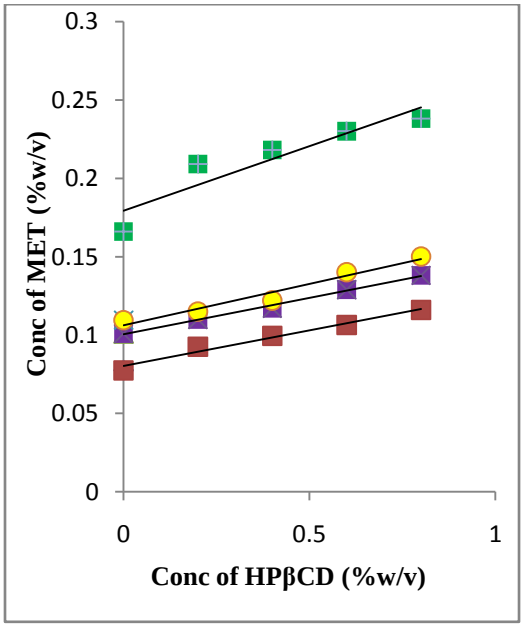


Figure.4.10.Phase solubility diagram of HPβCD in DDW at different temperature

Study of aqueous solubility of solid dispersion at 37°C:

Binary system	mcg/mL in DDW	mcg/mL in pH7.4	mcg/mL in pH 6.8	mcg/mL in pH 5.5
HP 0:1	191.83	1367.3	3363.6	5553.2
HP 1:1	202.04	1448.9	3727.3	8085.1
HP 2:1	353.06	1836.7	4386.3	14680.8
HP 3:1	483.67	2469.4	5727.3	22340.4
PVP 0:1	191.83	1346.9	3363.6	5553.2
PVP 1:1	383.67	1734.7	3772.7	10212.7
PVP 2:1	489.79	2224.5	4454.5	15744.7
PVP 3:1	602.04	2918.3	6181.8	21914.9
PLX0:1	191.83	1346.9	3363.6	8723.4
PLX 1:1	204.08	1612.2	3863.6	15957.4
PLX 2:1	212.24	1918.3	4727.3	18936.2
PLX 3:1	232.65	2714.3	6409.1	22978.7

Table 4.7.: Study of solubility of binary solid dispersions of metoclopramide with various carriers at 37°C.

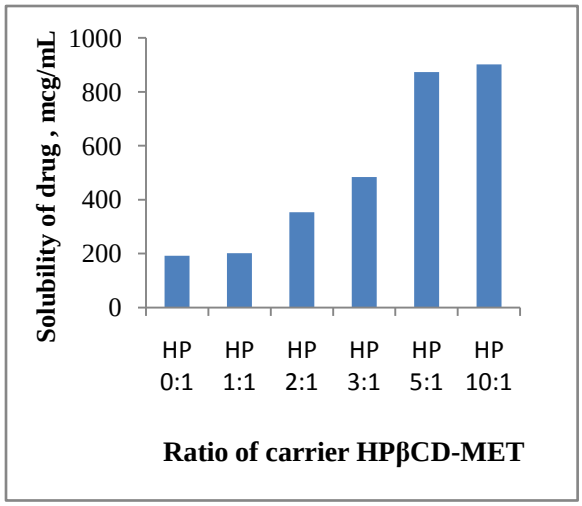


Fig 4.11. : Effect of carrier (HPBCD) drug ratio of SD on the solubility of MET. in DDW.

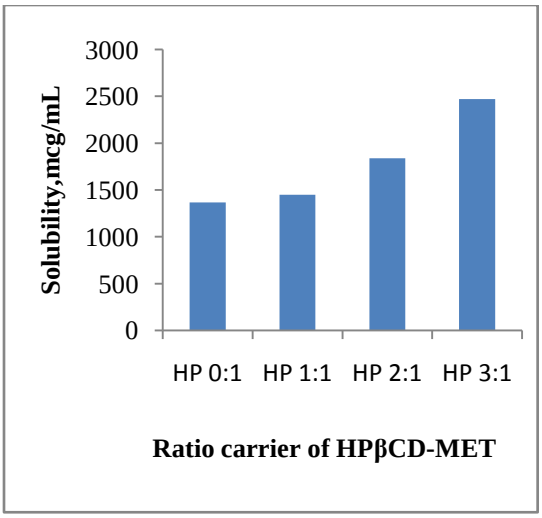


Fig 4.12 : Effect of carrier (HPBCD) drug ratio of SD on the solubility of MET. in pH 7.4

In Fig.4.11 & Fig.4.12, Table.4.7, saturation solubility of solid dispersions of metoclopramide prepared with various carriers was shown. Metoclopromide is sparingly soluble (191.83 mcg/mL) in double distilled water (DDW). Its aqueous solubility in DDW increases linearly keeping drug amount fixed when fraction of carrier substance (HPβCD) in solid dispersion of drug is increased. As drug amount was fixed (100 mg) its solubility was enhanced upto 5:1 (w/w) and drug amount was not much higher on further increase of HPβCD (>5:1) ,it is obvious that solubility will not show much enhancement appreciably (fig.2 & Fig.3). Enhancement of solubility was observed in binary system of carrier- drug (3:1) in DDW ,approximately 2-3 times.

Solubility of pure drug metoclopramaide increases in acidic pH. The results are as follows: in pH 5.5 (5553.2 mcg/mL) , pH 6.8 (3363.6 mcg/mL) and pH 7.4 (1367.3 mcg/mL) which are higher than that of double distilled water (191.8 mcg/mL) at 37°C.

Various solubility data were compared and it was observed that solubility of drug in pH 5.5 is 28.95 (=5553.2 /191.8) times greater than that of pure drug in DDW in samples without any carrier substances.

In medium DDW, enhancement of solubility of SD-HPβCD-Drug (5**:**1) is 4.55 times more than that of pure drug. In acidic medium (pH5.5), enhancement is very high (~97 and ~21 times) in comparison with that of pure drug in DDW and SD in DDW respectively when ratio 10:1 . Similar observation was evident in case of SD with other carrier systems.

In case of poloxamer effect (50.67 times) was higher .In case of solid dispersion of PVP K30-drug solubility enhancement in DDW was lesser in comparison with that of HPβCD. Its solubility increases with the increase of amount of carrier in SD.

Dissolution of solid dispersion:

Study of dissolution of solid dispersions (5:1) in two media were studied .In double distilled water Cumulative % dissolution in DDW was in the order of PVP K30-Met > PLX-Met > HPβCD-Met and in pH 7.4 it was in the order of PLX-Met > PVPK30-Met > HPBCD-Met. (Figure 4.13 and Figure 4.14)

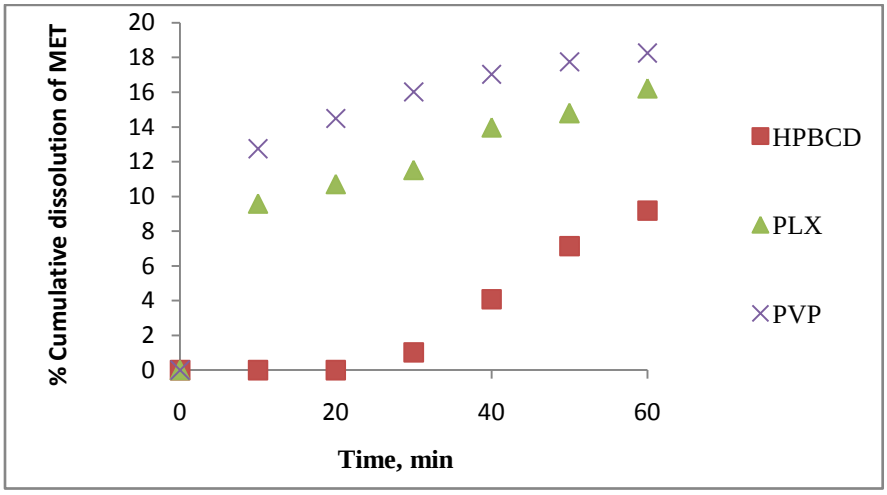


Figure 4.13: Dissolution study of SD of different polymers of MET in media DDW

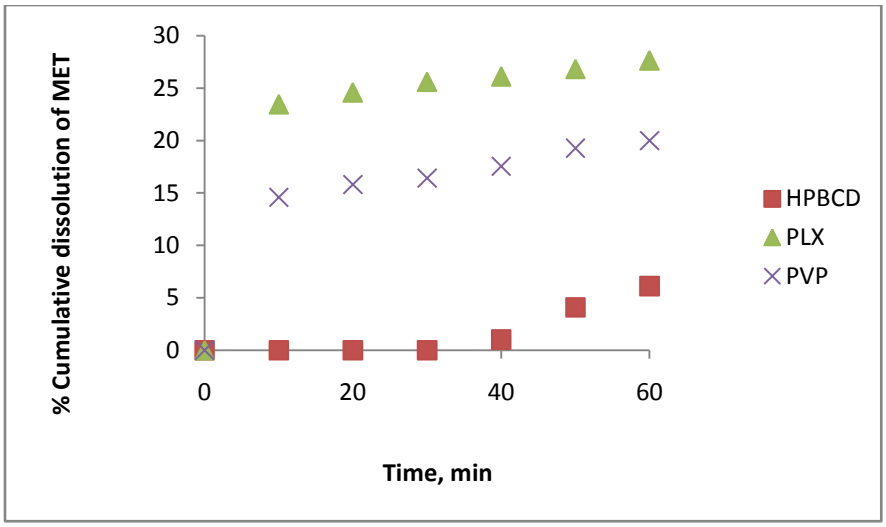


Figure.4.14 : Dissolution study of SD of different polymers of MET in media pH 7.4

Study of dissolution of SD of HPβCD : MET (5:1) in four different media were studied. In this study dissolution was increased by the increasing of buffer pH. The ordering of pH 5.5 > pH 6.8 > DDW > pH 7.4. (which shows on figure : 4.15)

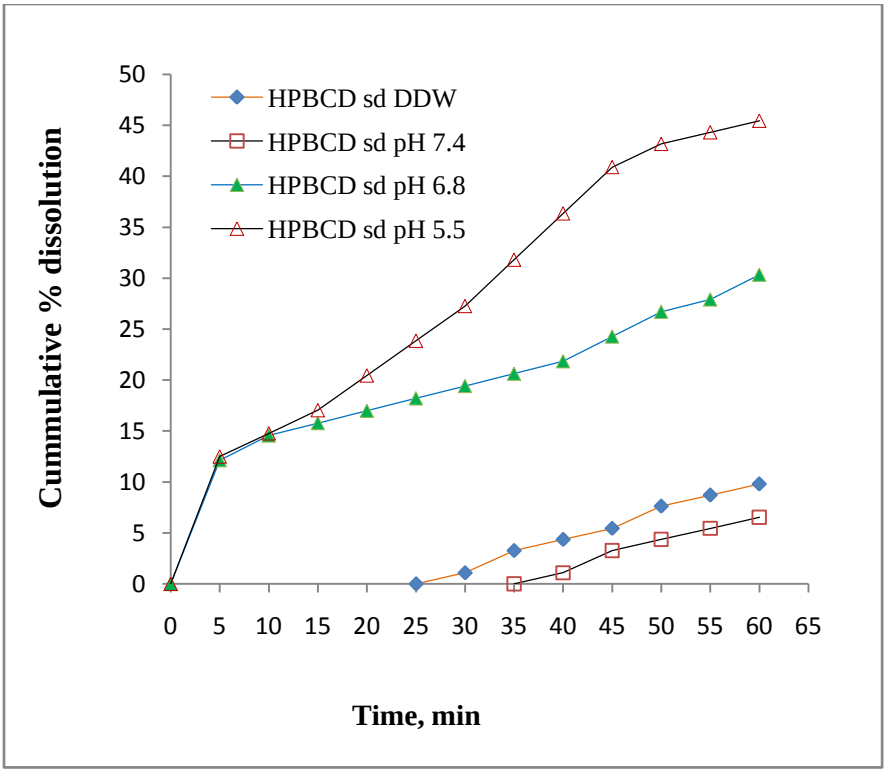


Figure.4.15 : Effect of pH on MET : HPβCD - SD (1:5) of different dissolution media on rate of dissolution.

Drug content of solid dispersion products:

Various binary combinations of MET-solid dispersion were prepared with different carriers such as, HPβCD, PVP K-30 and PLX-188 by solvent evaporation technique, and data of drug content were displayed in Table 4.2. HPβCD have ability to enhance solubility by complex formation (Buera et al., 2011). But it depends on the type of CD. Nowadays their derivatives are found more effective (Duchene and Wouessidjewe, 1990). Hydroxypropyl-β-cyclodextrin (HβCD) is a hydroxyl alkyl derivative of βCD, has wide application increasing the field of drug solubility because of its inclusion ability along with its high water solubility (Misiuk and Zalewska, 2009). In case of water soluble polymers, PVPK-30 and PLX-188, the solubility of MET was enhanced with increasing amount of carrier substances in each medium.

Polymer	Absorbance in media DDW [Y=0.049x +0.009]	Drug (1mg) present in SD products (mg)
HPβCD	0.775	6.473
PVP K30	0.745	6.658
PLX-188	0.860	5.7579

Table.4.8: Drug content of **MET: HPβCD/PVP K30/PLX** (1:5) solid dispersions

Study of permeation:

Study of permeation (Table.4.9) was performed with three SD (5:1) in which PLX-Met showed higher rate of permeation rate in comparison with that of others. Polaxamer may have some effect on human skin as it has some surface activity. So it is concluded that HPBCD- Met may be used for developing transdermal dosage form.

Sl. No	**Permeation Exp.Code**	**Average slope, mcg/min**	**Sl. No**	**Permeation Exp.Code**	**Average slope, mcg/min**
1	A1 (1mg,ET), Pure Drug	4.316	1	A3(1mg,PBS), Pure Drug	3.443
2	B2 (5mg,ET), Pure Drug	3.453	2	B3(5mg, PBS), Pure Drug	4.143
3	C1 (1mg,ET), HPβCD-SD	4.506	3	C3 (1mg,PBS), HPBCD-SD	2.120
4	D1 (5mg,ET), HPβCD-SD	5.073	4	D3 (5mg,PBS), HPBCD-SD	5.107
5	E1 (1mg,ET), PLX-SD	3.923	5	E3 (1mg,PBS), PLX-SD	1.630
6	F1 (5mg,ET), PLX-SD	5.976	6	F3 (5mg,PBS), PLX-SD	5.930
7	G1(1mg,ET), PVP K30-SD	5.113	7	G3 (1mg,PBS), PVP K30-SD	2.935
8	H1(5mg,ET), PVP K30-SD	5.450	8	H3 (5mg,PBS),PVP K30-SD	4.718

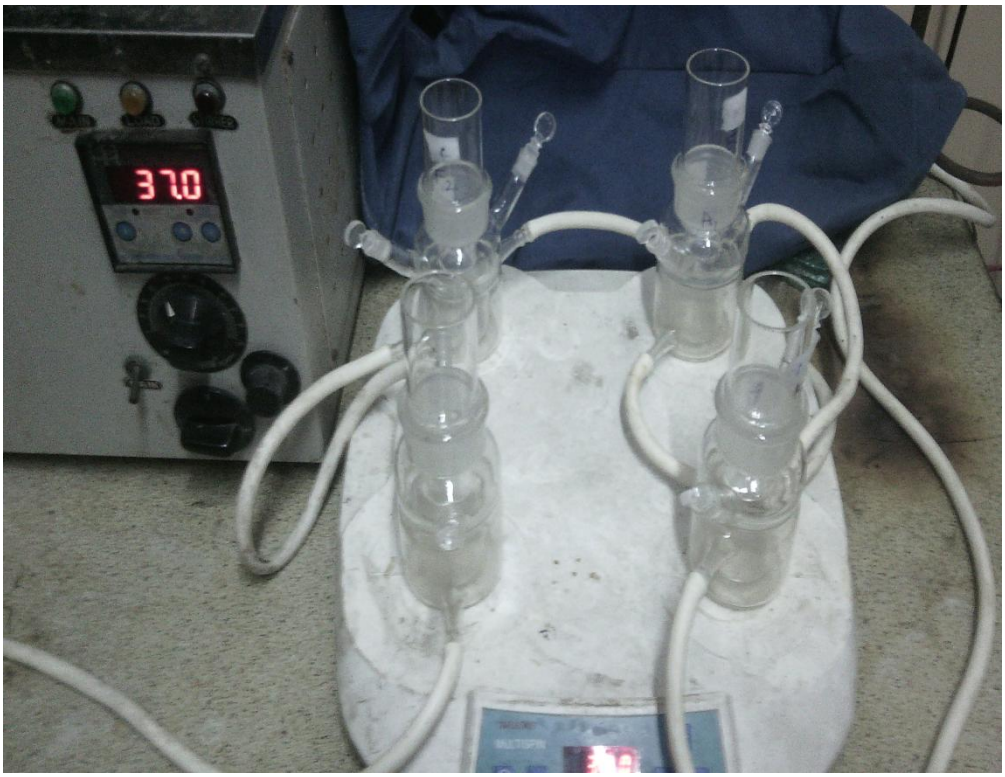
Drug /SD dissolved in **ET-ethanol (96%), **PBS** phosphate buffer, 7.4 pH, **1mg** - 1mg/mL, **5 mg**- 5mg/mL.

Table.4.9.: Ex-vivo permeation study of MET pure drug and its solid dispersions.

Ex-vivo study of Patchs:

Patches were:

- Patch A: HPMC (50mg) + EC (100mg) + PVPK30 (100mg)
- Patch B : HPMC (50mg) + EC (100mg) + PVPK30 (100mg) + MET base pure drug(100mg)
- Patch C : HPMC (50mg) + EC (100mg) + PVPK30 (100mg) + SD of MET-HPβCD (1:5) [equivalent to 100mg drug]
- Patch D : HPMC (50mg) + EC (100mg) + PVPK30 (100mg) + SD of MET- PLX-188 (1:5) [equivalent to 100mg drug]
- Patch E : HPMC (50mg) + EC (100mg) + PVPK30 (100mg) + SD of MET- PVP K30 (1:5) [equivalent to 100mg drug]
- Patch F : HPMC (50mg) + EC (100mg) + PVPK30 (100mg) + MET HCl (100mg drug)



Diffusion and permeation study done in Franz diffusion cell in the Laboratory

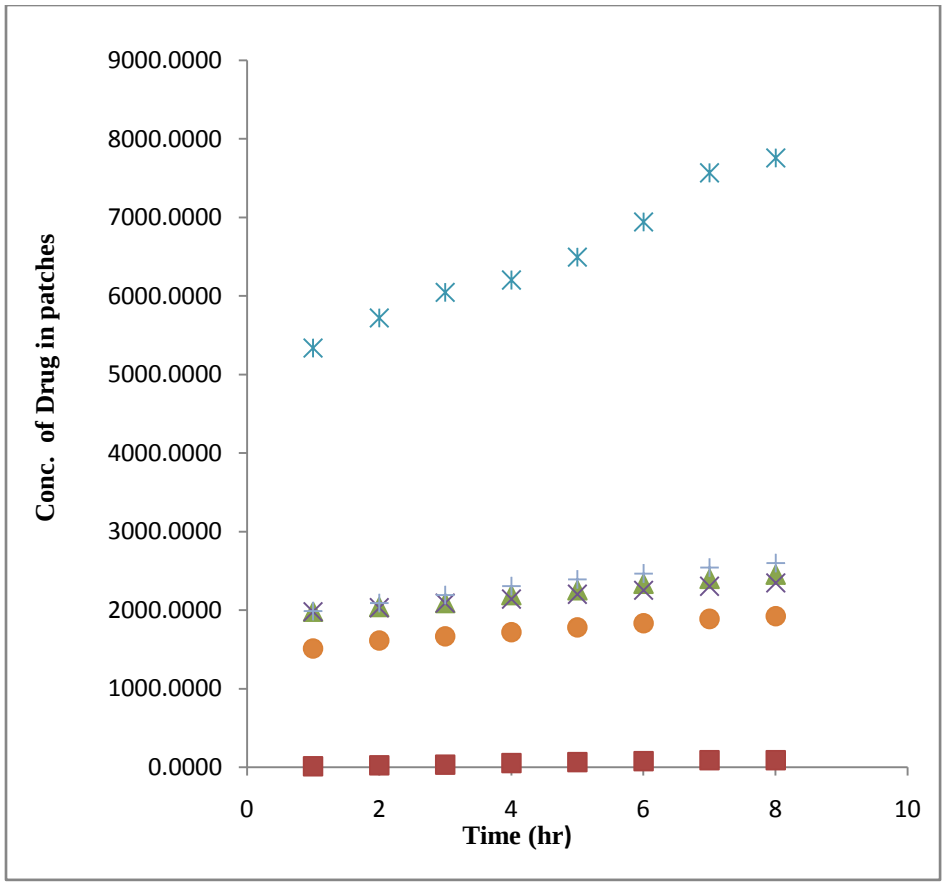


Figure. 4.16. Different Patches diffusion study in Franz diffusion cell

In the figure 4.16, showed that the diffusion linearity of various patches such as without drug patch, MET HCl patch, MET base patch and patches formed by MET : HPβCD/PVP K 30/PLX-188 solid dispersion. Patch – A (without drug) was considered as blank for other patches study. It was the lower most in the figure 4.16. The next linear curve represent the patch- E (SD of MET:PVPK30 1:5), patch – B(MET base pure drug) , patch- F(MET HCl) , patch – C(SD of MET:HPβCD 1:5) respectively showed the same linearity in this figure. The patch- D (SD of PLX-188) showed the highest linearity in the figure. From the above graph we said that the PLX-188 used patch was dissolving and diffuse very quickly. Patches which formulated by MET HCl, MET base and MET:HPβCD were dissolving and diffuse at a same rate, whereas MET:PVPK30 was the different.

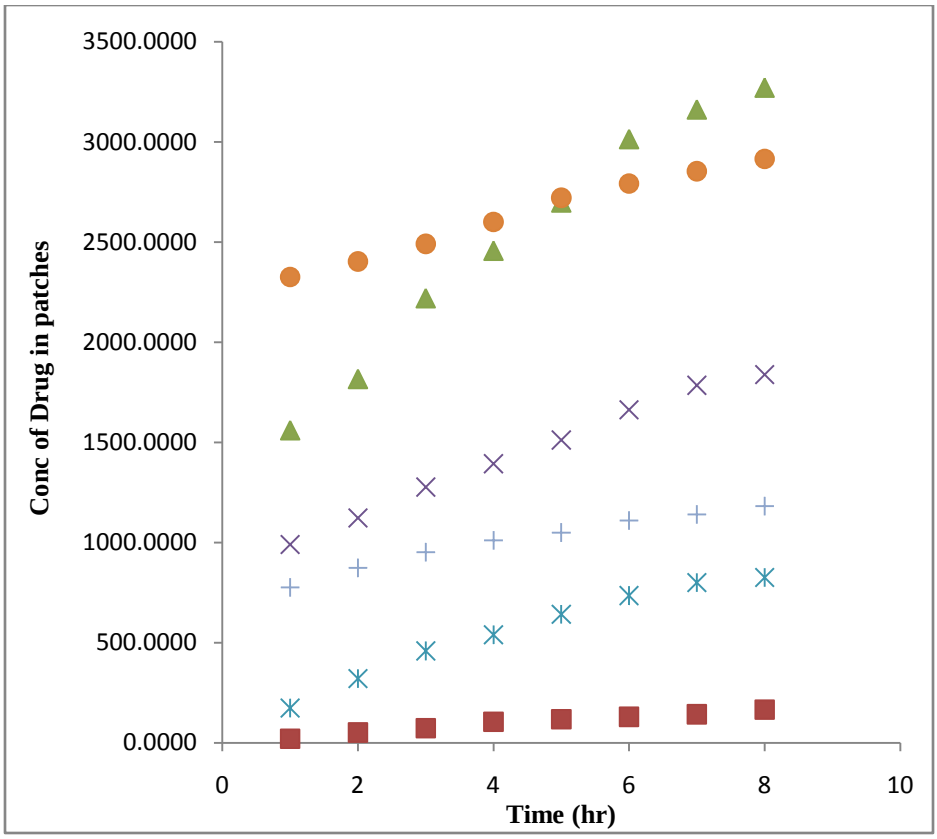


Figure 4.17. Different Patches permeation study in Franz diffusion cell

In the figure 4.17, showed that permeation curve of various patches such as without drug patch, MET HCl patch, MET base patch and patches formed by MET:HPβCD/PVP K 30/PLX-188 solid dispersion. Patch – A (without drug) was considered as blank for other patches for permeation study. It was the lower most in the figure 4.17. The next upper curve represent the patch- D (SD of MET:PLX-188, 1:5), patch – F(MET HCl) , patch- C(SD of MET:HPβCD) , patch – B(MET base drug) respectively showed the different curve in this figure. The patch-E (SD of MET: PVPK30, 1:5) showed the linear curve in the figure. From the above graph found that patch formed by MET:HPβCD (SD of 1:5) were permeated at a constant rate, whereas were slow or very quick permeation.

DSC analysis

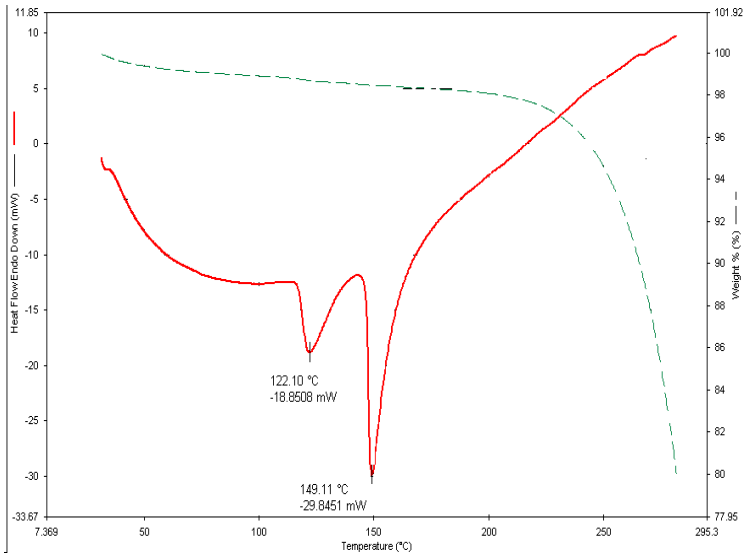


Figure.4.18. DSC of MET

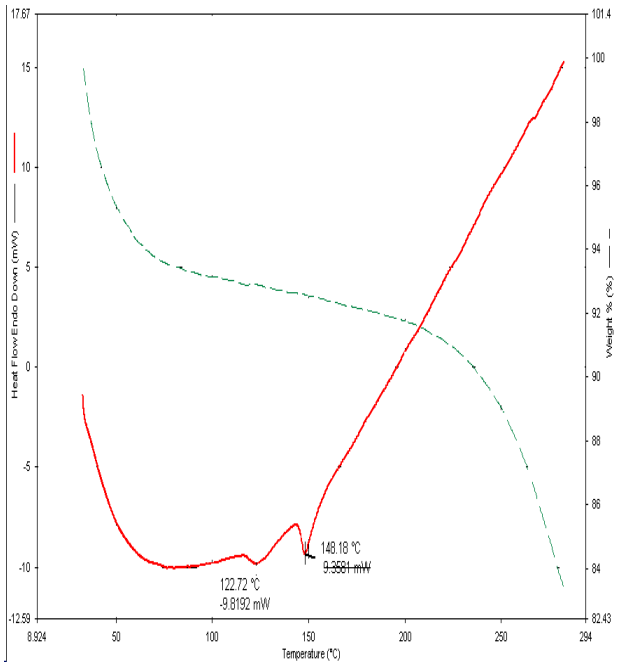


Fig.4.19. DSC physical mixture of MET-HPβCD

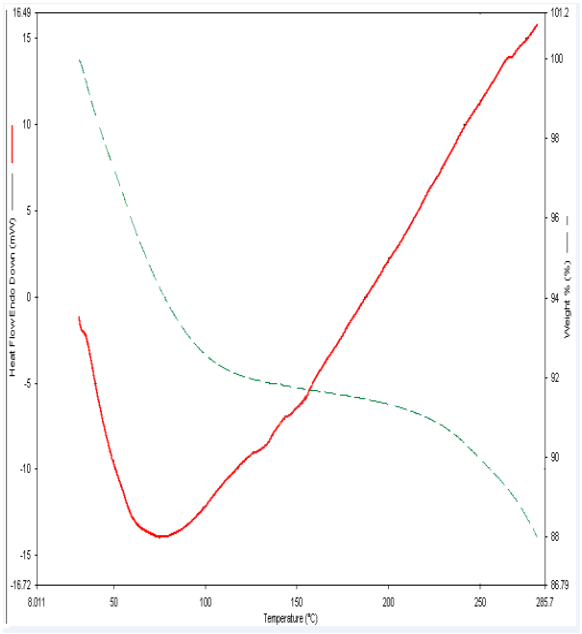


Fig.4.20.DSC of SD of MET-HPβCD(1:5)

Differential scanning calorimetry confirms about crystalline or amorphous nature of compounds. DSC thermogram of metoclopramide base showed a sharp endothermic peak at its melting point (147□C) which exhibits in crystalline form complying with that of metoclopramide hydrochloride form, melting point was found to be (85□C). DSC thermogram of physical mixture (drug: carrier= metoclopramide base: Hydroxypropyl-β-cyclodextrin= 1:5) had depicted a small endothermic peak similar to that of metoclopramide base. Thermograms of solid dispersion (drug: HPβCD=1:5) revealed disappearance of endothermic peak of metoclopramide base corresponding to its melting point. This is due to its uniform homogeneous dispersion within the drug and carrier, amorphization by overcoming crystal lattice energy and subsequent binding by hydrogen bond within the amorphous carrier HPβCD.

FTIR analysis

Fourier transform infrared spectrophotometric analysis

The solid-state interaction between the carrier and drug can be explained by FTIR spectroscopy. The metoclopramaide hydrochloride, metoclopramaide base (pure drug), different carriers (HPβCD, PVP K 30 and PLX-188) and MET: HPβCD (1:5) of physical mixture and solid dispersion were characterized in the FTIR figures.

The FTIR spectrum of MET HCl exhibited characteristic peaks at 3341.84 cm^{-1} and 3199.36 cm^{-1}corresponding to the N-H stretching vibration of the secondary amine, 2941cm^{-1} corresponding to C-H aliphatic stretching, and 1540.74 cm^{-1} corresponding to N-H bending and 1631.74cm^{-1} of NH_2 scissoring. The band of MET base (pure drug) showed as follows: at 3322.87 cm^{-1} corresponding to the N-H stretching vibration of the secondary amine, 2971.70cm^{-1} corresponding to C-H aliphatic stretching, and 1590.48 cm^{-1} corresponding to N-H bending and 1633.20cm^{-1} of NH_2 scissoring. Some of bonds are invisible for the purification of drug. Spectrum of PVPK-30 showed important bands at 2926.77 cm^{-1}, 1639.10 cm^{-1} denoting stretching vibrations for C-H, C=O, respectively. However, a broad band was also observed at 3403.87 cm^{-1}, which was due to presence of water (Paradkar et al., 2004).The spectrum of PLX-188 were 3464.83cm^{-1} O-H stretching, 2887.01 cm^{-1} C-H stretching, 1645 cm^{-1} C=O stretching and 1469.75 cm^{-1} O-H bending. The spectrum of HPβCD showed prominent absorption bands at 3401.89 cm^{-1} (O–H stretching vibrations), 2932 cm^{-1} (C–H stretching vibrations), 1593 cm^{-1}(C–C stretching vibration – aromatic ring) and 1156cm^{-1} and 1031 cm^{-1} (C–H, C–O stretching vibration) (Yuvaraja 2014). FTIR spectra of the physical mixtures MET:HPβCD (1:5) depicted most of the common spectral peaks present in pure drug and carriers. FTIR spectra of solid dispersions, MET:HPβCD showed absence of MET characteristic peaks at 3322.87.5 cm^{-1} corresponding to the N-H stretching. N-H stretching vibration at 3401cm^{-1} was completely overlapped with that of hydroxyl group of cyclodextrin. The intensity and shape of these bands changed significantly for the solid dispersion as compared to those of pure MET and physical mixture.

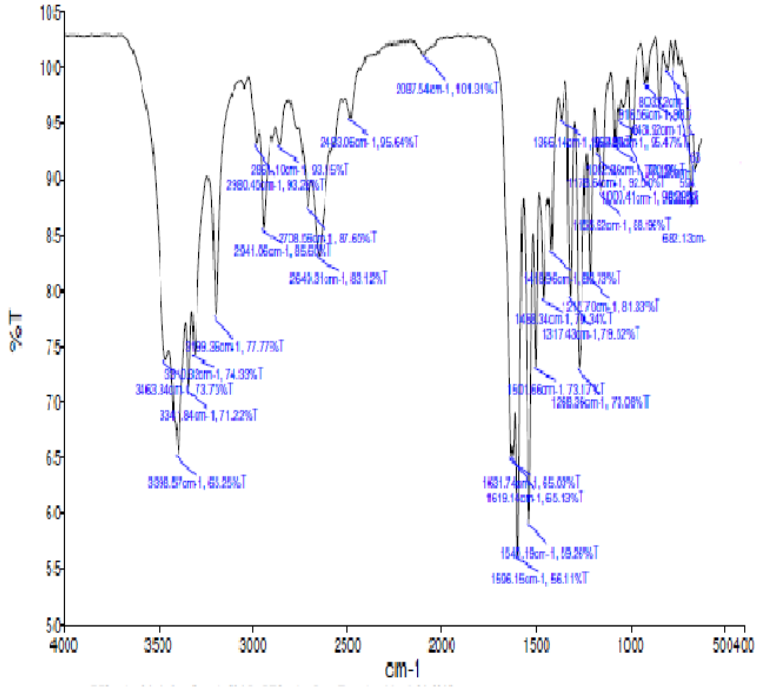


Fig.4.21. FTIR of MET. HCl

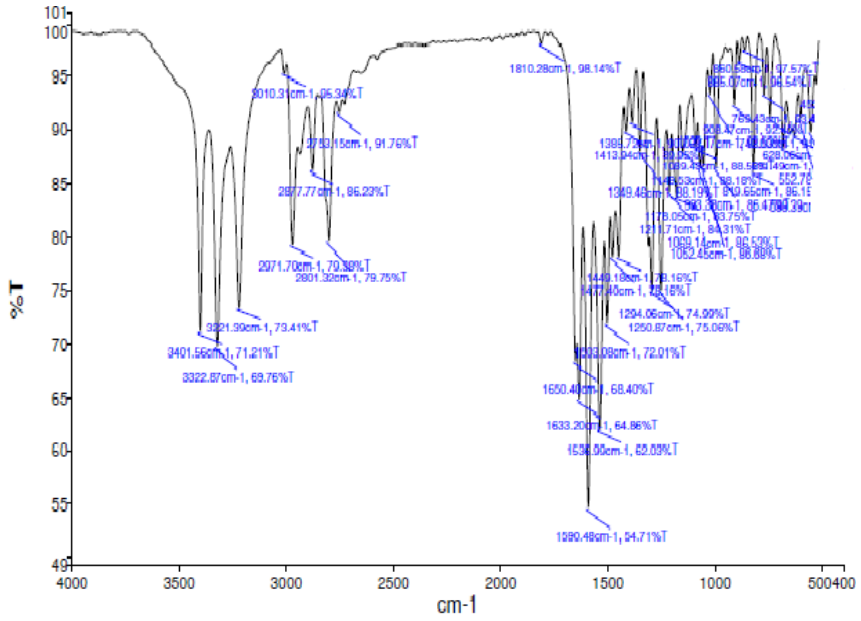


Fig.4.22. FTIR of MET. Base

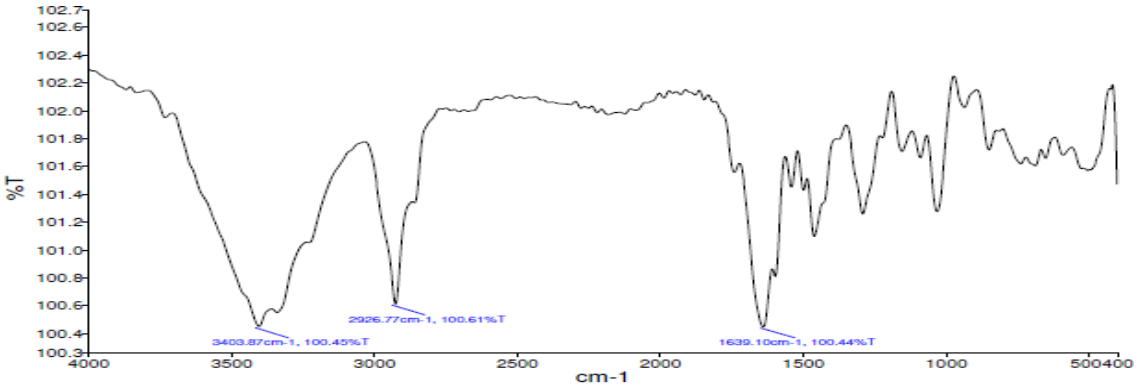


Fig.4.23.FTIR of PVP K 30

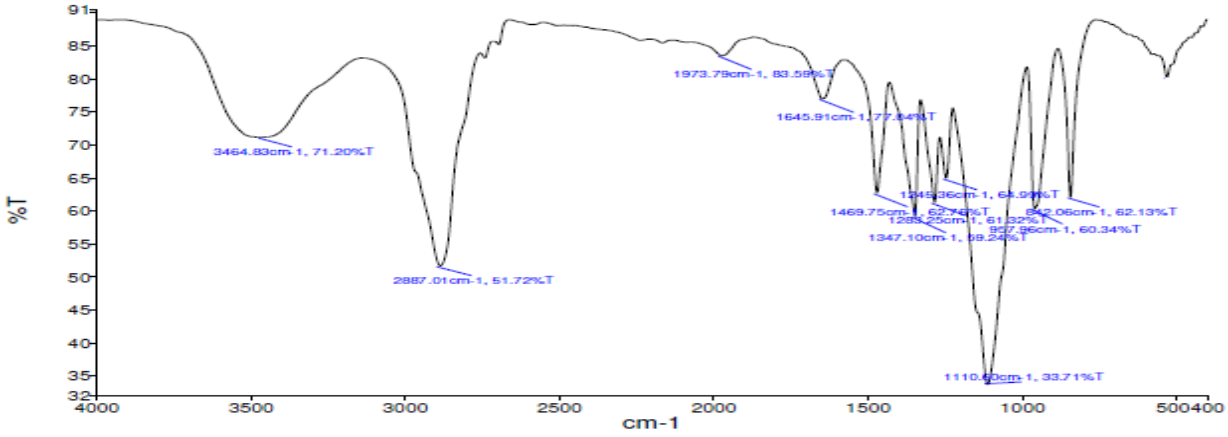


Fig.4.24. FTIR of PLX- 188

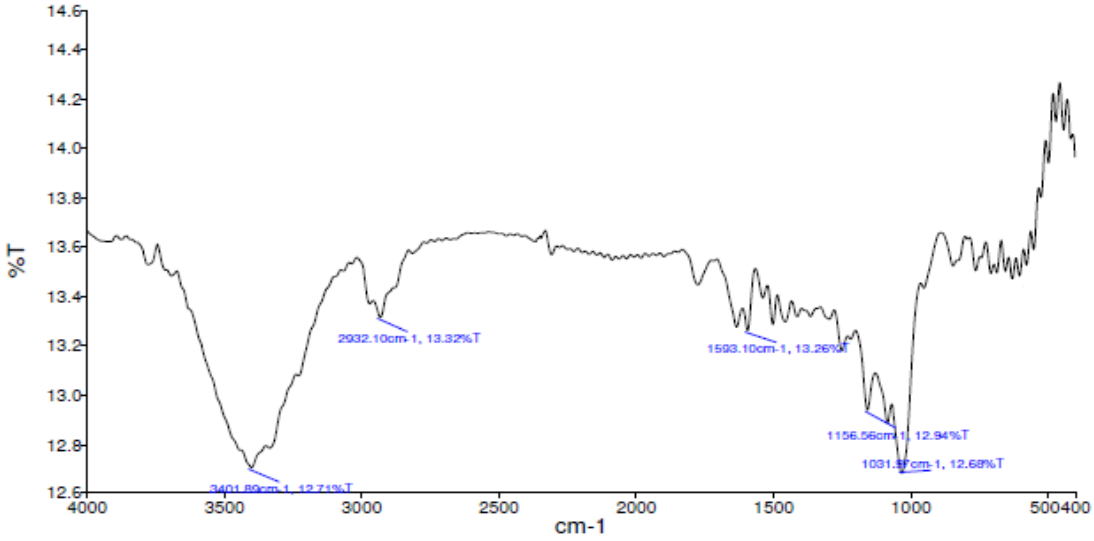


Fig.4.25. FTIR of HPβCD

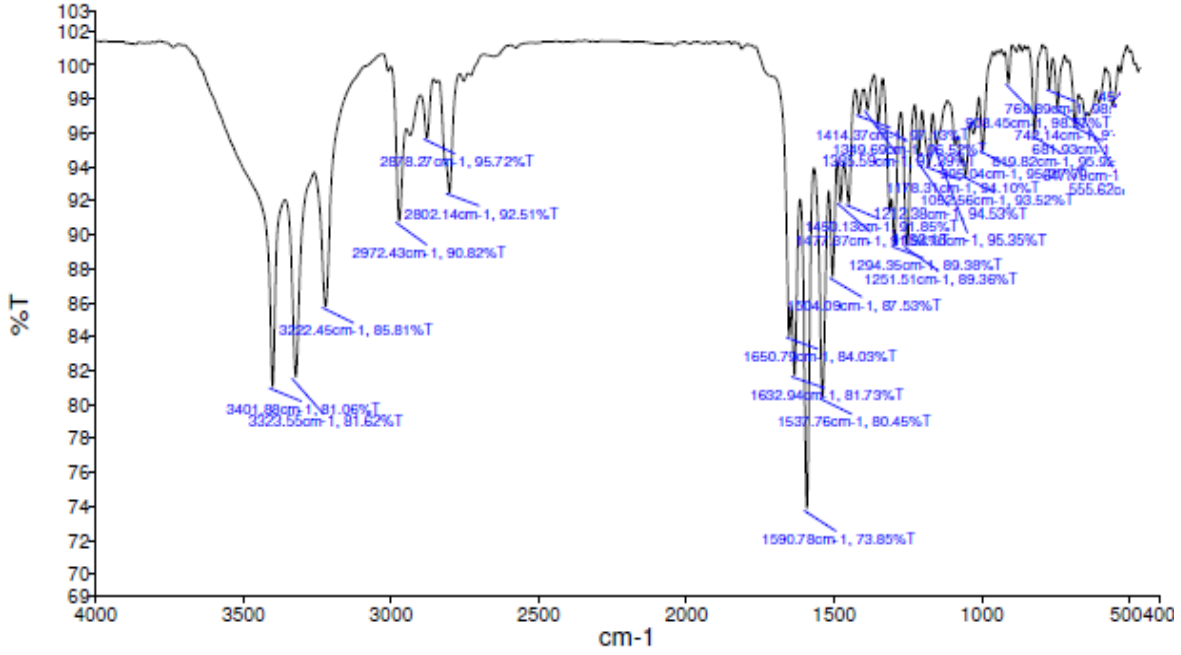


Fig.4.26. FTIR of physical mixture of MET:HPβCD(1:5)

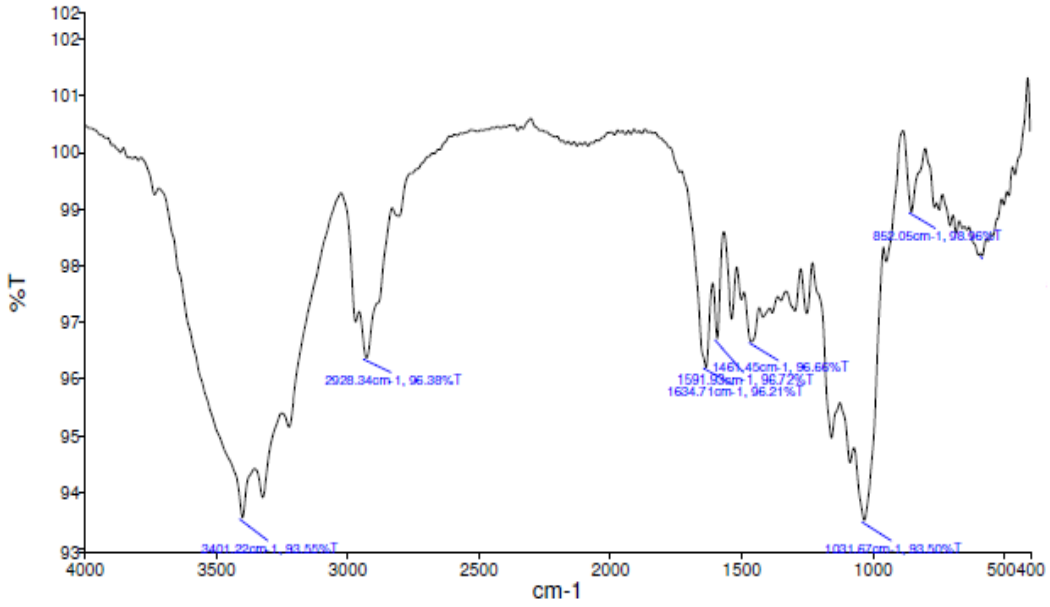


Fig.4.27. FTIR of SD of MET:HPβCD(1:5)

Chapter 5

SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

Poor solubility of new chemical entities is a well-known problem for the past few decades. Several formulation strategies have been proposed to overcome this. Despite the imbalance between significant research efforts and the few successful marketed formulations, the solid dispersion technology still holds a key position among the various formulation strategies to enhance the aqueous solubility/dissolution rate and thereby oral bioavailability of poorly soluble compounds. But only few solid dispersion products are available in market because many others have stability problem. The various processing parameters are involved in the preparation of solid dispersion, which influence the effectiveness, usefulness, stability and safety of the formulation. The use of systemic experimental design along with mathematical optimization is both time and cost efficient and its application assures the formulation quality.

The main objective was to develop modified release dosage form of poorly water soluble drugs in an attempt to improve oral bioavailability. In this present study carvedilol and nifedipine were chosen as drug candidates, because both of them are BCS Class II drugs with very low aqueous solubility and low dissolution rate.

Preparation and Characterization of Metoclopramaide Solid Dispersion

The solubility of metoclopramaide base drug was enhanced by using ionization process and various carriers like HPβCD, PVP K-30 and Poloxamer-188. The phase solubility study gave a support to explain drug-carrier complexation on the basis of thermodynamic parameters. The dissolution rate and solubility of prepared solid dispersions were dramatically improved when compared with that of pure drug, this happened because of conversion of drug from crystalline to amorphous nature and formation of complexation between drug and hydrophilic carriers. Among the all formulations, the solid dispersion of drug prepared with HPβCD by ion solvent evaporation technique showed the better dissolution rate in pH 7.4 and solubility (1367.3 mcg/mL in pH 7.4).

The FTIR spectroscopy of metoclopramaide confirmed that some interaction between the drug and carrier (HPβCD) may occur because of hydrogen bonding in hydroxyl group of carrier. The DSC study suggested that MET base drug is completely converted to amorphous state in solid

dispersion form. Preparation of MET solid dispersion with HPβCD by solvent evaporation method is a promising approach to improve the solubility and dissolution rate of MET base.

After enhancing the solubility and dissolution rate of poorly soluble drugs, the development of dosage form is often necessary to achieve the desired release pattern and effective therapeutic response. Therefore, to achieve as well as to maintain the drug concentration within the therapeutically effective range, the prepared MET base solid dispersion was developed as a transdermal drug delivery system using controlled release polymers and 3M backing layer membrane. Transderml patches were formulated by without drug and polymers, MET HCl and polymers, MET base drug and polymers, SD of MET:HPβCD and polymers , SD of MET:PVP K30 and polymers, SD of MET:PLX-188.

The ex-vivo study were performed of those patches through the pig ear skin in a Franz diffusion cell in phosphate 0.9% saline buffer pH 7.4 at a constant temperature 37° C in 30 minutes time intervals. Among all the patches that was formed SD of MET:HPβCD (1:5) [patch- C] showed that the controlled release permeation. SD of MET: PLX-188 (1:5) [patch- D] was permeate slowly through the skin, patch- B, patch – E higher in permeation not controlled release permeation at a time

Chapter 6

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