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Review on Solubility enhancement of Metoclopramide base by solid dispersion technique for Transdermal drug delivery system

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ABSTRACT

Modern drug discovery has led to the development of drug molecules that exhibit high lipophilicity and poor water solubility, which leads to problematic bioavailability. Approaches have thus been made to enhance dissolution of poorly water soluble drugs through modifications and creation of specific formulations. Metoclopramide is an antiemetic and gastroprokinetic agent, commonly used to treat nausea and vomiting. It is absorbed well after oral administration but a significant first pass effect in some human patients may reduce systemic bioavailability to 30%.The Metoclopramide base is thus modified from Metoclopramide hydrochloride to enhance solubility .This has been achieved by the formulating in solid dispersion since Metoclopramide is poorly water soluble. Though it is absorbed well after oral administration,a significant first pass effect in some patients reduces systemic bioavailability, which can cause adverse side effects. This solid dispersion has then been used through transdermal drug delivery. Enhancement of solubility of poorly water soluble drug by solid dispersion may be attributed to particles modified characters such as particle size reduction, improved wettability, higher porosity, decreased lattice energy, amorphous state. Transdermal drug delivery system has a lot of advantages such as bypassing hepatic first pass, avoidance of risks of I.V therapy, enhancing therapeutic efficiency and others but limitations like skin irritations are also prevalent.

Keywords: Solid dispersion, Metoclopramide, solubility, bioavailability, transdermal drug delivery system.

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Introduction:

Metoclopramide chemically 4-amino-5-chloro-N-[2-(diethyl amino)ethyl]-2methoxybenzamide..The antiemetic action of Metoclopramide is due to its antagonist activity at D2 receptors in the chemoreceptor trigger one in the central nervous systemand this action prevents nausea and vomiting triggered by most stimuli. The gastroprokinetic activity is mediated by muscarinic activity,D2 receptor antagonist activity and 5 HT-4 receptor agonist activities. It has a molecular weight of 299.8 and its melting point is 147 degree Celsius.

Enhancement of solubility of poorly water soluble drug can be done by solid dispersion technique.[1,2,3,4]Though there are simple techniques to prepare solid dispersionsproblems are often encountered ,such as physicochemical stability of drug and vehicle,making suitable formulation of solid dispersion of into dosage forms and scale up of process.

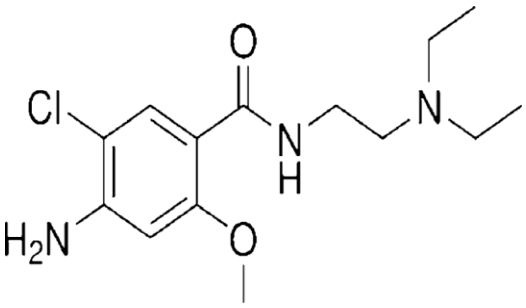

Fig-1:-Structure of Metoclopramide

R.Vijaya et, al (2012) expressed [5] that transdermal drug delivery delivers the drug through topical route for systemic effect at a predetermined andcontrolled rate. In this study, transdermal films of amitriptyline HCl has been formulated using polymers of hydroxypropyl cellulose and polyvinyl pyrolidone in different compositions, the films were then evaluated for their physicochemical properties.

Complexation is one such technique of preparing a solid dispersion,wherein the drug is bound to a carrier because of weak Vander waals forces and it is released from its bound state only when it gets exposed to a suitable chemical environment.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 widely used complex carriers is within the class of cyclodextrins[6,7,8] Cyclodextrins are a family of cyclic oligosaccharides composed of α- (1,4)linked glucopyranosesubunits.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.[9] Complex formation between cyclodextrin and a substrate is assessed by its binding/stability constant.

Yvaraja et al,in(2014)[10]prepared solid dispersion of carvedilol for enhancement of aqueous solubility. To increase solubility polymers like Beta Cyclodextrin, Hydroxypropyl-beta-cyclodextrin were used. Thefollowing solid dispersion were then evaluated through phase solubility studies, determination of partition coefficient, drugcontent (%) and in vitro dissolution studies.

Domanska et al in 2011 investigated [11] the guest host complex formation of three drug derivatives of anthranilicacid, mefenamicacid, niflumic acid with 2-hydroxypropyl-β-cyclodextrin in aqueoussolutions. It was found that solubility of sparingly soluble drugs has been improved by the addition of 2-hydroxypropyl-β-cyclodextrin at two temperatures 298.15 K and 310.15 K and two pH values 2 and 7.

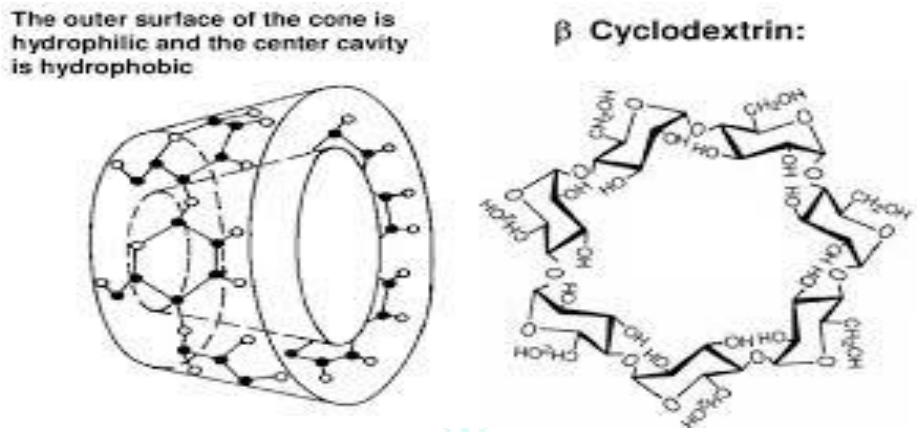

Fig 2:-Structure of Cyclodextrin molecule

Skin and transport through the skin:

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

The human skin[12] is divided into the following layer

(i)The subcutaneous layer

(ii)The dermis

(iii)The epidermis

(iv)The stratum corneum

The 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. Initially drug molecules must be presented to the skin surface. Consequently if theformulation contains solid drug ,then dissolution and diffusion through the formulation is the initial step in delivery. If the formulation contains dissolved drug,then as molecules nearest to skin surface [13,14]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 potentialroutes to cross the skin.

Transdermal drug delivery system*:*

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.

B.Anroopet al.,(2014) [15]in the work studied that, co-aadministration of levodopa and carbidopa through skin using a drug in adhesive transdermal system and assessed the formulation by the methods of in-vitro release,ex-vivo permeation ,and in vivo pharmacokinetics in rat model. This study therefore encloses that the transdermal delivery route [16,,17,18,19]could be a feasible alternative to oral therapy for the successful delivery of levodopa in Parkinson's disease.

B. Anroop[20]et al worked on the transdermal delivery system of Vildagliptin and its comparison with oral therapy.

Ali M.M et al.,in this study,[21]to prepare adomperidone transdermal adhesive matrix patch to improve its therapeutic efficacy ,patient compliance and to reduce the frequency of dosing and side effects,as well to avoid its extensive first pass metabolism.And then evaluate the physicochemical and mechanical properties as well as to in vitro release and rat skin permeation of domperidone. Different formulas of the patches were prepared by solvent using Chitosan, Eudragit E100,Eudragit RS 100 as polymers

with many suitable plasticizer. The physicochemical parameters were then evaluated.

The transdermal drug delivery system 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.topical and transdermal products remain key formulation for delivering drugs not only to the skin,but also through it for systemic action.

Ideal properties of a drug that can be used for transdermal drug delivery system-

(i)Dose should be less than 20 mg/day

(ii)Molecular weight should be less than 400 Dalton

(iii)Melting point of drug should be less than 300 degree Celsius

(iv)Partition coefficient should be between -1 to 4

(v)Skin permeability coefficient more than 0.5 * 10^(-3) cm/h

(vi)Skin reaction must be non irritant and non sensitizing

(vii)Therapeutic index must be low.

The Biopharmaceutics classification system:

It is a system to differentiate 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.

According to the Biopharmaceutics[22,23,24,25]Classification System, drug substances are classified as follows:

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

2. Class II-high permeability, low solubility: The bioavailability of those products is limited by their solvation rate.

3. 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.

4. Class I-high permeability, high solubility: Thosecompounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected.

Preparation and Characterization of Metoclopramide Solid dispersion*:*

Many drugs are under great challenge owing to their poor aqueous solubility and dissolution rates. As per BCS classification both solubility and permeability of a drug regulate extent of maximum absorbable dose. Here, the Metoclopramide base and carrier(HPβCD, poloxamer 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, upon removal of solvent solid powder was obtained.

Conversion of Metoclopramide Hydrochloride to Metoclopramide Base form*:*

Metoclopramide base form is required which is usually available in its in its hydrochloride form. Required amount of Metoclopramide hydrochloride was dispersed in sufficient double distilled water followed by stirring until the total amount of drug gets fully dissolved. Thesolution was neutralized by 1 M sodium hydroxide solution and gradually a precipitate was formed. The precipitate was collected by filtration 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 hot air oven at 50 degrees Celsius. Afterwards the solid material was cooled up to room temperature (25 degrees Celsius).Next; dried solid material was treated with acetone to make a saturated solution ad stirred continuously at 50 degree Celsius. The solution was allowed to attain room temperature and thereafter it was kept in a refrigerator and crystal particles of Metaclopramide (base form) was formed and collected and dried in 50 degrees Celsius in hot air oven. The material was cooled at room temperature and it was weighed.

Preparation of Metoclopramide Solid dispersion:

Various methods of preparation of solid dispersion had been reported in earlier literature such as Fusion method, Solvent evaporation technique, Kneading methods and use of surface active agents.

Solvent evaporation technique was carried out by dispersing physical mixture and polymer at certain common ratio and then it was evaporated until transparent solvent free thin layer of mass was obtained. Then the film was dried till constant weight at 50 degrees Celsius

Sadozai et al.,(2013) The objective of this study[26] 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 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 xanthan gum was directly proportional to the concentration of 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 fluctuation due to uneven distribution of drug and polymer.

Characterization of Metoclopramide solid dispersion:

Characterization of solid dispersion was performed by instrumental analysis like Fourier Transform Infrared Spectroscopy (FTIR) analysis and Differential Scanning Calorimetry (DSC) analysis[27, 28]. FTIR analysis was done to observe the stability of drug and also to confirm drug polymer interaction if any.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.

Studies such as aqueous solubility study, Dissolution study, Ex-vivo permeation study, in vitro diffusion study was also performed.

Solubility of pure drug Metoclopramide increases in acidic pH. Metoclopramide is sparingly soluble in double distilled water. Its aqueous solubility in double distilled water increases linearly keeping drug amount fixed when fraction of carrier substance (HPβCD) in solid dispersion is increased. Various solubility data were compared and it was observed that solubility of drug in pH 5.5 was 28.95 times

greater than that of pure drug in double distilled water samples without any carrier substances.

The solubility of Metoclopramide base drug was enhancedby using ionization process and various carriers like HPβCD, PVP K-30, 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 to 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. When solid dispersion was prepared using various carriers, the solid dispersion of drug with HPβCD by ion solvent evaporation technique showed better dissolution rate in pH 7.4.

The FTIR spectroscopy of Metoclopramide confirmed that some interaction between the drug and carrier may occur because of hydrogen bonding in hydroxyl group of carrier whereas the DSC study suggested that base drug is completely converted to amorphous state in solid dispersion form.

After enhancing the solubility and dissolution rate of poorly soluble drug. 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 Metoclopramide base solid dispersion was developed as a transdermal drug delivery system using controlled release polymers and 3M backing layer membrane. Transdermal patches were thus formulated.

The ex-vivo study when performed of those patches through the pig ear skin in Franz diffusion cell in phosphate 0.9% saline buffer pH 7.4 at a constant temperature 37 degree Celsius in 30 minutes time interval. Among all the patchesthatwas formed MET:HPβCD (1:5) (patch C) showed that the controlled release permeationMET:PLX (1:5)[patch D] was permeate slowly through the skin.

Conclusion:

Several double distilled water formulation strategies have been proposed to overcome the problems of solubility, which is a well known problem. Though there have been loads of research efforts made, there are a very few successful marketed formulations available in the market. To counter this problem, development of solid dispersion is a very promising approach and it holds a key position among various other strategies proposed. Development of solid dispersion is thus done to enhance aqueous solubility and thus to ensure oral bioavailability of poorly soluble drugs.

But only very few solid dispersion products are available in the market due to stability factors.Various processing parameters that are involved in the development of solid dispersion affect the effectiveness, stability[29,30], usefulness and safety of the formulation prepared which in turn affects the fact that whether it can be marketed or not.The use of systemic experimental design along with mathematical optimization is both time and cost efficient and its application assures the formulation quality.

Thus this review provides a brief insight of research works performed by various scientists relating to solid dispersion and using it for transdermal drug delivery system. Formulating solid dispersions is a promising field and in future can be used thoroughly for preparing formulations for sparingly soluble drugs. However, not much research has been done to check its therapeutic efficacy of the drug molecule when formulated in solid dispersions remains the same or not , and this is therefore an area that can still be explored a lot. We must also try to prepare formulations other than solid dispersions for sparingly soluble drugs as solid dispersions have stability problems in the physiological systems.

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