ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF LOPINAVIR BY SOLID DISPERSION TECHNIQUE

A Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the requirement for the award of the degree of

MASTER OF PHARMACY

(PHARMACEUTICS)

Submitted By

Reg. No: 26104208

Under the guidance of

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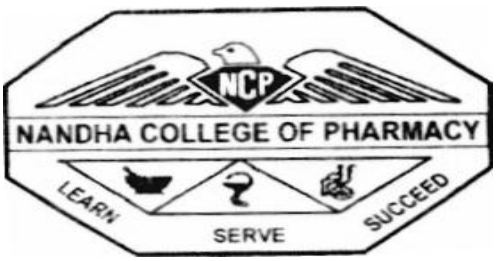

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CERTIFICATE

This is to certify that the work embodied in this thesis entitled, "**ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF LOPINAVIR BY SOLID DISPERSION TECHNIQUE"** submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai, was carried out by (Reg.No: 26104208)**,** Department of Pharmaceutics, Nandha College of Pharmacy, Erode-52 for the partial fulfillment for the award of degree of Master of Pharmacy in Pharmaceutics under my supervision.

This work is original and has not been submitted in part or full for any other degree or diploma of this or any other university.

Place : Erode

Date :

Dr. Prof. P. R. Radhika
Research Guide

DECLARATION

The work presented in this thesis entitled "**ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF LOPINAVIR BY SOLID DISPERSION TECHNIQUE"** was carried out by me in the Department of Pharmaceutics, Nandha College of Pharmacy, Erode-52 under the direct supervision of **Prof. P. R. Radhika, M.Pharm, Ph.D.,** Nandha College of Pharmacy, Erode-52.

This work is original and has not been submitted in part or full for the award of any other degree or diploma of any other University.

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LIST OF ABBREVATIONS

GIT	: Gastrointestinal tract
Tg	: Gastrointestinal temperature
FT –IR	: Fourier transforms infrared spectroscopy
%	: Percentage
Mg/ml	: Microgram per liter
nm	: Nanometer
°C	: Degree centigrade
Amt	: Amount
PVP	: Poly vinyl pyrrolidone
SLS	: Sodium lauryl sulphate.

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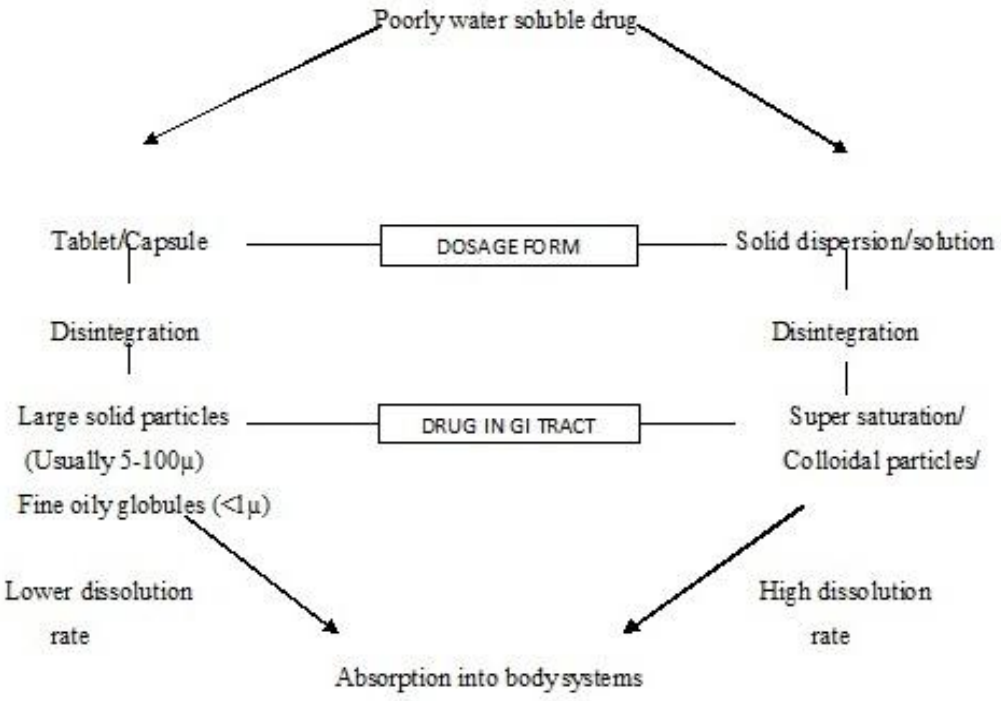
Introduction

1.1 Introduction to Solid Dispersions: [1]

As early as in 1961, Sekiguchi et al. developed the concept of solid dispersion to enhance absorption of poorly water-soluble drugs. It involved formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixtures, and once the carriers dissolved, the drug precipitated in a finely divided state in water. Later, Goldberg et al. demonstrated that a certain fraction of the drug may also be molecularly dispersed in the matrix, forming solid solutions, while other investigators reported that the drug may be embedded in the matrix as amorphous materials. On the basis of these considerations, Chiou and Riegelman defined solid dispersion as "the dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredients could exist in finely crystalline, solubilized, or amorphous states."



Flow Chart: Advantages of a solid dispersion formulation, as compared to conventional capsule or tablet formulations, for enhancing dissolution rate, and consequent bioavailability of poorly water-soluble drugs.

Need of Solid Dispersion: [1, 3]

Compared to conventional tablet and capsule dosage forms, solid dispersion formulations are relatively complex drug delivery systems, requiring a substantially greater commitment of time, effort, and resources for development.

Therefore, whether there is a need for solid dispersion and whether the desired bioavailability enhancement will not be achieved by other relatively less complex techniques such as particle size reduction or salt formation, should be assessed by careful in-vitro assessment of the NCE's biopharmaceutical properties and the relevance of these findings to the projected in-vivo formulation performance.

Horter and Dressman defined a poorly water-soluble drug as one for which the dissolution time of a single dose in the GI fluids exceeds the normal transit time through the absorptive regions of the GIT.

Hence, the absorption of poorly water-soluble compounds is dose dependent and controlled by the dissolution rate in the GIT and solubility in GI fluids. The fraction of the dose absorbed will decrease with an increase in the dose size if the drug particle size or surface area is held constant, while, on the other hand, if the dose size is held constant, the fraction of the dose absorbed will increase with a reduction in particle size or an increase in the particle surface area. If it is determined that complete absorption of the dose might be obtained by reducing the particle size, for instance, to approximately 2–5µm (within the range of standard manufacturing capability), a conventional tablet or capsule dosage form may still be feasible.

However, if it is determined that particle size reduction to the submicron range is necessary; a solid dispersion may provide a viable alternative. In silico absorption modeling with software packages, such as Gastro Plus® (Simulations Plus, Lancaster, California), have demonstrated utility in determining the impact of particle size reduction on drug absorption.

Advantages:

- Processing equipment available at small and large scale
- Thermolabile products
- Most carriers can act as "solid" solvent
- Carriers (mainly surface active agents) can maintain super saturation in GI tract
- Downstream processing is possible

Disadvantages:

- Understanding the physics of amorphous materials
- Understanding the physical structure of solid dispersions
- Understanding the relationship between physical structure and drug release
- Stability issues; residual solvents
- Prediction of shelf life of amorphous materials
- Increasing number of drugs with low solubility in organic solvents
- Few new carriers

Preparation Methods:

Fusion Method: [14]

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term fusion method is preferred. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method.

The dispersion consisted of sulfathiazole and urea as a matrix which were melted using a physical mixture at the eutectic composition, followed by a cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling.

This procedure resulted in solid dispersions of type I. PEG (Poly ethylene glycol) is a hydrophilic polymer often used to prepare solid dispersions with the fusion method. This often results in solid dispersions of type III since many drugs are incorporated as separate molecules in the helical structure present in a crystalline PEG. The helices are aligned in orderly fashion, illustrating that PEG easily crystallizes. Another polymer frequently applied as a matrix in the fusion method is PVP (polyvinyl pyrollidone). PVP, supplied in the amorphous state, is heated to above its *Tg* (Glass transition temperature).

The drug has to fuse with or dissolve in the rubbery matrix, which is subsequently cooled to vitrify the solid dispersion. When PVP is used as matrix, solid dispersions of type V or VI are obtained.

The mode of incorporation of the drug depends on the PVP-drug miscibility and the preparation procedure. Grinding is required to obtain the solid dispersion as powder that is easy to handle.

Although frequently applied, the fusion method has serious limitations. Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture, which results in an inhomogeneous solid dispersion.

This can be prevented by using surfactants. Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions. Thirdly, degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug.

For example, to melt a sugar matrix of galactose a temperature of 169°C was required and in order to get the glassy PVP in the rubbery state a temperature of about 170°C is required. PEG's melted at around 70°C and are therefore often used for the preparation of solid dispersions with the fusion method.

Hot melt extrusion: [14]

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem.

Solubility parameters are investigated to predict the solid-state miscibility and to select matrices suitable for melt extrusion. High shear forces resulting in high local temperatures in the extruder be a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.

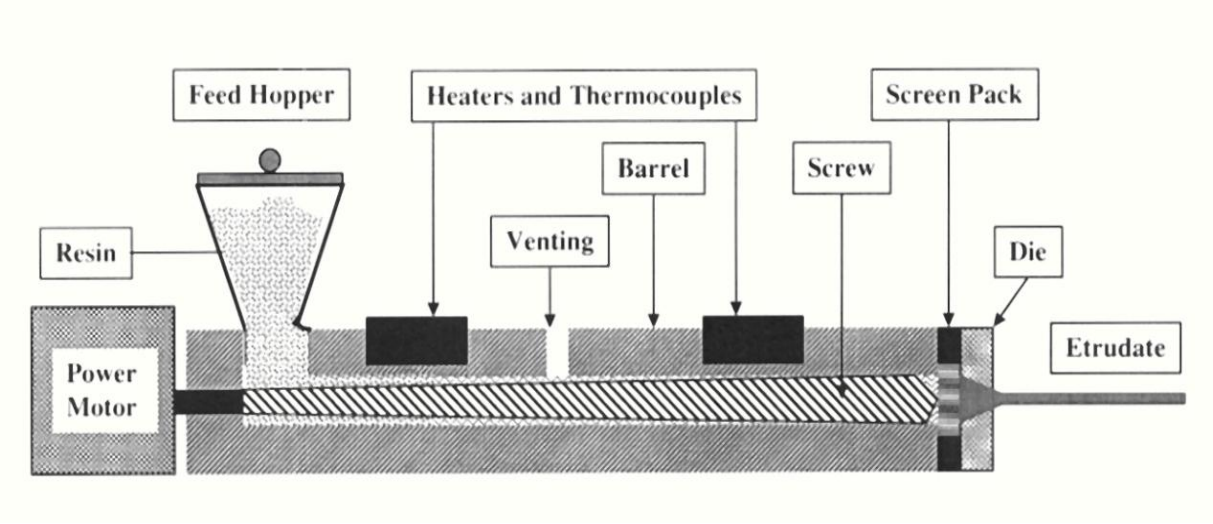


Fig-2

Solvent evaporation method: [14]

The first step in the solvent evaporation method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. Using the solvent method, the pharmaceutical engineer faces two challenges. The first challenge is to mix both drug and matrix in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible, preferably drug and matrix material are in the dissolved state in one solution.

Various strategies have been applied to dissolve the lipophilic drug and hydrophilic matrix material together in one solution. Low drug concentrations are used to dissolve both drug and matrix material in water, but this requires evaporation of tremendous amounts of solvent, making the process expensive and impractical. Solubilisers like cyclodextrins or surfactants like Tween80® increase the aqueous solubility of the drug substantially.

However, the amounts of solubilisers or surfactants in the final product are often eminent. This results in solid dispersions that, to a significant extent, consist of solubilisers or surfactants, materials that significantly change the physical properties of the matrix (e.g.

decrease of Tg). Moreover, only dosage forms with low drug loads are possible. In addition, they are not always tolerated well in the body or may even be toxic. Chloroform or dichloromethane have been used to dissolve both drug and PVP as matrix simultaneously.

These solvents are used also in other preparation methods. However, according to the ICH-Guidelines, these solvents belong to Class I, comprising the most toxic solvents. Therefore, the use of these solvents is unacceptable and impractical because the amount of residual solvent present in the solid dispersion after drying has to be below the detection limits. The last strategy for the dissolution of both drug and matrix is the use of solvent mixtures. Water and ethanol, or dichloromethane and ethanol have been used for this purpose.

However, dissolution of drug and matrix in these mixtures is not always possible in the required concentration or ratio. The second challenge in the solvent method is to prevent phase separation, e.g. crystallization of either drug or matrix, during removal of the solvent(s). Drying at high temperatures speeds up the process and reduces the time available for phase separation. On the other hand, at high temperatures the molecular mobility of drug and matrix remains high, favouring phase separation (e.g. crystallization).

To dry the solutions, vacuum drying is often used. The solution is dried by the application of vacuum and moderate heating. Sometimes, the solvent evaporation is accelerated by using a rotary evaporator. Afterwards the formed solid dispersion is often stored in a vacuum desiccator to remove the residual solvent. Vacuum drying at elevated temperature bears the risk of phase separation because the mobility of drug and matrix decreases slowly.

Another drying technique is spray drying. The solution is dispersed as fine particles in hot air. Due to the large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation. Moreover, the solid dispersions prepared by spray drying consist of particles of which the size may be customized by changing the droplet size to meet the requirements for further processing or application (e.g. free flowing particles or particles for inhalation). Spray drying usually yields drug in the amorphous state, however sometimes the drug may have (partially) crystallized during processing.

An alternative to these drying techniques is freeze drying. Although it is concluded in literature that this is a promising and suitable technique to incorporate drug substances in stabilizing matrices, the technique is poorly exploited for the preparation of solid dispersions. One of the reasons might be the low freezing temperature of most organic solvents. Obviously, sublimation during freeze drying is only possible when the solvent stays frozen.

In addition when the formation of a glass is envisaged, the sample temperature should be kept below the Tg of the maximally freeze concentrated fraction. Therefore, low sample temperatures are required which slows down the process. Betageri and Makarla used a condenser temperature of -75°C, to dry a solution with cyclohexanol as the solvent. In table 6 an overview is presented of several organic solvents. To obtain a lyophilization process of acceptable duration, the solvent should have a sufficiently high vapour pressure. As can be seen in table 6, dimethylsulphoxide DMSO has a high melting temperature but it has a very low vapour pressure. Therefore, DMSO is not suitable as a solvent for freeze drying.

A suitable solvent that meets both requirements is 2-methyl-2-propanol or tertiary butanol (TBA), because it has a high melting temperature as well as a high vapour pressure. The application of TBA in lyophilization is discussed by Teagarden. Also mixtures of solvents can be considered. However, in that case the phase diagram of the mixture should be consulted. For example, while water and DMSO have melting points of 0°C and 19°C, the mixture has eutectic points below -60°C. The sample temperature of such a mixture should be kept below this value, which causes a slow sublimation.

An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified.

An even more promising drying technique is spray-freeze drying. The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. The large surface area and direct contact with the cooling agent result in even faster vitrification, thereby decreasing the risk for phase separation to a minimum. Moreover, spray freeze drying offers the potential to customize the size of the particle to make them suitable for further processing or applications like pulmonary or nasal administration.

Spray Drying: [14]

Spray drying is a process where a solution of drug substance and carrier is evaporated by spraying the solution as a droplet into a chamber that is maintained under controlled conditions of heat, humidity, and air flow. The dissolution rate of many poorly water-soluble drugs has been enhanced using spray drying.

Organic solvents are normally used during spray-drying process as they are easy to evaporate and possess good solvent capacity for many poorly water-soluble drugs. The morphology form of solid dispersion, and consequently the drug dissolution and stability, can be impacted by the process parameters and geometry of equipment. For instance, the particle size of spray-dried solid dispersion can be controlled by varying the concentration of solute in spray-drying liquid and the droplet size during spray-drying process.

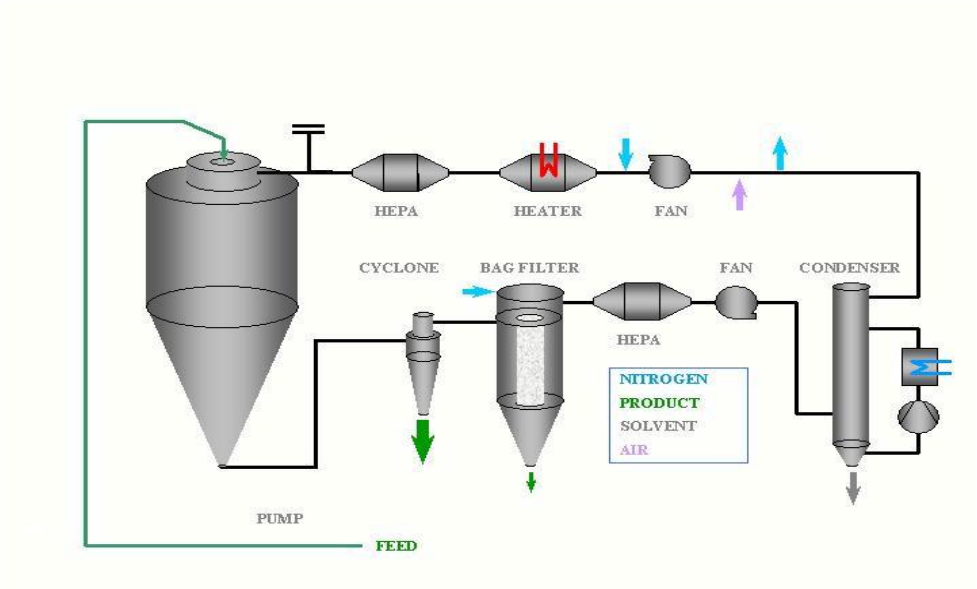


Fig-3

Supercritical fluid methods: [15]

Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used as either a solvent for drug and matrix or as an anti-solvent. When supercritical CO_2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO_2 is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is known as Rapid Expansion of Supercritical Solution (RESS). However, the application of this technique is very limited, because the solubility in CO_2 of most pharmaceutical compounds is very low (<0.01wt-%) and decreases

with increasing polarity. Therefore, scaling up this process to kilogram-scale will be impractical.

All other supercritical techniques are precipitation methods. Although generally labelled as solvent-free, all these supercritical fluid methods use organic solvents to dissolve drug and matrix and exploit the low solubility of pharmaceutical compounds in CO_2. In fact, these techniques represent alternative methods to remove solvents from a solution containing typically a drug and a polymer. Moneghini and co-workers reported their method as solvent-free, but they dissolved PEG and carbamazepine in acetone. They used a technique that is called the Gas-Anti-Solvent technique (GAS) or Precipitation from Gas Saturated Solutions (PGSS). The solution is brought into contact with compressed CO_2. The conditions are chosen so that CO_2 is completely miscible with the solution under supercritical conditions, whereas drug and matrix will precipitate upon expansion of the solution. When the volume of the solution expands the solvent strength (i.e. the ability to dissolve the drug) decreases. This results in precipitation of matrix and drug. Since this technique is often applied with PEG as matrix, this technique results in formation of a solid dispersion with a crystalline matrix (mostly type II or III).

The second type of precipitation technique involves the spraying of a solution containing drug and matrix through a nozzle into a vessel that contains a liquid or supercritical anti-solvent. The supercritical anti-sol droplets, in which drug and matrix become supersaturated, crystallize and form particles. The general term for this process is Precipitation with Compressed Anti- Solvent (PCA). More specific examples of PCA are Supercritical Anti Solvent (SAS) when supercritical CO_2 is used, or Aerosol Solvent Extraction System (ASES), and Solution Enhanced Dispersion by Supercritical fluids (SEDS).

However, as with the other solvent techniques described in the previous section, the critical step in these precipitation techniques might be the dissolution of drug and matrix in one solution. The use of water is limited, because the water solubility in compressed CO_2 is limited. Usually organic solvents like dichloromethane or methanol have to be applied to dissolve both drug and matrix.

Other methods:

Evaporative precipitation into aqueous solutions (EPAS) was used to coat a colloidal suspension of carbamazepine with block-copolymers as stabilizing surfactants. A solution of drug in dichloromethane was sprayed in an aqueous solution containing polymeric surfactants as stabilizers. The obtained colloidal suspension was spray dried, freeze dried or spray freeze dried, resulting in solid dispersions of type IV/V. It was concluded that the amorphous state of the drug was best preserved with the spray freeze drying process.

In another process called supercritical fluid impregnation, the drug is dissolved in a supercritical fluid and exposed to solid matrix material that swells and absorbs the supercritical solution. By varying the pressure and the time of exposure, the diffusion process can be controlled. The absorption stops when the pressure is reduced. This process is investigated for polymethyl methacrylate but can be applied for other polymers as well.

In an electrostatic spinning process a drug-matrix solution is pumped through an orifice and then subjected to an electrical field to form fibres with a diameter of micro- or nano-scale. This process is restricted to a limited amount of matrices, because only a few high molecular weight materials are fibre forming materials. The fibre diameter can be adjusted by surface tension, electrical field and dielectric constant. After rapid evaporation of the solvent, the fibres can be directly used or milled and further processed.

Carriers: [11, 13]

Selection criteria for polymeric carriers:

- High Tg
- Super saturation potential
- screening studies from DMSO, DMF in aqueous carrier solutions
- Possibility of interactions with drug
- Solid state solubility (miscibility) of drug in the carrier (molecular dispersion)
- phase behavior studies ("*one Tg*") films
- Theoretical models (e.g. Flory-Huggins)
- Solubility in monomers (e.g. NMP)
- Ternary phase diagrams
- Solubility in water (organic solvents depending on manufacturing process)
- manufacturing process.

Type of carriers:

Sugars: Dextrose, Sucrose, galactose, Sorbitol, Maltose, Xylitol, Mannitol, lactose.

Acids: Citric acid, Succinic acid.

Poymeric Materials*:* Povidone, PVP, PEG, HPMC, Methyl Cellulose, HEC, Cyclo dextrins, HPC, Pecttin.

Insoluble and Enteric Polymers**:** HPMC phthalate, Eudragit L-100, Eudragit S-100, Eudragit RL, and RS.

Surfactants: Polyoxy Etthylene Stearate, Renex poloxamer 188, Texafor AIP, Deoxycholic acid, Tweens, Spans.

Miscellaneous: Penta erithrytol, Penta erithryl tetra acetate, Urea, Urethane, Hydroxy alkyl Xanthins.

Current Trends in Solid dispersions: [2]

In recent years due to application of combinational chemistry and high-throughput screening during drug discovery, a majority of new drug candidates exhibits poor aqueous solubility, compounds to be very challenging for formulation scientists in development of bioavailable dosage forms for such.

A poorly water soluble compound has classically been defined as one dissolving in less than 1part per 10000 part of water. A poorly water soluble drug, more recently, has been defined in general terms to require more time to dissolve in the gastrointestinal fluid than it take to be absorbed in the gastrointestinal tract. Thus a greater understanding of dissolution and absorption behaviors of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products.

Although salt formation, particle size reduction, etc. have commonly been used to increase dissolution rate of the drug, there are practical limitation with these techniques the desired bioavailability enhancement may not always be achieved. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate/prepare solid dispersion.

Chiou and Riegelman defined the term solid dispersion as **"a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures"**.

The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method. Sekiguchi and Obi suggested that the drug was present in a eutectic mixture in a microcrystalline state, after few years Goldberg et.al. Reported that all drug in solid dispersion might not necessarily be presents in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution.

Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high. The commercial use of such systems has been limited primarily because of manufacturing problems with solid dispersion systems may be overcome by using surface active and self-emulsifying carriers. The carriers are melted at elevated temperatures and the drugs are dissolved in molten carriers.

Surface-active agents are substances that at low concentrations adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy and the surface and the interfacial tension. Surface-active agents have a characteristic structure, possessing both polar (hydrophilic) and non-polar (hydrophobic) regions in the same molecule. The surface active carriers are said to be amphipathic in nature.

Surface active carriers uses in Pharmaceutical preparation: [9]

Because of their unique functional properties, surface active carriers find a wide range of uses in pharmaceutical preparations. These include, depending on the type of product, improving the solubility or stability of the drug in the liquid preparation, stabilizing and modifying the texture of semisolid preparations, or altering the flow properties of the final tablet dosage form. In addition to their use as excipients to improve the physical and chemical characteristics of the formulation, surface active carriers may be included to improve the efficacy or the bio performance of the product.

The properties of surfactant are such that they can alter the thermodynamic activity, solubility, diffusion, disintegration, and dissolution rate of a drug. Each of these parameters influences the rate and extent of drug absorption. Furthermore, surface active carriers can exert direct effects on biological membranes thus altering drug transport across the membrane.

The advantage of a surface-active carrier over a non-surface-active one in the dissolution of drug from a capsule formulation is shown schematically in Figure below. The physical state of drug if a solid dispersion must, however, is carefully considered an evaluating the advantage of a surface-active vehicle. As mentioned earlier, the drug can be molecularly dispersed in the carrier to form a solid solution or it can be dispersed as particles. It can also be both partially dissolved and partially dispersed in the carrier.

The potential for the formation of a continuous drug rich surface layer is possibly greater if the drug is molecularly dispersed, whereas the drug dispersed, as particulates may be more prone to dissociation from the water-soluble matrix. It is however, rare that the drug is dispersed just as particulates and is not at least partially dissolved in the vehicle. Therefore, a surface-active carrier is preferably in almost all cases for the solid dispersion of poorly water-soluble drugs.

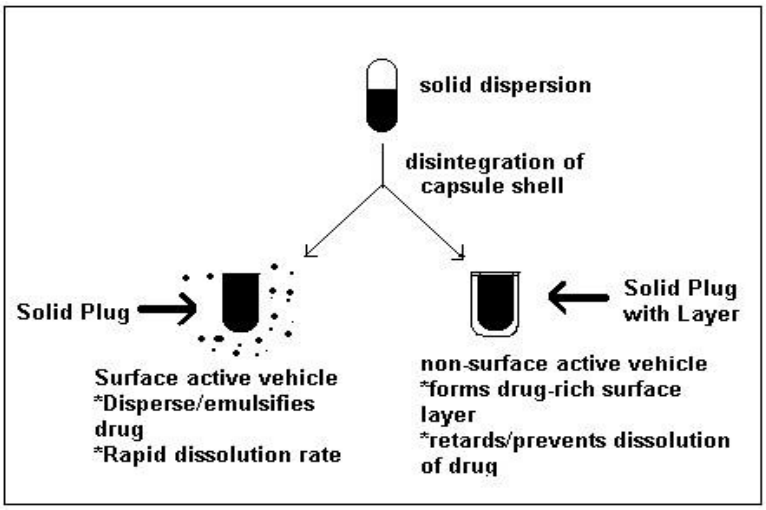


Figure: 4 A schematic representation of the comparative dissolution of a poorly water-soluble drug from surface-active versus non surface-active vehicle.

Block Copolymers as Pharmaceutical Surface active carriers:

The toxicity of many pharmaceutical surface active carriers has led to the search of more acceptable solubilizers. Soluble surface-active block copolymers of polyoxyethylene and polyoxypropylene have been used widely in pharmaceuticals and significantly found favor for such critical applications as emulsifiers for intravenous lipids and as priming agents for heart lung apparatus.

A range of commercial block copolymer surface active carriers are available under the Pluronic, Pluronic R, Tetronic, and pluradot trade names; their preparation and properties have been reviewed by schmolka. The corresponding nonproprietary names of the first three

types are Poloxamer, Meroxapols and Poloxamine, respectively, there being no equivalent name for the plurodot compounds.

Poloxamers are polyoxyethylene-polyoxypropylene-polyoxyethylene (ABA) block copolymers; The Meroxapols are polyoxypropylene-polyoxyethylene- polyoxypropylene (BAB) copolymers; The Poloxamine structure, $(AB)_2NCH_2CH_2N(BA)_2$, is in full form as below.

$[H(C_2H_4O)_a(C_3H_6O)_b]_2NCH_2CH_2N[(C_3H_6O)_b(C_2H_4O)_aH]_2$

The Poloxamers have been most widely studied to date, yet there has been considerable confusion in the literature over the exact nature of their colloidal behavior, in particular whether micelles are formed. Recently, surface tension measurement on a series of Poloxamers in aqueous solution and photon correlation spectroscopy has helped to resolve some of these problems, but as benefits their structure their behavior patterns tend to be complex.

At low concentrations, approximating those at which more conventional nonionic detergents form micelles, the Poloxamers monomers are thought to form monomolecular micelles by a change in configuration in solution. At higher concentration these monomolecular micelles associate to form aggregates of varying size, which have the ability to solubilize drugs and to increase the stability of solubilized agents.

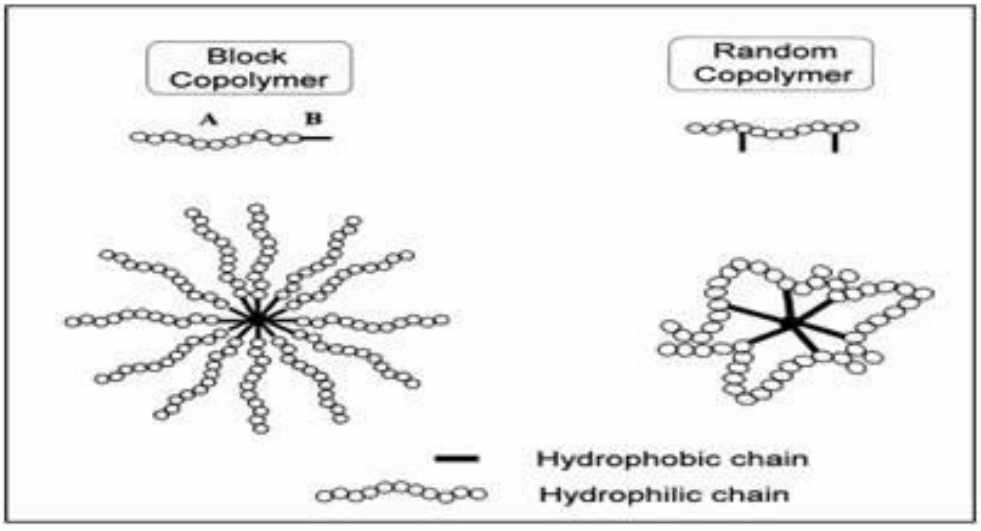


Figure: 5 Schematic representations of block and random copolymer micelles

The solubilities of some Para substituted acetanilide in aqueous Poloxamers solutions increase with increasing ox ethylene content of the polymer, although the more hydrophobic solutes do not show this trend. The results show that, e.g., 4-nitroacetanilide is less soluble in more hydrophilic Poloxamers, and this is the general trend shown by the halogenated

derivatives. Pluronic F68 solubilizes some benzocaine, which above an apparent CMC of 0.23% w/v has a slope for the solubility curve K, of 0.019, i.e., $S= S_O + K (C_{surfactant} - CMC) =S_O +0.019(C_{surfactant} – CMC)$. The order for solubilization of benzocaine is Triton WR1339 (a tert-octylphenol with ethylene oxide) > Brij 35 > Tetronic 908 > Pluronic F68. At 3% levels the half-life of benzocaine is increased 4 times by Brij 35 and triton WR1399, but the limited solubility of benzocaine in Pluronic solutions results in only a marginal increase in half-life. Pluronic F68 lowers blood viscosity and has been advocated. Intravenous administration of Pluronic F38 is followed by rapid excretion in the urine; F68 appears in bile to the extent of 6% of the injected IV dose. Poloxamers 108 (Pluronic F38), although rapidly phagocytosed, is well tolerated even when administered intravenously in large doses.

Pluronic block copolymers are synthesized by sequential polymerization of propylene oxide and ethylene oxide. It consists of combined chain of oxyethylene with oxy propylene where oxyethylene impart hydrophillicity whereas oxypropylene impart lipophilicity. Each molecule is synthesized as long segment of the hydrophilic portion combined with long segment of hydrophobic portion referred to as block copolymer. A defining property of Pluronic is ability of individual block copolymer molecules termed as “unimers” to self-assemble into micelles in aqueous solution.

The “unimers” form a molecular dispersion in water at block copolymer concentrations below the critical micelle concentration. At concentration above CMC, the unimers molecule aggregate, forming micelles with propylene oxide bock in the inner core of micelles covered by the hydrophilic corona from ethylene oxide block. The water insoluble compounds are transpired into the propylene core of the micelles.

Block copolymer micelles are aggregates that resemble many properties of micelles formed by low molecular weight surface active carriers. They are the consequence of a self-assembling tendency displayed by block copolymers when dissolved in a so-called selective solvent, which is a good solvent for one of the blocks, but a poor one for the other. Solvent selectivity and, hence, copolymer self-assembling, have been observed for a variety of block copolymers in water, polar and non-polar organic solvents and, more recently, in supercritical fluids.

For this generality and for the possibility of tuning the aggregate properties by varying either the kind of monomer or the size and proportion of the constituting blocks, these aggregates are able to provide a much wider range of applications than that observed for normal surface active carriers, involving solubilization of drugs or pollutants, as nonreactors, in controlled drug delivery and as potential DNA carriers, among others.

Limitations of Surface active carrier based Solid Dispersions: [9]

Solid dispersion in surface-active carriers may not be the answer to all bioavailability problems with poorly water-soluble drug. One of the limitations of bioavailability enhancement by this method might be the low solubility of drug in available carriers. The desired dose of a drug cannot be solubilized and filled into the hard gelatin capsules if adequate solubility in a carrier cannot be obtained.

Dordunoo et al reported that the particle size of a drug in a solid dispersion remained unchanged if it is just mixed with the carrier instead of dissolving in it. On the other hand, if the drug is dissolved by heating in excess of its solubility in a carrier under normal storage condition, it may subsequently crystallize out from the solid dispersion. Either situation would defect the purpose of bioavailability enhancement of poorly water-soluble drugs by solid dispersion.

Another possible limitation of the use of surface-active carrier reported by Aungst et al. is that the bioavailability of a drug may vary depending on the amount of carrier administered along with it. This variation is because different amounts of a surface-active carrier may have different solubilization or dispersion effects on a drug in the gastrointestinal fluid. Serajuddin et al. reported a method whereby the rate and efficiency of dispersion of drug in aqueous media from different formulations can be studied.

Hydrophilic Polymers:

Polymers like PEG, PVP, UREA has become extremely popular in controlling the release rate of drugs from solid dosage forms. When a matrix containing a swellable glassy polymer comes into contact with a solvent, a progressive alteration from the glassy to the rubbery state leads to a swelling process. For matrix system, drug is often released by diffusion, because a sort of receding drug boundary comes to exist within the system. Hydroxypropylmethylcellulose (HPMC) is non-ionic aqueous-soluble cellulose ether derivative for use in controlled-release dosage forms. Owing to high swellability and high gelling strength formation this polymer effectively prolongs drug release, which has a significant effect on the release kinetics of an incorporated drug.

Newer techniques:

The two important breakthrough in formulation of solid dispersion are, the development of technologies to fill solid dispersions directly in to hard gelatin capsule and the ability of surface active & self-emulsifying agents carriers. The technique to fill solid dispersion directly into hard gelatin capsule as melts, which gets solidify at room temperature, was first described by Francol's & Jones in 1978. But the potential application of that technique was fully realized by Chatham. For ease of manufacturing the carriers must be amenable to liquid filling into hard gelatin capsules as melts. The melting temperature of carriers should be such that the solutions do not exceed ~70°C which is the maximum acceptable temperature for hard gelatin capsule shells.

The water soluble carriers dissolves more rapidly than the drug, the drug rich layer has to form over the surface of dissolving plug, which prevent further dissolution of drug from solid dispersion because of this directly filled hard gelatin capsule is not a good method of preparation of solid dispersion unless the formation of drug rich layer on the surface of dissolving plug can be prevented.

The self-emulsifying agent will act as dispersing or self –emulsifying agent on drug through which the dissolution of drug can be increase by preventing the formation of any water insoluble surface layer, although the liberated drug remain un dissolved in the dissolution medium. When its concentration exceeded its saturation solubility, it will disperse or emulsify into a finely divided state because of the surface activity of the dissolved vehicle the high surface area will be made available which will facilitate its dissolution in gastrointestinal fluid.

Serajuddin et al. has also studied improve dissolution of dispersions of REV-5901. He prepared solid dispersion of poorly water-soluble REV-5901 (alpha-pentyl-3- (2-quinolinylmethoxy) benzene methanol) in various PEG's & in Gelucire® 44/14 filled in to hard gelatin capsule, Gelucire® 44/14 formulation were able to promote complete & rapid drug dispersion in water & simulated gastric fluid. The PEG's formulations by contrast were only effective in achieving partial drug dispersion. When the formulation with Gelucire® 44/14 can be filled into soft gelatin capsule without any change in solubilization characteristic of REV-5901 conversely the formulation with PEG-400 gives rise to drug crystallization due to water migration from the gelatin envelop to the fill, which lead to a 45% reduction in REV-5901 solubility.

The most commonly used surface-active carrier is Gelucire® 44/14 & other grades of Gelucire® the carriers are prepared to have a high melting point but not more than 70 C so as to compatible to be filled in hard gelatin capsule. The grades of Gelucire® denote different no like Gelucire® 44/14, Gelucire® 50/13 in that first digit denote the melting point of carrier and second digit denote HLB value of carrier, on which the grades are differentiated & used as per for its different applications. Gelucire® 44/14 is a mixture of glyceryl & PEG-1500 ester of long-chain fatty acid & is official in European pharmacopoeia as a lauryl macrogolglycerides.

Dordunoo et al studied the effect of Gelucire® 44/14 for improving the solubility of Temazepam in comparison with various PEG's & found Gelucire® 44/14 has shown large increase in its water solubility. Dordunoo et al has also studied the comparative dissolution of the hard gelatin capsule contain 12.5% of Triamterene dispersion in various PEG's or in Gelucire® 44/14 with that of capsule containing the drug alone. The result of dissolution studies shown that dissolution of Triamterene without excipients was limited up to 30% only & with Gelucire® 44/14 or PEG-1000 was found to be 100% of active ingredient in less than an hour.

For in-vivo study Aungst B.J. et al & his co-worker has work on improvement of oral bio-availability of an HIV Protease inhibitor using Gelucire® 44/14 & Labrasol vehicle.

DMP-323 is an HIV-Protease inhibitor exhibiting poor water solubility (< 10 micrograms /ml.). Aungst et al measured the apparent solubility of DMP-323 in aqueous dispersion of Gelucire® 44/14 or PEG-400 as a function of excipients concentration Gelucire® clearly improved the apparent solubility of drug while PEG-400 had no solubilization effect on the drug.

Chen et al improved the dissolution and bioavailability of ABT-963, a poorly water-soluble compound by preparing solid dispersion using Pluronic F-68 as a carrier by evaporation and hot melt method. The results show that solid dispersion is a promising approach for increasing oral bioavailability.

Passerini et al prepared granules containing Ibuprofen, a poorly soluble model drug by melt granulation. The aim was to improve dissolution and its availability; using lactose as a diluent and Poloxamer 188 (Lutrol F68) as a new metastable hydrophilic binder. In the conclusion, it was suggested that melt granulation technique is an easy and a fast method to improve the dissolution rate of ibuprofen, using Poloxamer 188 as a new hydrophilic metastable binder.

Vippagunta et al characterized the nature and solid state properties of solid dispersion system of Nifedipine in a polymer matrix consisting of Pluronic F 68 and Gelucire 50/13 in 1:1:1 ratio. The results indicate that the Nifedipine solid dispersion is physically stable. The release of Nifedipine was faster in solid dispersion than pure crystalline drug of the same particle.

Table: 1 Examples of surface-active carriers used for dissolution enhancement.

S. No.	Carrier	Drug	Scientist
1.	Poloxamer 188	Ibuprofen	Passerini et al
2.	Poloxamer 188	ABT-963	Chen et al
3.	Poloxamer 407	Nifedipine	Chutinawarapan et al
4.	Poloxamer 188, Gelucire 50/13	Nifedipine	Vippagunta et al
5.	Gelucire 44/14	REV 5901	Sheen et al
6.	Gelucire 44/14	LAB-687	Serajuddin et al
7.	Mixture Gelucire 44/14-lecithin	Ubidecarenone	Pozi et al
8.	Gelucire 44/14 and PEG 6000	Glibenclamide	Tashtoush
9.	Gelucire 44/14, Vitamin E TPGS	Carbamazepine	Squillanate et al
10.	Gelucire, Capmul, Capmul MCM C10	Ceftriaxone	Seong-Wan CHO et al
11.	Polyethylene glycol	DMP 323	Aungst et al
12.	Mixture of Gelucire 50/13, Polysorbate 80, Polyox	Ritonavir	---

Future Prospects: [15]

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up, and stability limited its use in commercial dosage forms for poorly water-soluble drugs. Successful developments of solid dispersion systems for preclinical, clinical and commercial use have been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. The preparation of dosage forms involves the dissolving of drugs in melted carriers and the filling of the hot solutions into gelatin capsules.

Because of the simplicity of manufacturing and scale up processes, the physicochemical properties and as expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion systems to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. Because the dosage form can be developed and prepared using small amounts of drugs substances in early substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation.

One major focus of future research will be identification of new surface-active carriers and self-emulsifying carriers for solid dispersion. Only a small number of such carriers are currently available for oral use. Some carriers that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion system may be the inadequate drug solubility in carriers, so a wider choice will increase the success of dosage form development.

Research should also be directed toward identification of vehicles or excipients that would retard or prevent crystallization of drugs from supersaturated systems. Attention should also be given to any physiological and pharmacological effects of carriers used. Many of the surface-active and self-emulsifying carriers are lipid in nature, so potential roles of such carriers on drug absorption, especially on their p-glycoprotein-mediated drug efflux, will require careful consideration. In addition to bioavailability enhancement, much recent research on solid dispersion systems was directed towards the development of extended-release dosage forms. It may be pointed out that this area of research has been reinvigorated by the availability of surface-active and self-emulsifying carriers and the development of new

capsule filling processes. Because the formulation of solid dispersion for bioavailability enhancement and extended release of drugs may employ essentially similar processes, except for the use of slower dissolving carriers for the later use, it is expected that the research in these two areas will progress simultaneously and be complementary to each other.

Introduction to HIV / AIDS

Introduction: [4, 5]

Drugs which are active against human immune deficiency virus (HIV) which is a retro virus. These are useful in prolonging and improving the quality of life and postponing complications of acquired immune deficiency syndrome (AIDS) or AIDS related complex (ARC), but do not cure the infection. The clinical efficiency is monitored primarily by plasma HIV – RNA assays and CD4 lymphocyte count carried out at regular intervals.

Classification:

1) **Nucleoside reverse transcriptase inhibitors (NRTI'S):**
    - Zidovudine, Didanosine, Stavudine, Lamivudine. Are the drugs comes under this classification.
2) **non – nucleoside reverse transcriptase inhibitors:**
    - Nevirapine, Efavirenz. Are the drugs comes this under classification.
3) **retroviral protease inhibitor (PI'S):**
    - Indinavir, Neflinavir, Saquinavir, Ritonavir, Lopinavir. Are the drugs comes this under classification.

Mechanism of action:

- ❖ Retroviral protease inhibitors:
- ❖ Lopinavir:
    - ➢ An aspartic protease enzyme encoded by HIV is involved in the production of structural proteins and enzymes (including reverse transcriptase) of the virus.
    - ➢ The large viral poly protein in broken into various functional components by this enzyme.
    - ➢ This protease acts as a late step in HIV replication, i.e. Maturation of the new virus particles when the RNA genomes acquire the core proteins and enzymes.
    - ➢ These protease inhibitors bind to protease molecule, interfere with its cleaving function and acts at late step of viral life cycle.

- Under the influence of both newly and chronic infected cells HIV – infected cells produce immature noninfectious viral progeny. This leads to viral replication prevention.

Symptoms:

- Dizziness
- Mood changes
- Depression
- Anxiety
- Paraxoia
- Fatigue
- Weakness
- Frequent urination
- Increased thirst
- Nausea and vomiting
- Additional pain
- Tiredness
- Abnormal heart beat
- Weight loss
- Jaundice
- Fever
- tuberculosis

Pathophysiology: [5]

Cells affected:

The virus entering through which ever route, acts primarily on following cells

Lymph reticular system:

CD_4 T – helper, Macrophages, Monocytes, β- Lymphocytes, Certain endothelial cells

Central nervous system:

Microglia of nervous system, Astrocytes, Oligodendrocytes, Neurons.

Diagnosis:

WHO:

Stage – I: HIV infection is a symptomatic and not categorized as AIDS.

Stage – II:

Includes minor mucocutaneous manifestations and recurrent upper respiratory tract infection.

Stage – III:

Includes unexplained chronic diarrhea for longer than a month, severe bacterial infections and pulmonary tuberculosis.

Stage – IV:

Includes toxoplasmosis of the brain, candidiasis of the esophagus, trachea, bronchi/lungs and kaposis sarcoma. These diseases are indicators of AIDS.

Antibody tests:

HIV **Antibody tests** are specifically designed for routine diagnostic testing of adults; these tests are inexpensive and extremely accurate.

Window period

Antibody tests may give false negative (no antibodies were detected despite the presence of HIV) results during the *window period*, an interval of three weeks to six months between the time of HIV infection and the production of measurable antibodies to HIV seroconversion. Most people develop detectable antibodies approximately 30 days after infection, although some seroconvert later. The vast majority of people (97%) have detectable antibodies by three months after HIV infection; a six-month window is extremely rare with modern antibody testing. During the window period, an infected person can transmit HIV to others although their HIV infection may not be detectable with an antibody test. Antiretroviral therapy during the window period can delay the formation of antibodies

and extend the window period beyond 12 months. This was not the case with patients that underwent treatment with post exposure prophylaxis (PEP). Those patients must take ELISA tests at various intervals after the usual 28 day course of treatment, sometimes extending outside of the conservative window period of 6 months. Antibody tests may also yield false negative results in patients with X-linked agammaglobulinemia; other diagnostic tests should be used in such patients.

Three instances of delayed HIV seroconversion occurring in health-care workers have been reported; in these instances, the health-care workers tested negative for HIV antibodies greater than 6 months post exposure but were seropositive within 12 months after the exposure. DNA sequencing confirmed the source of infection in one instance. Two of the delayed seroconversions were associated with simultaneous exposure to hepatitis C virus (HCV). In one case, co-infection was associated with a rapidly fatal HCV disease course; however, it is not known whether HCV directly influences the risk for or course of HIV infection or is a marker for other exposure-related factors.

ELISA:

The *enzyme-linked immunosorbent assay* (ELISA), or *enzyme immunoassay* (EIA), was the first screening test commonly employed for HIV. It has a high sensitivity.

In an ELISA test, a person's serum is diluted 400-fold and applied to a plate to which HIV antigens have been attached. If antibodies to HIV are present in the serum, they may bind to these HIV antigens. The plate is then washed to remove all other components of the serum. A specially prepared "secondary antibody" — an antibody that binds to human antibodies is then applied to the plate, followed by another wash. This secondary antibody is chemically linked in advance to an enzyme. Thus the plate will contain enzyme in proportion to the amount of secondary antibody bound to the plate. A substrate for the enzyme is applied, and catalysis by the enzyme leads to a change in color or fluorescence. ELISA results are reported as a number; the most controversial aspect of this test is determining the "cut-off" point between a positive and negative result.

Western blot:

Like the ELISA procedure, the western blot is an antibody detection test. However, unlike the ELISA method, the viral proteins are separated first and immobilized. In subsequent steps, the binding of serum antibodies to specific HIV proteins is visualized

Specifically, cells that may be HIV-infected are opened and the proteins within are placed into a slab of gel, to which an electrical current is applied. Different proteins will move with different velocities in this field, depending on their size, while their electrical charge is leveled by a surfactant called sodiumlaurylsulfate. Some commercially prepared Western blot test kits contain the HIV proteins an already on a cellulose acetate strip. Once the proteins are well-separated, they are transferred to a membrane and the procedure continues similar to an ELISA: the person's diluted serum is applied to the membrane and antibodies in the serum may attach to some of the HIV proteins. Antibodies that do not attach are washed away, and enzyme-linked antibodies with the capability to attach to the person's antibodies determine to which HIV proteins the person has antibodies.

There are no universal criteria for interpreting the western blot test: The number of viral bands that must be present may vary. If no viral bands are detected, the result is negative. If at least one viral band for each of the GAG, POL, and ENV gene-product groups is present, the result is positive. The three-gene-product approach to western blot interpretation has not been adopted for public health or clinical practice. Tests in which less than the required number of viral bands is detected are reported as indeterminate: a person who has an indeterminate result should be retested, as later tests may be more conclusive. Almost all HIV-infected persons with indeterminate western blot results will develop a positive result when tested in one month; persistently indeterminate results over a period of six months suggest the results are not due to HIV infection. In a generally healthy low-risk population, indeterminate results on western blot occur on the order of 1 in 5,000 patients: However for those individuals that have had high-risk exposures to individuals where HIV-2 is most prevalent, Western Africa, an inconclusive western blot test may prove infection with HIV-2.

The HIV proteins used in western blotting can be produced by recombinant DNA in a technique called *recombinant immunoblot assay* (RIBA)

Rapid or point-of-care tests:

Rapid antibody tests are qualitative immunoassays intended for use as a point of care test to aid in the diagnosis of HIV infection. These tests should be used in conjunction with the clinical status, history, and risk factors of the person being tested. The positive predictive value of Rapid Antibody Tests in low-risk populations has not been evaluated. These tests

should be used in appropriate multi-test algorithms designed for statistical validation of rapid HIV test results.

If no antibodies to HIV are detected, this does not mean the person has not been infected with HIV. It may take several months after HIV infection for the antibody response to reach detectable levels, during which time rapid testing for antibodies to HIV will not be indicative of true infection status. For most people, HIV antibodies reach a detectable level after two to six weeks.

Although these tests have high specificity, false positives do occur. Any positive test result should be confirmed by a lab using the western blot.

Home Access Express HIV-1 Test It is the only FDA-approved home test: the patient collects a few blood drops from a finger stick, and mails the sample to a laboratory; results and counseling are obtained over the phone. All results are anonymous and confirmed before they are released.

OraQuick is an antibody test that provides results in 20 minutes. The blood, plasma or oral fluid is mixed in a vial with developing solution, and the results are read from a sticklike testing device. Usually detects HIV 1 and HIV 2.

Orasure is an HIV test that uses mucosal transudate from the tissues of cheeks and gums. It is an antibody test that first employs ELISA, then western blot.

Uni-Gold is a rapid HIV antibody test that provides results in 10–12 minutes. A drop of blood is placed on the device with developing solution. Uni-Gold is only FDA approved to test for HIV 1.

Clear view Complete HIV 1/2 and **Clear view HIV 1/2 Stat-Pak** are rapid tests for the detection of HIV 1 and HIV 2 antibodies in blood, serum, or plasma samples. Results are provided within 15 minutes.

There is also a **urine test**; it employs both the ELISA and the western blot techniques.

I Diagnostics Rapid HIV Test is, according only to their website, a non-FDA-approved home test. The company sells a blood test and a urine test produced by Intec PRODUCTS, INC. Similar to a home pregnancy test the patient collects a drop of blood/urine and drops the sample onto a cassette. Results are read visually in 15 minutes. The accuracy of this test has not been confirmed by the FDA, and it is not authorized for sale in the United States.

The INSTI HIV-1/HIV-2 Rapid Antibody Test is a rapid in vitro qualitative test for the detection of antibodies to Human Immunodeficiency Virus Type 1 in human whole blood, serum or plasma. The test is intended for use by trained personnel in medical facilities, clinical laboratories, emergency care situations, and physicians' offices as a screening assay capable of providing test results in less than 60 seconds. The assay is packaged as a kit containing INSTI Membrane Units, Sample Diluent, Color Developer and Clarifying Solution, and is available in point-of-care use packaging, or packaging suitable for laboratory use.

Reveal HIV is a rapid *in vitro* qualitative test for the detection of antibodies to HIV in whole blood, serum or plasma. Reveal is among the fastest rapid HIV test available and it detects signs of early infection better than some other rapid tests. Reveal HIV is approved in Canada, the United States, Europe, Africa, Asia, and South America.

Interpreting antibody tests:

ELISA testing alone cannot be used to diagnose HIV, even if the test suggests a high probability that antibody to HIV-1 is present. In the United States, such ELISA results are not reported as "positive" unless confirmed by a Western Blot.

The ELISA antibody tests were developed to provide a high level of confidence that donated blood was *NOT* infected with HIV. It is therefore not possible to conclude that blood rejected for transfusion because of a *positive* ELISA antibody test is in fact infected with HIV. Sometimes, retesting the donor in several months will produce a *negative* ELISA antibody test. This is why a confirmatory Western Blot is always used before reporting a "positive" HIV test result.

Rare false positive results due to factors unrelated to HIV exposure are found more often with the ELISA test than with the Western Blot. False positives may be associated with medical conditions such as recent acute illnesses and allergies. A rash of false positive tests in the fall of 1991 was initially blamed on the influenza vaccines used during that flu season, but further investigation traced the cross-reactivity to several relatively non-specific test kits. A false positive result does not indicate a condition of significant risk to health. When the ELISA test is combined with Western Blot, the rate of false positives is extremely low, and diagnostic accuracy is very high (see below).

HIV antibody tests are highly sensitive, meaning they react preferentially with HIV antibodies, but not all positive or inconclusive HIV ELISA tests mean the person is infected

by HIV. Risk history, and clinical judgment should be included in the assessment, and a confirmation test (Western blot) should be administered. An individual with an inconclusive test should be re-tested at a later date.

Antigens test:

The **p24 antigen test** detects the presence of the p24protein of HIV (also known as CA), the capsid protein of the virus. Monoclonal antibodies specific to the p24 protein are mixed with the person's blood. Any p24 protein in the person's blood will stick to the monoclonal antibody and an enzyme-linked antibody to the monoclonal antibodies to p24 causes a color change if p24 was present in the sample.

This test is no longer used routinely in the US [2] or the EU [3] to screen blood donations since the objective was to reduce the risk of false negatives in the window period. Nucleic acid testing (NAT) is more effective for this purpose, and p24 antigen testing is no longer indicated if a NAT test is performed. The p24 antigen test is not useful for general diagnostics, as it has very low sensitivity and only works during a certain time period after infection before the body produces antibodies to the p24 protein

Nucleic-acid-based tests:

Nucleic-acid-based tests amplify and detect one or more of several target sequences located in specific HIV genes, such as HIV-I GAG, HIV-II GAG, HIV-env, or the HIV-pol. Since these tests are relatively expensive, the blood is screened by first pooling some 8-24 samples and testing these together; if the pool tests positive, each sample is retested individually. Although this results in a dramatic decrease in cost, the dilution of the virus in the pooled samples decreases the effective sensitivity of the test, lengthening the window period by 4 days (assuming a 20-fold dilution, ~20hr virus doubling time, detection limit 50 copies/ml, making limit of detection 1,000 copies/ml). Since 2001, donated blood in the United States has been screened with nucleic-acid-based tests, shortening the window period between infection and detectability of disease to a median of 17 days (95% CI, 13-28 Days, assumes pooling of samples). A different version of this test is intended for use in conjunction with clinical presentation and other laboratory markers of disease progress for the management of HIV-1-infected patients.

In the **RT-PCR test**, viral RNA is extracted from the patient's plasma and is treated with reverse transcriptase (RT) to convert the viral RNA into cDNA. The polymerase chain reaction (PCR) process is then applied, using two primers unique to the virus's genome. After

PCR amplification is complete, the resulting DNA products are hybridized to specific oligonucleotides bound to the vessel wall, and is then made visible with a probe bound to an enzyme. The amount of virus in the sample can be quantified with sufficient accuracy to detect threefold change.

In the **Quantiplex bDNA** or **branched DNA test**, plasma is centrifuged to concentrate the virus, which is then opened to release its RNA. Special oligonucleotides that bind to viral RNA and to certain oligonucleotides bound to the wall of the vessel are added. In this way, viral RNA is fastened to the wall. Then new oligonucleotides that bind at several locations to this RNA are added and other oligonucleotides that bind at several locations to those oligonucleotides. This is done to amplify the signal. Finally, oligonucleotides that bind to the last set of oligonucleotides and that are bound to an enzyme are added; the enzyme action causes a color reaction, which allows quantification of the viral RNA in the original sample. Monitoring the effects of antiretroviral therapy by serial measurements of plasma HIV-1 RNA with this test has been validated for patients with viral loads greater than 25,000 copies per milliliter.

Other tests for HIV treatment:

The **CD4 T-cell count** is not an HIV test, but rather a procedure where the number of CD4 T-cells in the blood is determined.

A CD4 count does not check for the presence of HIV. It is used to monitor immune system function in HIV-positive people. Declining CD4 T-cell counts are considered to be a marker of progression of HIV infection. A normal CD4 count can range from 500 cells/mm3 to 1000 cells/mm3. In HIV-positive people, AIDS is officially diagnosed when the count drops below 200 cells/μL or when certain opportunistic infections occur. This use of a CD4 count as an AIDS criterion was introduced in 1992; the value of 200 was chosen because it corresponded with a greatly increased likelihood of opportunistic infection. Lower CD4 counts in people with AIDS are indicators that prophylaxis against certain types of opportunistic infections should be instituted.

Low CD4 T-cell counts are associated with a variety of conditions, including many viral infections, bacterial infections, parasitic infections, sepsis, tuberculosis, coccidioidomycosis, burns, trauma, intravenous injections of foreign proteins, malnutrition, over-exercising, pregnancy, normal daily variation, psychological stress, and social isolation.

This test is also used occasionally to estimate immune system function for people whose CD4 T cells are impaired for reasons other than HIV infection, which include several blood diseases, several genetic disorders, and the side effects of many chemotherapy drugs.

In general, the lower the number of T cells the lower the immune system's function will be. Normal CD4 counts are between 500 and 1500 CD4+ T cells/microliter, and the counts may fluctuate in healthy people, depending on recent infection status, nutrition, exercise, and other factors. Women tend to have somewhat lower counts than men

PRECAUTIONS: [5]

Transmission-Based Precautions:

Transmission-Based Precautions, also known as additional infection control precautions in health care, are the latest routine infection prevention and control practices applied for patients who are known or suspected to be infected or colonized with infectious agents, including certain epidemiologically important pathogens. The latter require additional control measures to effectively prevent transmission.

Contact Precautions:

Contact Precautions Contact Precautions are intended to prevent transmission of infectious agents, including epidemiologically important microorganisms, which are spread by direct or indirect contact with the patient or the patient's environment. The specific agents and circumstance for which Contact Precautions are indicated are found in Appendix A of the Guidance. The application of Contact Precautions for patients infected or colonized with MDROs is described in the 2006 HICPAC/CDC MDRO guideline. Contact Precautions also apply where the presence of excessive wound drainage, fecal incontinence, or other discharges from the body suggest an increased potential for extensive environmental contamination and risk of transmission. A single-patient room is preferred for patients who require Contact Precautions. When a single-patient room is not available, consultation with infection control personnel is recommended to assess the various risks associated with other patient placement options (e.g., cohorting, keeping the patient with an existing roommate). In multi-patient rooms, >3 feet spatial separation between beds is advised to reduce the opportunities for inadvertent sharing of items between the infected/colonized patient and other patients. Healthcare personnel caring for patients on Contact Precautions wear a gown and gloves for all interactions that may involve contact with the patient or potentially

contaminated areas in the patient's environment. Donning PPE upon room entry and discarding before exiting the patient room is done to contain pathogens, especially those that have been implicated in transmission through environmental contamination (e.g., VRE, C. difficile, noroviruses and other intestinal tract pathogens; RSV)

Universal precautions:

Universal precautions refers to the practice, in medicine, of avoiding contact with patients' bodily fluids, by means of the wearing of nonporous articles such as medical gloves, goggles, and face shields. The practice was introduced in 1985–88. In 1987, the practice of universal precautions was adjusted by a set of rules known as body substance isolation. In 1996, both practices were replaced by the latest approach known as standard precautions (health care). Nowadays and in isolation, practice of universal precautions has historical significance.

Under universal precautions all patients were considered to be possible carriers of blood-borne pathogens. The guideline recommended wearing gloves when collecting or handling blood and body fluids contaminated with blood, wearing face shields when there was danger of blood splashing on mucous membranes and disposing of all needles and sharp objects in puncture-resistant containers.

Universal precautions were designed for doctors, nurses, patients, and health care support workers who were required to come into contact with patients or bodily fluids. This included staff and others who might not come into direct contact with patients.

Pathogens fall into two broad categories, blood borne (carried in the body fluids) and airborne.

USE:

Universal precautions were typically practiced in any environment where workers were exposed to bodily fluids, such as:

Blood

- Semen
- Vaginal secretions
- Synovial fluid
- Amniotic fluid

- Cerebrospinal fluid
- Pleural fluid
- Peritoneal fluid
- Pericardial fluid

Bodily fluids that did not require such precautions included:

- Feces
- Nasal secretions
- Urine
- Vomitus
- Perspiration
- Sputum
- Saliva

Universal precautions were the infection control techniques that were recommended following the AIDS outbreak in the 1980s. Every patient was treated as if infected and therefore precautions were taken to minimize risk.

Essentially, universal precautions were good hygiene habits, such as hand washing and the use of gloves and other barriers, correct handling of hypodermic needles and scalpels, and aseptic techniques.

PREVENTION:

HIV PREVENTION STRATAGIES:

Pharmaceutical strategies:

Some commonly considered pharmaceutical interventions for the prevention of HIV include the use of the following:

- microbicides for sexually transmitted diseases
- pre-exposure prophylaxis
- post-exposure prophylaxis
- HIV vaccines
- circumcision (see also Circumcision and HIV)
- antiretroviral drugs to reduce viral load in the infected, and

- condoms

Of these, the only universally medically proven method for preventing the spread of HIV during sexual intercourse is the correct use of condoms, and condoms are also the only method promoted by health authorities worldwide. For HIV positive mothers wishing to prevent the spread of HIV to their child during birth, antiretroviral drugs have been medically proven to reduce the likelihood of the spread of the infection. Scientists worldwide are currently researching other prevention systems.

Increased risk of contracting HIV often correlates with infection by other diseases, particularly other sexually transmitted infections. Medical professionals and scientists recommend treatment or prevention of other infections such as herpes, hepatitis A, hepatitis B, hepatitis C, human papillomavirus, syphilis, gonorrhea, and tuberculosis as an indirect way to prevent the spread of HIV infection. Often doctors treat these conditions with pharmaceutical interventions.

Social strategies

Social strategies do not require any drug or object to be effective, but rather require persons to change their behavior in order to gain protection from HIV. Some social strategies which people consider include the following

- sex education
- LGBT sex education
- needle-exchange programs
- safe injection sites
- safe sex
- serosorting
- sexual abstinence

These strategies have widely differing levels of efficacy, social acceptance, and acceptance in the medical and scientific communities.

Populations which receive HIV testing are less likely to engage in behaviors with high risk of contracting HIV, so HIV testing is almost always a part of any strategy to encourage people to change their behavior to become less likely to contract HIV.

TREATMENT: [12]

Lopinavir/ritonavir is a fixed dose combination drug for the treatment of HIV infection. It combines lopinavir (not available as a single drug) with a sub-therapeutic dose of ritonavir (trade name *Norvir*) into a fixed-dose pill.

The combination is marketed by Abbott as **Kaletra** (high-income countries) and **Aluvia** (low-income countries), as a component of combination therapy to treat HIV/AIDS. The Kaletra formulation has also been used successfully as monotherapy in some studies.

As of 2006, lopinavir/ritonavir forms part of the preferred combination for first-line therapy recommended by the US DHHS. It is available as capsules, tablets and oral solution.

REVIEW OF LITERATURE

Sameer H Lakade *et al.*,**(2010)**[16] reported that Solid dispersions are used to obtain a homogeneous distribution of a small amount of drug in solid state. To stabilize the unstable drug. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage. To formulate a fast release primary dose in a sustained released dosage form. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers. Polymorphs in a given system can be converted into isomorphs, solid solution, eutectic or molecular addition compounds. Many more different types of polymers are used to solve the solubility problem by using solid dispersion method, hence solid dispersion is a very use full method for Pharmaceutical point of view because of this simple and convenient reason this method is widely used to study various approaches & application of drug property and polymers used in Pharmaceutical research.

Abu T. M. Serajuddin *et al.*,**(1999)** **[17]** reported that although there was a great interest in solid dispersion systems during the past four decades to increase dissolution rate and bioavailability of poorly water-soluble drugs, their commercial use has been very limited, primarily because of manufacturing difficulties and stability problems. Solid dispersions of drugs were generally produced by melt or solvent evaporation methods. The materials, which were usually semisolid and waxy in nature, were hardened by cooling to very low temperatures. They were then pulverized, sieved, mixed with relatively large amounts of excipients, and encapsulated into hard Gelatin capsules or compressed into tablets. These operations were difficult to scale up for the manufacture of dosage forms. The situation has, however, been changing in recent years because of the availability of surface-active and self-emulsifying carriers and the development of technologies to encapsulate solid dispersions directly into hard gelatin capsules as melts. Solid plugs are formed inside the capsules when the melts are cooled to room temperature. Because of surface activity of carriers used, complete dissolution of drug from such solid dispersions can be obtained without the need for pulverization, sieving, mixing with excipients, etc. Equipment is available for large-scale manufacturing of such capsules. Some practical limitations of dosage form development might be the inadequate solubility of drugs in carriers and the instability of drugs and carriers at elevated temperatures necessary to manufacture capsules.

Ali Nokhodchi *et al.*,**(2007)** [18] worked on solid dispersions of chlordiazepoxide techniques to improve its dissolution rate. To this end, three techniques namely, two solvent methods

and co-grinding technique were used. Solid dispersions of chlordiazepoxide in polyvinylpyrrolidone (PVP), Eudragit E100, Mannitol and Sorbitol with two different ratios of drug to carrier (5:5 and 1:9) were prepared. These solid dispersions were evaluated using dissolution tester to monitor dissolution behavior and Fourier-transform infrared spectroscopy to investigate interaction between the drug and carriers in solid dispersion samples. Solid dispersion ofchlordiazepoxide with all three carriers (PVP, mannitol and eudragit E) prepared by solvent method showed Considerable increase in the dissolution rate of chlordiazepoxide in comparison with physical mixture and pure drug at different pH values. According to the results of this investigation co grinding technique yields solid dispersions with a less improved dissolution rate than doe's the solvent deposition technique. Infrared studies showed no interaction between chlordiazepoxide and carriers in solid dispersions in solid state.

Dehghan *et al.*,**(2010)** [19] worked on the solubility and dissolution of Glipizide in water by solid dispersion. The solid dispersion of glipizide was prepared using water soluble carriers such as polyethylene glycol (PEG) andmannitol by fusion method and PVP K 30 by solvent evaporation method in an attempt to increase the solubility and dissolution rate of Glipizide- a practically insoluble drug in water. IR spectroscopy and in-vitro dissolution studies were used to characterize the solid dispersion. FTIR studies show no chemical interaction between Glipizide and PEG6000, mannitol and PVP K 30. The solid dispersion prepared in this study was found to have higher dissolution rate and solubility compared to plain drug and physical mixture of drug and carriers. It was found that the optimum weight ratio 1.5 for PEG-6000 shows higher solubility and dissolution rate. Finally it was concluded that PEG-6000 shows greater dissolution enhancing capacity than mannitol and PVP K 30.

Mohamed Hassan *et al.*,**(2006)** [20] reported that Meloxicam is a poorly water soluble non-steroidal anti-inflammatory drug and antipyretic agent. The aim of the present work was to investigate the effect of different types of carriers on in vitro dissolution of meloxicam. Meloxicam solid dispersions were prepared by physical mixing, co-grinding and solvent evaporation methods with polyethylene glycol (PEG) 6000.The effect of solubilization by sodium lauryl sulphate (SLS) was also studied. The dissolution was determined by USP XXVII Apparatus I, using phosphate buffer with a pH of 7.4 as the dissolution medium. The maximum in vitro dissolution of meloxicam, i.e. 97.45% in 60 min,was observed for solid dispersions containing meloxicam (150 mg), PEG 6000 (350 mg) and SLS (75 mg) prepared

by solvent evaporation method containing a sum of 3 g of Lactose and MCC (4:1) as additives. The general trend indicated that there was an increase in dissolution rate for solid dispersions containing the solubilizer SLS. The best-fit model indicating the mechanism of dissolution from the formulation showing the highest release for was found to be Higuchi matrix release (r=0.9774, b=13.042, a=2.4798). Infra-red spectroscopy (IR) indicated that meloxicam in solid dispersions showed physical entrapment. The increased in dissolution rate of meloxicam by solid dispersion technique may be due to increase wettability and hydrophilic nature of carrier.

Kothawade *et al.,***(2010)** [21] reported that Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. In the present investigation, an attempt was made to improve the solubility and dissolution rate of a poorly soluble drug, Telmisartan. Solid dispersions were prepared using polyvinyl pyrrolidone (PVP), Polyethyleneglycol-1500 (PEG-1500) and Polyethylene glycol-4000(PEG-4000) to increase its aqueous solubility. Telmisartan solid dispersions were prepared in 1:1, 1:2 and 1:4 ratios of the drug to polymer ratio (by weight) using solvent evaporation method. The formulations were characterized for solubility parameters, drug content studies, drug release studies and drug-polymer interactions by using FTIR spectrum. Formulation containing 1:2 ratio of drug: PEG-4000 showed the best release with a cumulative release of 99.49% as compared to 35.82 % for the pure drug. The interaction studies showed no interaction between the drug and polymer. It was concluded that PEG-4000 as a carrier can be very well
Utilized to improve the solubility of poorly soluble drugs.

Ganesh Chaulang *et al.,***(2009)** [22] reported that enhancement of the dissolution rate of furosemide using solid dispersion (SD) withcrospovidone (CPV) by using kneading technique. 1:1 (w/w) and 1:2 (w/w) solid dispersions were prepared by kneading method using solvent water and ethanol in 1:1 ratio. Dissolution studies using the USP paddle method were performed for solid dispersions of furosemide at 37 ± 0.5oC and 50 rpm in simulated gastric fluid (SGF) of pH 1.2. Fourier transformer infrared (FTIR) spectroscopy, differential scanning calorimetric (DSC), and x-ray diffractometry (XRD) were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. Tablets

were formulated containing solid dispersion products and compared with commercial products. IR spectroscopy, XRD, and DSC showed change in the crystal structure towards amorphous one of furosemide (FRMD). Dissolution of furosemide improved significantly in solid dispersion the 1:2 solid dispersion indicated increase in dissolution 5.11 fold. Tablets containing solid dispersion exhibited better dissolution profile than commercial tablets. Thus, the solid dispersion technique can be successfully used for improvement of dissolution of furosemide.

Apparao *et al.*,**(2010)** [23] reported that Aceclofenac is a novel non-steroidal anti-inflammatory drug (NSAID) having anti-inflammatory and analgesic properties, and is widely used in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Therefore, solid dispersions (SDs) of Aceclofenac were prepared using lactose, mannitol and urea to increase its aqueous solubility. Aceclofenac SDs was prepared in 9:1, 7:3 and 4:1 ratios of the drug to polymer (by weight).*In vitro* release profiles of all SDs (F-1 to F-9) were comparatively evaluated and also studied against pure Aceclofenac. Faster dissolution was exhibited by solid dispersion containing 9:1 ratio of drug: lactose. The increase in dissolution rate of the drug may be due to increase in wettability, hydrophilic nature of the carrier and due to reduction in drug crystallinity.The prepared solid dispersion was subjected for % practical yield, drug content and infrared (IR) spectroscopic studies. Absence of significant drug-carrier interaction was confirmed by infrared spectroscopic (IR) data.

Muralidhar *et al.*,**(2011)** [24] worked on Etoricoxib, a non-steroidal anti-inflammatory drug, is used to Osteoarthritis, Rheumatoid arthritis and Acute Gouty arthritis. Etoricoxib is practically insoluble in water; hence present study was carried out to enhance dissolution properties of Etoricoxib through the preparation of Solid Dispersions using PEG 6000 as carrier at various proportions by using different techniques like Physical mixtures, Kneading Method and Solvent Evaporation Method. The drug release profile was studied in 0.1N HCl containing 1 % SLS. U.V. Spectrophotometric method was selected for assay as well as in-vitro dissolution studies at 234nm.All the solid dispersions exhibited superior dissolution than pure drug. The drug dissolution studies followed first order kinetics. Solvent evaporation method was found to be superior to other methods.

Guptha *et al.,***(2011)** [25] reported that Ibuprofen is (NSAID) non-steroidal anti-inflammatory drug and used as analgesic & anti-inflammatory drug. It can be also used in the treatment of rheumatoid arthritis, osteoarthritis, and primary dysmenorrhea. Ibuprofen is absorbed rapidly, bound avidly to protein, but it has low aqueous solubility so, it also lowers the dissolution profile of drug. To overcome this problem, various techniques are used, like solid dispersion, complexation, co-solvency, hydro trophy, Nano technology approach. In this study, the dissolution rate of poorly soluble drug Ibuprofen was increased by preparing solid dispersion with urea in ratio of (1:1), (1:3) & (1:5) by using melt dispersion method & solvent evaporation method. The rate of dissolution of Ibuprofen was increased with the proportion of (1:5) when compared to the other formulations.

Tejas Patel *et al.,***(2010)** [26] worked on Fenofibrate is a lipid lowering drug used in the treatment of hyperlipidemia, which is not soluble in water and lower absorption in gastric fluid. In order to improve the solubility and oral absorption of the drug in gastric fluid and to enhance its dissolution rate solid dispersions and Lyophilization of dispersion is designed and evaluated. Solid dispersions of Fenofibrate were prepared using PEG 6000, Poloxamer 407 and a mixture of PEG 6000 and Poloxamer 407(1:1 mixture). The effect of melt and solvent methods of preparation of solid dispersion on dissolution behavior was also investigated. Dissolution studies indicated a significant increase in dissolution of Fenofi-brate when dispersed in PEG6000 and Poloxamer 407. Physical mixtures containing PEG and Poloxamer 407 also showed improved dissolution of Fenofibrate as compared with that of pure drug, indicating the solubilizing effect of PEG6000 and Poloxamer 407. Solid dispersions containing Fenofibrate /Poloxamer 407, 1: 8, showed a 14-fold increase in dissolution after 60 min (D60) and another dispersion containing Fenofibrate /PEG 6000, 1:10, showed an 8-fold increase in the 0.1 N HCl systems. The dispersion containing six parts of the PEG 6000: Poloxamer 407 mixture (PEG 4000/PEG 6000, 1:1 mixture) showed a 12-fold increase in D60 as compared with pure drug. When multi-carrier solid dispersion containing six parts of mixture was prepared by the solvent method, the D60 value was about 2-fold that of the same dispersion prepared by the melt method. The dissolution of lyophilized solid dispersions further increased the dissolution of Fenofibrate significantly.

Arun Prasad *et al.,***(2010)** [27] reported that the study was aimed to formulate solid dispersion tablet of Terbinafine Hydrochloride by using carrier's polyethylene glycol 6000 (by melting

method) and polyvinyl pyrrolidone K 30 (by solvent method) in the drug carrier ratio of 1:1, 1:2 and 1:3. The prepared solid dispersions were characterized for their drug content, thermal studies, infrared spectral studies, differential scanning calorimetric studies, aqueous solubility studies and in-vitro release studies. From the results, it was clear that solid dispersion formulation showed improved

Dissolution rate than pure drug and physical mixture. The solid dispersion showing better release profile was chosen to formulate into tablet dosage form of weight 600mg.Thetabletscompressed were evaluated for its physical parameters like thickness, hardness, weight Variation, friability, drug content and disintegration tests. The dissolution profile of formulated tablet was compared with the marketed product and the formulated tablet showed better release profile than the marketed product.

Dhirendra *et al.*,**(2009)** [28] reported that Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs. This article reviews the various preparation techniques for solid dispersion and compiles some of the recent technology transfers. The different types of solid dispersions based on the molecular arrangement have been highlighted. Some of the practical aspects to be considered for the preparation of solid dispersions, such as selection of carrier and methods of physicochemical characterization, along with an insight into the molecular arrangement of drugs in solid dispersions are also discussed. Finally, an in-depth rationale for limited commercialization of solid dispersions and recent revival has been considered.

Klein Cheri Enders *et al.*,**(2010)** **[29]** reported that Lopinavir, an HIV protease inhibitor, is co -formulated with ritonavir to enhance the bioavailability and pharmacokinetics of lopinavir. The original solid oral formulation of lopinavir/ritonavir, a soft-gelatin capsule (SGC), requires refrigerated storage, is taken as 6 capsules daily at the recommended adult dose, and is administered with food to maximize the bioavailability of lopinavir. Melt extrusion technology was used to produce a tablet formulation reducing the number of dosage units administered per day and simplifying storage requirements. Three studies assessed the bioavailability of tablet doses of lopinavir/ritonavir at 800/200 mg or 400/100 mg under different meal conditions compared with equal doses of the SGC after a moderate-fat meal. The tablet was bioequivalent to the SGC after a moderate-fat meal with respect to lopinavir and ritonavir areas under the concentration-time curve. Compared with the SGC formulation,

the tablet formulation resulted in more consistent lopinavir and ritonavir exposures within and across studies and across meal conditions. The diminished food effect and decreased variability of the tablet are likely to result in more consistent lopinavir and ritonavir exposures, minimizing the likelihood of extreme high or low values compared with the SGC.

Rahul hastel *et al.*,**(2009)** [30] reported that over the years, a variety of solubilization techniques have been studied and widely used, by many estimates up to 40 per cent of new chemical entities discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The various techniques are available for enhancement of solubility. Solid dispersion is one of the most promising approaches for solubility enhancement. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous.

Shrotriya *et al.*,**(2007)** [31] reported that Embelin 2, 5-dihydroxy-3-undecyl-1, 4-benzoquinone, a chemical component available in dried fruits of Embeliaribesburm F. shows its anthelmintic activity against tapeworms. Embelin is practically insoluble in water. There is a need for solubility enhancement of Embelin in order to enhance its absorption through intestine. The study was aimed to formulate solid dispersions of Embelin by using various carriers (PVP, PVP- K 30, PEG 6000 & PEG 4000) in three different ratios (1:0.5, 1:1 and 1:1.5) using solvent evaporation technique. The prepared solid dispersions were characterized using infrared spectral studies, differential scanning calorimetric studies, aqueous solubility studies, drug content and in-vitro release profile. From FT-IR, XRD, and DSC studies no interaction between Embelin and carrier was observed. Solid dispersion of Embelin with PVP in 1:1 ratio showed maximum enhancement in the solubility of Embelin as well as % drug release after 2 hrs. in phosphate buffer pH 7.4. Thus, the solid dispersion technique can be successfully used for improvement of solubility and dissolution profile of Embelin. Successful attempt was made to enhance the solubility of Embelin using solid dispersion technique. Keywords: : Solid dispersion, Embelin, Solvent Evaporation, Dissolution enhancement.

Shinde *et al.*,**(2010)** [32] reported that the solubility behavior of drug is one of most challenging aspect in formulation development. Thus a greater understanding of dissolution & absorption behavior of drug with low aqueous solubility is required to successfully

formulate them into more soluble and hence bioavailable drug product. Therefore different approaches are being explored to enhance the solubility of poorly water soluble drugs, one of such approach is using solid dispersion by solvent evaporation method. In this study, we are trying to increase the solubility of Aceclofenac, poorly water soluble drug with low bioavailability. Objective of this work is to improve the solubility and dissolution rate of poorly water soluble Aceclofenac by solid dispersion method followed by solvent evaporation method. And to compare effectiveness of hydrophilic polymer PVP-k30, HPMC E-5, using porous carrier Aerosil 200. , resultant complexes were evaluated for drug content, infrared spectroscopy, and XRD and dissolution study. The present study successfully utilized the solvent evaporation method for preparation of stable, amorphous solid dispersions of Aceclofenac by encapsulation with hydrophilic carrier with adsorbents agent (Batch 4, 1:1:2) drug: PVPK30: aerosil, showed maximum release in phosphate buffer pH 6.8 The present study demonstrates high potential of solvent evaporation method for obtaining large surface area and amorphicity of drug using hydrophilic carrier

Sheikh Tasnim Jahan *et al.*,**(2008)** [33] reported that the objective of present work is to investigate the enhancement of dissolution profile for oral delivery of Fexofenadine Hydrochloride (FH) through solid dispersion (SD) technique by the method of solvent evaporation. The SD was prepared by using ethanol as a solvent. Tablets were formulated containing solid dispersion of FH and compared with tablets of same formula without solid dispersion of FH. The using of ethanol to prepare solid dispersion found a significant effect on the dissolution of FH. Dissolution studies using the USP-33 paddle method were performed for tablets formulated with and without solid dispersions of FH. Dissolution of FH improved significantly in tablets formulated with SD (85% in 10 minutes) exhibited better dissolution profile than tablets formulated without SD. Infrared (IR) spectroscopy was also performed to identify the physicochemical interaction between drug and solvent, hence its effect on dissolution.

Rakesh *et al.*,**(2010)** [34] reported that the Solid dispersions traditionally have been used as effective methods to improve the dissolution properties and bioavailability of poorly water-soluble drugs. The aim of the present study was to improve the solubility and dissolution rate of a poorly water-soluble drug, furosemide, by a solid dispersion technique. Solid dispersions were prepared using polyethylene glycol 6000 (PEG 6000) and polyvinylpyrrolidone K30 (PVP K30) in different drug-to-carrier ratios. Dispersions with PEG 6000 were prepared by fusion-cooling and solvent evaporation, while dispersions containing PVP K30 were prepared

by solvent evaporation technique. These new formulations were characterized in the liquid state by phase solubility studies and in the solid state by differential scanning calorimetry, powder X-ray diffraction, and FTIR spectroscopy. The aqueous solubility of furosemide was favored by the presence of both polymers. Solid state characterizations indicated that furosemide was present as an amorphous material and entrapped in polymer matrix. In contrast to the very slow dissolution rate of pure furosemide, the dispersion of the drug in the polymers considerably enhanced the dissolution rate. Solid dispersion prepared with PEG showed the most improvement in wettability and dissolution rate of furosemide. Even physical mixtures of furosemide prepared with both polymers also showed better dissolution profiles as compared with that of pure furosemide. Tablets prepared using solid dispersions showed significant improvement in the release profile of furosemide as compared with conventional tablets prepared using furosemide without PEG or PVP.

Sruti Ranjan Mishra *et al.*,**(2009)** [35] reported that the Pioglitazone hydrochloride is a novel antidiabetic drug in thiazolidinediones group and it improves insulin sensitivity in insulin resistant patients. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. The present study is an attempt to enhance the dissolution rate of pioglitazone HCl by solvent evaporation and physical mixture techniques using pioglitazone HCl and PEG 6000 as carrier in the ratios of 1:1, 1:2 and 1:3 respectively. The drug carrier interaction study was carried out by Fourier Transform Infrared Spectroscopy (FTIR). The prepared solid dispersions were characterized for percentage yield, bulk density, tapped density, Carr's Index, Hausner's ratio, angle of repose, drug content, drug dissolution and stability study. The FTIR study suggesting no interaction between drug and carrier of solid dispersion. The solvent evaporation and physical mixture techniques were found to be efficient method to obtained good yield solid dispersions with good flow properties. The drug content was found in the ranges of 75.6±0.34 to 85.2±0.22 %. Dissolution study revealed that there is marked enhancement in the dissolution rate of pioglitazone from all the solid dispersions when compared to pure pioglitazone itself. From the in vitro drug release profile, it can be seen that formulation F3 (1:3 ratio of drug: PEG 6000, prepared by solvent evaporation) shows higher dissolution rate compared with other formulations. All pioglitazone solid dispersions were found to be stable in various storage temperatures. The solvent evaporation is suitable method for development of solid dispersion of pioglitazone HCl.

Evangelos Karavas *et al.*,**(2010)** [36] reported that the Polyvinylpyrrolidone (PVP) and poly (ethylene glycol) (PEG) solid dispersions with Felodipine or Hesperetin having up to 20 wt.% drug were prepared using solvent evaporation method. Solid dispersions in comparison with their physical mixtures were studied using differential scanning calorimetry (DSC), wide-angle X-ray diffraction (WAXD), scanning electron microscopy (SEM) and hot stage polarizing light microscopy (HSM).PVP formulations with low drug load proved to be amorphous, since no crystalline Felodipine or Hesperetin drugs were detected using DSC and WAXD. Low and fast heating rates were applied for DSC study, to prevent changes in the samples caused during heating. Similarity between results of WAXD and DSC was also found in the case of physical mixtures, where the drug was in the crystalline state. However, though specific tests showed the high sensitivity of the DSC technique, it was difficult to arrive to reliable results for PEG solid dispersions or physical mixtures with low drug content by DSC, even by high heating rates. Crystalline drug could not be detected by DSC, leading to erroneous conclusions about the physical state of the drug, in contrast to WAXD. On the other hand, HSM proved the presence of small drug particles in the solid dispersions with PEG and the dissolution of the drug in the melt of PEG on heating. In such systems, in which a polymer with low melting point is used as drug carrier, DSC is inappropriate technique and must be used always in combination with HSM. The coupling of WAXD with thermal analysis, allowed complete physicochemical characterization and better understanding which is essential for a first prediction of dissolution characteristics of such formulations.

Arora *et al.*, **(2007)** [37] reported that the Cefuroxime Axetil (Poorly water soluble drug), when prepared as solid dispersion showed improved solubility and dissolution. Therefore, the main purpose of this investigation was to increase the solubility and dissolution rate of Cefuroxime Axetil by the preparation of its solid dispersion with urea, using the solvent evaporation method. Physical mixtures and solid dispersions of Cefuroxime Axetil were prepared by using urea as a water-soluble carrier in various proportions (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, and 1:7 by weight), by employing the solvent evaporation method. The drug release profile was studied and it was found that the dissolution rate and the dissolution parameters of the drug from the physical mixture as well as solid dispersion were higher than those of the intact drug. The Fourier Transform Infrared (FTIR) spectra revealed no chemical incompatibility between the drug and urea. Drug-polymer interactions were investigated using differential scanning calorimetry (DSC)

Aim and Objective

The main aim and objective of this project is to improve the dissolution rate of Lopinavir by improving its solubility in dissolution medium by **Solid Dispersion Technique**.

Poorly water soluble drugs require high doses in-order to reach therapeutic plasma levels after oral administration. Improvement in-extent and rate of dissolution is highly desirable for such compound as this can lead to an increased and more re-producible oral bio-availability and sub-sequent to clinical relevant dose reduction to more reliable therapy.

Now-a-days, pharmaceutical techniques provide many approaches to enhance the dissolution rate of poorly water soluble drugs. Solid dispersion technique can be used to enhance the solubility dissolution rate and absorption of several insoluble drugs. Various hydrophilic carries like, PEG, PVP, HPMC, SLS, Gums have been investigated for improvement of dissolution characteristics, bio-availability for poorly aqueous soluble drugs.

Lopinavir is an anti-retroviral drug of protease inhibitor. According to biopharmaceutical classification system (B.C.S)-II. It is a poorly water soluble drug, having bio-availability of less than 5% and high permeability so it was chosen as a model for this research work.

Plan of Work

- **Preparation of Solid dispersions** using Poly Vinyl Pyrrolidine (PVP), Mannitol, Sodium Lauryl Sulphate (SLS) and Urea as carriers to increase its aqueous solubility in the ratios 1:2 and 1:4 of the drug to carrier (by weight) using solvent evaporation method.
- **FT-IR studies**
- **Characterization of formulations for:**
  - ✓ **Pre-formulation studies**
    - Bulk density
    - Tapped density
    - Compressibility index
    - Angle of repose
    - Drug content studies
- **Formulation of conventional tablets of Lopinavir from solid dispersed powder**
  - ✓ **Evaluation tests**
    - Hardness test
    - Friability test
    - Weight variation test
    - Disintegration test
    - Drug release studies
    - Stability test

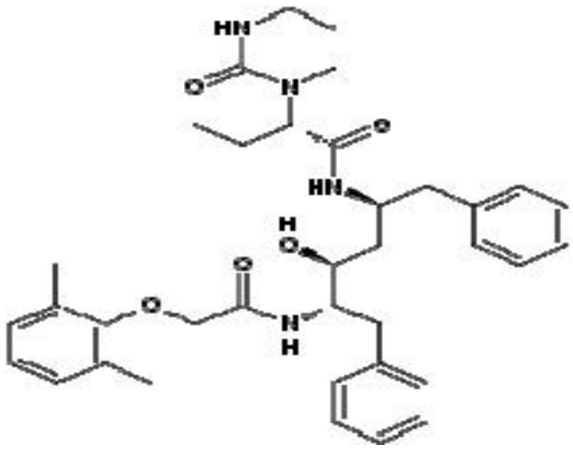
DRUG PROFILE [6, 7, 8]

Drug: LOPINAVIR

IUPAC Name:

[(2, 6- dimethylphenoxy) acetyl] amino]-3-hydroxytetrahydro-_-(1-methylethyl)-2-oxo-1-(2*H*)-pyrimidineacetamide hydroxy-5-phenyl-1-pyrimidineacetamide.

Structure:



Molecular Formula:

$C_{37}H_{48}N_4O_5$

Molecular weight:

628.8g/mol

Melting point:

124-127°C

Description:

White powder.

Solubility:

Freely soluble in methanol and dichloromethane, iso- propanol, insoluble in water

Stability/Storage:

Stable at 15°C to 30°C, should be kept in a tightly closed container, and protected from light.

Dosage form:

Lopinavir 200mg, 100mg (tablets), oral solution (80mg).

Dose:

400mg/day orally.

Mechanism of action:

Lopinavir is an antiretroviral of the protease inhibitor class. Inhibiting HIV-1 protease (Responsible for protein cleavage), results in selectively inhibiting the cleavage of HIV gag and Gag-pol polyproteins, thereby preventing viral maturation. This subsequently results in noninfectious, immature viral particles.

Pharmacodynamics /kinetics:

Bioavailability: <5%

Protein binding: 98-99%

Metabolism: Hepatic CYP3A

Plasma half-life: 5-6 hrs.

Time to peak: 4 hours following multiple doses of 400 mg of lopinavir

For 3 to 4 weeks

Peak plasma concentration:

Lopinavir: 9.6± 4.4 micrograms per mL following multiple doses of

400 mg of Lopinavir for 3 to 4 weeks.

Excretion: Renal 10.4% and Feacal 82.6%.

Adverse effects:

The most common side effects associated with Lopinavir/ritonavir include: diarrhoea, Nausea, stomach pain, feeling weak, vomiting, headache, and upset stomach. Rare side effects include Pancreatitis, yellowing of the skin or eyes (jaundice), Hypersensitivity Reaction (unusual Skin rash, peeling of the skin, hives, swelling of the face or tongue, difficulty breathing), Sensation of abnormal heartbeats, Hemophilia**,** Diabetes or Hyperglycemia, fat redistribution or Accumulation, Increases in cholesterol and triglycerides.

Applications:

Lopinavir is an antiretroviral of the protease inhibitor class-II. It is marketed by Abbott as Kaletra, a co-formulation with a sub-therapeutic dose of ritonavir, as a component of combination therapy to treat HIV/AIDS.

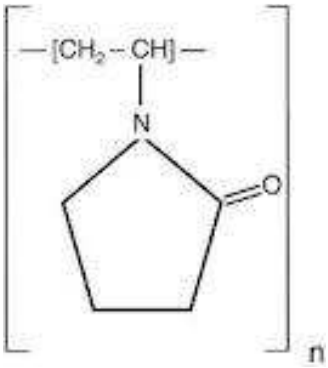
Polymer Profiles[9]

Poly Vinyl Pyrrolidone (PVP):

PVP is a water soluble polymer made from the monomer N- Vinyl pyrrolidone. It is represented by the formula $(C_6H_9NO)_n$PVP is soluble in water and other polar solvents. In water it has the useful property of Newtonian viscosity.

Description: White to tan powder; supplied in two molecular weight forms; the molecular weight value is an average molecular weight for the two forms.

Structure:



Functional Uses: Clarifying agent, stabilizer, bodying agent, tableting adjunct, dispersing agent.

Identification:

*Solubility:*Soluble in water, in ethanol and in chloroform; insoluble in ether.

P^H*:*3.0 - 7.0 (5% sol).

*Precipitate formation:*To 5 ml of a 1 in 50 solution of the sample add 5 ml of dilute hydrochloric acid TS, 5 ml of water and 2 ml of 1 in 10 solution of potassium dichromate. A yellow precipitate forms.

Add 5 ml of a 1 in 50 solution of the sample to 75 mg of cobalt nitrate and 0.3 g of ammonium thiocyanate dissolved in 2 ml of water, mix and acidify with dilute hydrochloric acid TS. A pale blue precipitate forms.

To 5 ml of a 1 in 50 solution of the sample add 1 ml of 25% hydrochloric acid and 5 ml of 5% barium chloride solution and 1 ml of 5% phosphomolybdotungstic acid solution. A voluminous white precipitate is formed which becomes gradually blue on standing in daylight.

(Note: The blue coloration on exposure to light distinguish polyvinylpyrrolidone from polyethylene oxide adducts which give similar precipitates with the same reagents but which retain their white colour in light).

Tests:

*Water:*Not more than 5% (Karl Fischer Method)

*Relative Viscosity:*Between 1.188 and 1.325 for lower molecular weight product, and between 3.225 and 5.662 for higher molecular weight product.

Total ash: Not more than 0.02%.

*Aldehyde:*Not more than 0.2% (as acetaldehyde).

Monomer content: Not more than 1% (as vinylpyrrolidone).

Hydrazine: Not more than 1 mg/kg.

Lead: Not more than 2 mg/kg.

Sodium Lauryl Sulphate (SLS):

Description:

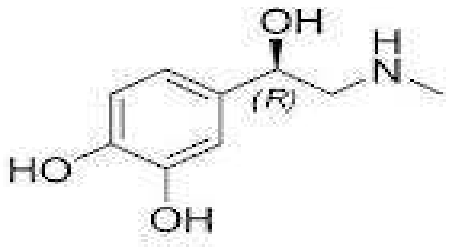
A white or pale yellow powder or crystals

It is a mixture of sodium alkyl sulphates consisting mainly of sodium dodecyl sulphate,

$CH_3 (CH_2)_{10}CH_2OSO_3Na$.

SLS contains not less than 85% of sodium alkyl sulphates calculated as $C_{12}H_{25}NaO_4S$.

Structure:



Identification:

- A 1% w/v solution, when shaken, produces plenty of foam.
- Mix 0.1ml of a 1% w/v solution with 0.1ml of a 0.1% w/v solution of methylene blue and 2ml of 1M H_2SO_4, add 2ml of dichloromethane and shake; the dichloromethane is intensely blue.

Tests:

*Alkalinity:*Dissolve 1.0g in 100ml of CO_2 free water and add 0.1ml of phenol red solution. Not more than 0.5 ml of 0.1M HCl is required to change the colour of solution.

Non-esterified Alcohols: Not more than 4% determined by yellowing method.

NaCl and Sodium Sulphate: Not more than a total of 8%.

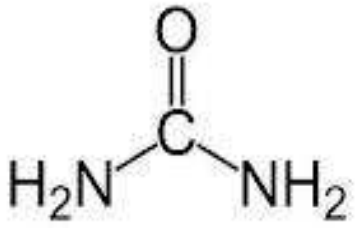
Storage: Store protected from moisture.

Urea:

Urea is the diamide of carbonic acid. Urea contains not less than 99% and not more than 101% of NH_2CONH_2, calculated on the dried basis.

Description: A white, crystalline powder or transparent crystals, odorless or almost odorless but may graphically develop a slight odour of ammonia upon long standing; slightly hygroscopic.

Structure:



Identification:

Test A may be omitted if tests B & C are carried out. Tests B & C may be omitted if test A is carried out.

A) Determine by infrared absorption spectrophotometry compare the spectrum it that of obtained with urea RS or with the reference spectrum of urea.

B) Heat 0.5g in a test tube, it liquefies and ammonia is evolved which is recognized by its characteristic odour. Heat further until the liquid is turbid, cool and dissolve in 10ml of water. Add 1ml of a 10% w/v solution of NaOH and 0.05ml of copper sulphate solution; a reddish violet colour is produced.

C) Dissolve 0.1g in 1ml of water and add 1ml of nitric acid, a white crystalline precipitate is produced.

Tests:

Appearance of solution: Solution A is clear and colorless.

Alkalinity: To 10ml of a 5% w/v solution (sol A) adds 0.1ml of methyl red solution and 0.4ml of 0.01M HCl, the resulting solution is red to orange.

Bi-uret: Not more than 0.1%, determined by the yellowing method.

Ethanol-insoluble matter: Not more than 0.04% determined by the yellowing method.

Heavy Metals: Dissolve 1g in 20ml of water and 0.1M HCl. The solution complies with the limit test for heavy metals- Method A(20ppm).

Sulphonated ash: Not more than 0.1%.

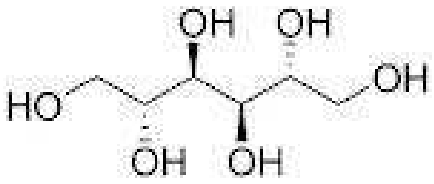
Loss on Drying: Not more than 1% determined on 1.0g by drying in an oven at 105˚ for 1hr.

Storage: Store protected from moisture.

Mannitol:

Description: Mannitol is a white, crystalline organic compound with the formula ($C_6H_8(OH)_6$). This polyol is used as an osmotic diuretic agent and a weak renal vasodilator. It was originally isolated from the secretions of the flowering ash, called manna after their resemblance to the Biblical food, and is also referred to as **mannite** and **manna sugar**. In plants; it is used to induce osmotic stress.

Structure:



Identification tests:

Appearance: white crystalline powder

Solubility: water soluble

Melting point:167^0c

Half-life: 100min

Bio availability: 7 %

Stability: stable combustible incompatible with strong oxidizing agents.

Materials

S. No	Chemical name	Supplier
1	Lopinavir	M.S.N chemicals, Hyderabad
2	PVP	National chemicals, Vadodara
3	SLS	NICE chemicals, pvt.ltd, Cochin
4	Mannitol	HI media laboratories, Mumbai
5	Urea	Loba chemie, Mumbai
6	Potassium.di.hydrogen phosphate	Qualigens fine chemicals, Mumbai
7	Sodium hydroxide	Loba chemie, Mumbai
8	Mg. Stearate	Sd. Fine chemicals, Mumbai
9	Talc	Sd. Fine chemicals, Mumbai

Equipment

S. No	Name of the equipment	Supplier
1	Pippetes,Beakers	Borosil
2	Hot air oven	Sunbim manfacture,pvt.ltd
3	UV-spectrophotometer	Shimadzu
4	Dissolution apparatus	Electro lab
5	Friability apparatus	The Asian scientific insts.co
6	pH meter	Elico
7	Disintegration apparatus	Shreeji pharmaceuticals pvt.ltd
8	Tablet punching apparatus	Cadmach machinery Pvt.ltd
9	FT –IR apparatus	Shimadzu
10	Hardness tester	The Asian scientific insts.co

Preparation of solid dispersions

Solvent evaporation method:

Solid dispersions of Lopinavir were prepared by solvent evaporation technique. Required quantities of Lopinavir, Urea, SLS, PVP and Mannitol were weighed accurately to get drug: polymer ratio of 1:2, 1:4. Drug and polymer were individually dissolved in a suitable solvent to get a homogenous solution. Now the drug solution was added to polymer solution with continuous stirring to form a molecular dispersion of drug and polymer. Slowly the solvent was evaporated to get a solid dispersion.

TABLE -2

S. No	COMPOSTION	RATIO	CODE
1	LOPINAVIR + PVP	1:2	**F1**
2	LOPINAVIR +SLS	1:2	**F2**
3	LOPINAVIR +MANNITOL	1:2	**F3**
4	LOPINAVIR +UREA	1:2	**F4**
5	LOPINAVIR + PVP	1:4	**F5**
6	LOPINAVIR + SLS	1:4	**F6**
7	LOPINAVIR + MANNITOL	1:4	**F7**
8	LOPINAVIR + UREA	1:4	**F8**

FT-IR STUDIES:

The FT-IR analysis was conducted for the analysis of drug polymer interaction and stability of the drug during solid dispersion processthe FT-IR spectrum of pure Lopinavir, PVP, SLS, UREA, and Mannitol. The physical mixture was recorded.

Preformulation studies:

The following parameters are determined for solid dispersed Lopinavir.

1. Bulk Density:

Bulk density is defined as a mass of powder divided by the bulk volume. Weigh 15gm of Solid dispersed Lopinavir powder taken into a 100 ml measuring cylinder of note the volume occupied by the powder as bulk volume. The bulk density was calculated in g/cm^2 by the following formula

$$\text{Bulk density} = \frac{\text{weight of the powder}}{\text{bulk volume}}$$

,

2. Tapped Density:

The above powder sample was tapped gently as surface till the powder occupies maximum volume and notes the volume as tapped volume. The mechanical tapping of cylinder was carried out manually 500 times. The tapped density was calculated in g/cm^2 by the following formula.

$$\text{Tapped density} = \frac{\text{weight of the powder}}{\text{tapped volume}}$$

3. Angle of Repose:

The frictional forces in a loose powder can be measured by the angle of repose θ. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane.

A funnel is fixed at a particular height 'h' on a burette stand. A white paper is placed bellow the funnel. The powder sample is passed slowly through the funnel until it forms a pile further addition of drug stopped as soon as the drug pile touches the tube of the funnel. Circle of the pile of drug is drawn without disturbing the pile of radius of the pile is noted. Angle of repose is calculated from the following formula:

$$\mathbf{Tan\theta = h/r}$$

Θ=angle of repose degrees, h=height of pile, r=radius of the pile in cm

4. Carr's compressibility index:

The same tapping method was used to determine percentage compressibility index. The percentage compressibility index was calculated according to following formula.

$$\%\text{compressibility index} = [1-V/V_0] \times 100$$

Where V and V_O are the volume of the sample after and before the standard tapping respectively. Each determination was made in triplicate.

TABLE No –3: Limitations for Preformulation studies.

S.N0	Angle of repose (θ)	Carr's index	Type of flow
1	<25	5-15	Excellent
2	25-30	12-16	Good
3	30-40	18-21	Passable
4	-	23-35	Poor
5	-	33-38	Very poor
6	>40	>40	Extremely poor

UV-Visible Spectroscopy:

Construction of Standard graph of Lopinavir:

The Stock solution of Lopinavirwas prepared by accurately dissolving 100mg in 100ml of phosphate buffer pH 6.8. From this 10ml was taken and diluted up to 100ml with phosphate buffer pH 6.8 to get 100µg/ml solution. From this 10µg/ml solution was prepared by diluting 10ml to 100ml with phosphate buffer pH 6.8. From this 2, 4, 6&8 to 10ml with phosphate buffer pH 6.8. Absorbance were measured at 258 nm and results were tabulated in table

Preparation of tablets:

Direct compression method:

The conventional tablets of Lopinavirwere prepared by direct compression method. The drug powder and excipients were weighed and mixed and passed through the sieve no 40.the powder was fed manually into the die of 12 stage tablet punching machine and then compressed at proper compression force.

Drug Content Estimation:

Drug content in solid dispersions was estimated by weighing 100 mg of solid dispersion accurately and dissolved in 100 ml of Phosphate buffer pH6.8. The solution was filtered, diluted suitably and drug content was analyzed at 258nm by UV spectrophotometer. Each sample analyzed in triplicate. Actual drug content was calculated for all batches using the equation as follows:

$$\text{Drug content (\%)} = \frac{\text{Actual Lopinavircontent in weighed quantity of solid dispersion}}{\text{Theoretical amount of Lopinavir in Solid dispersion}} \times 100$$

In vitro drug release studies:

Preparation of dissolution media:

Potassium Di-hydrogen Phosphate (0.2M):

Dissolve 21.218g of Potassium hydrogen phosphate in water and dilute with water to 1000ml.

Sodium Hydroxide (0.2M):

Dissolve NaOH in water to produce a 40-60% w/v solution and allow to stand. Taking precautions to avoid absorption of CO_2 siphon off the clear supernatant liquid and dilute with CO_2 free water a suitable volume of liquid to contain 8gm of NaOH in 1000ml.

Phosphate Buffer:

Place 50ml of 0.2M potassium Dihydrogen phosphate in a 200ml volumetric flask, add the specific volume of 0.2M NaOH and then add water to volume.

Dissolution rate determination:

After estimating the drug content in solid dispersions, dissolution was performed to assess the release rate from dispersions. The dissolution was carried out in multi station (8) dissolution apparatus. It was automated and digital equipment. The entire dissolution was carried out at a temperature 37˚c and at 75 rpm for one hr. The dissolution medium (p^H 6.8

phosphate buffer) was placed in basket-1. The pure drug, marketed formulation and the formulations with batch code F1,F2,F3,F4,F5,F6 in the baskets 2, 3, 4, 5, 6 and 7 respectively. The 8th basket is left for internal thermal probe, and it was filled with p^{H} 6.8 phosphate buffer. The solid dispersions of corresponding weights calculated from content evaluation studies were introduced into respective baskets.

5ml of samples were withdrawn at intervals of 5min, 10min, 15min, 20min, 30min, 45min and 60min from each basket. After each withdrawal the same volume of fresh dissolution medium was introduced. All the samples were taken into a series of test tubes which are labeled properly to avoid confusion. The dissolution test apparatus was stopped. Similar procedure was carried out for remaining batches F7, F8 respectively.

The absorbance of each series of test samples was recorded by using UV-Visible Spectrophotometer. Dilutions were also done in necessary cases and the dilution factor was noted down. And the values were given in tables

$$\text{Amount dissolved} = \frac{\text{Test OD}}{\text{Std. OD}} \text{ X Std.Conc. X } \frac{900}{1000} \text{ X Dilution Factor}$$

$$\text{Percent dissolved} = \frac{\text{Amount dissolved}}{\text{Amount taken}} \text{ X 100}$$

Table -4: Dissolution Monograph of Lopinavir

Apparatus	Speed	Temperature	Volume of Medium	Medium	Time Intervals For Withdrawn of Samples
Type-II (paddle type)	75 rpm	37˚c	900ml	pH 6.8 Phosphate buffer	5,10,15,20,30,45&60

EVALUATION TESTS:

Hardness test:

The apparatus used for finding hardness is Monsanto hardness tester. It consists of base containing plunger is taken in contact with the tablet and zero reading is taken. The upper plunger is forced against the spring by a thread belt tube until the tablet fractures the spring is compressed. For each batch three tablets were tested.

The hardness range varies between 4-7 kg/cm^2

Friability test:

The acceptable range for conventional compressed tablet is not less than 0.5% - 1.0%. 10 pre weighed tablets are taken in a friability apparatus and it is rotated at 25rpm for 4 min. then tablets are collected and recheck the weight and the percentage friability was calculated by the formula.

$$\text{percentage friability} = \frac{\text{loss of weight}}{\text{initial weight}} \times 100$$

Weight variation test:

Weight 20 tablets individually then find out the weight variation and percentage weight variation using the formula:

Weight variation = average weight – individual weight of tablet

$$\text{percentage weight variation} = \frac{\text{weight variation}}{\text{average weight}} \times 100$$

Limitation:

S. No	Average weight	Percentage difference
1	Less than 130 mg	± 10%
2	130mg – 324mg	± 7.5%
3	More than 324 mg	±5.0%

Disintegration test:

To determine disintegration time of 6 tablets are placed in each tube and the basket is positioned in 1 it beaker of which similar to gastric fluid at 37 c ± 0.5 c. the system is placed at a frequency of 28 – 30 cycles / min. perforated plastic disc is placed in the tube, in each

tube on the top of the tablet. That imparts an abrasive erosion to tablet. A tablet must disintegrate when all the particles pass through the main screen with the time specified.

Stability studies of the tablet:

Stability of a formulation can be defined as the time from date on manufacture of the formulation until its chemical or biological activity is not less than a pre-determined level of labeled potency and its physical characteristic have not changed appreciably or deleteriously. Formulation and the development of a pharmaceutical product are not complete without proper stability analysis, carried out on it to assess the physical and chemical stability and the safety. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environment factor such as temperature, humidity and light enabling recommended storage condition, re-test periods and shelf lives.

Generally the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid the undesirable delay, the principle of accelerated stability studies is adopted.

The international conference on harmonization (ICH) guideline titled "stability testing of new drug substance and product" (QIA) describes the stability test requirements for drug registrations application in the European Union, Japan and United States of America. ICH specifies the length of study and storage conditions.

- Long term testing: $25^0c \pm 2^0c$/60% RH ± 5% for 12 months.
- Accelerated testing: $40^0c \pm 2^0c$/ 75 % RH ± 5% for 6 months.

Method:

The selected formulation were packed in tightly closed container were plugged with cotton and capped. they were then stored at $40^0c \pm 2^0c$/ 75 % RH ± 5% for 3 months in humidity chamber and valuate for their physical appearance and drug solution were further scanned to observe any possible spectral changes T80% was calculated by using dissolution studies.

RESULTS AND DISCUSSION

Standard Graph:

Different concentrations of Lopinavir from 2 to 10µg/ml were prepared and the absorbance was taken at 258 nm against pH 6.8 Phosphate buffer and graph was plotted between concentration and absorbance.

TABLE -5:

S. No	Concentration(µg/ml)	Absorbance
1.	0	0
2.	2	0.127
3.	4	0.233
4.	6	0.402
5.	8	0.515
6.	10	0.642

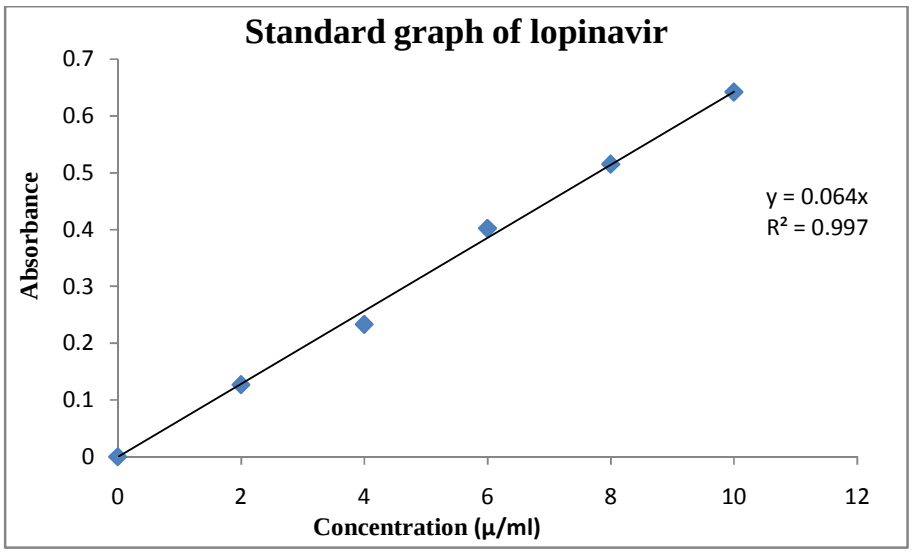


FIG –6

FT-IR studies:

FT-IR studies were conducted for Solid dispersions of Lopinavir to determine any interactions between drug and polymer. FT-IR spectrum for Lopinavir, PVP, and SLS, Mannitol, urea and different solid dispersions were obtained. The Charactestic peaks for Lopinavir, PVP, SLS, Mannitol and urea were identified and any notable shift in characteristic peaks were not observed in dispersion spectra. So that it was concluded that there was no interactions between drug and polymer.

IR spectrum of Lopinavir, PVP, and SLS, Mannitol, urea and different solid dispersions were given below.

Table - 6

S. no	Type of bond	Standard wave number	Observed wave number				
			Lopinavir	LPNVR+ PVP	LPNVR+ SLS	LPNVR+ MANNITOL	LPNVR+ UREA
1	O-H	3400-3200	3373.61	3376.50	3375.34	3373.61	3399.65
2	CO	1680-1630	1659.80	1652.90	1661.73	1661.69	1664.62
3	NH	3500-3100	3293.56	3411.22	3488.84	3373.61	3461.38
4	Aromatic	1600-1475	1527.67	1638.58	1524.34	1655.94	1508.38
5	Alkene	1680-1600	1610.61	1697.41	-	1526.71	-
6	C-H(CH_2 Bend)	1465	1459.55	1446.66	1455.34	1455.41	1455.34
7	C-O	1300-1000	1192.05	1293.31	1307.78	1306.82	1307.78
8	aromatics	900-690	767.96	918.15	919.11	926.76	840.03
9	C-H strch	2890-2690	2869.21	2872.10	-	2809.41	2870.17
10	C-H bend	1640-1550	1307.78	1524.78	-	-	1508.38
11	N-H bend	1640-1550	1527.67	3411.22	1524.78	-	1521.75
12	C-N	1350-1000	1307.78	1383.97	1307.78	-	1091.75
13	Alkane (strch)	3000-2850	2950.32	2953.12	2927.08	2907.48	-
14	CH_3 (bend)	1450-1375	1436.23	1422.55	1455.34	1465.95	-
15	CH_2 (bend)	1465	1449.55	1463.06	-	-	-
16	S=O	1050	-	-	1051.24	1084.99	-

FIGURE -7 IR SPECTRA OF LOPINAVIR

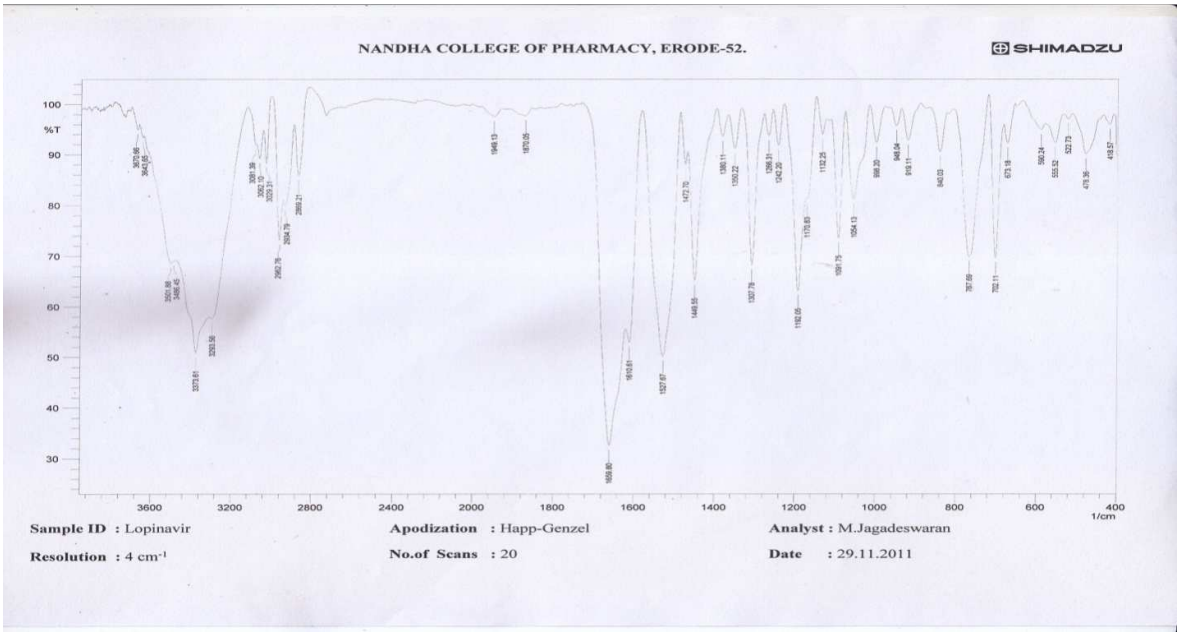


FIGURE – 8 IR SPECTRA OF PVP

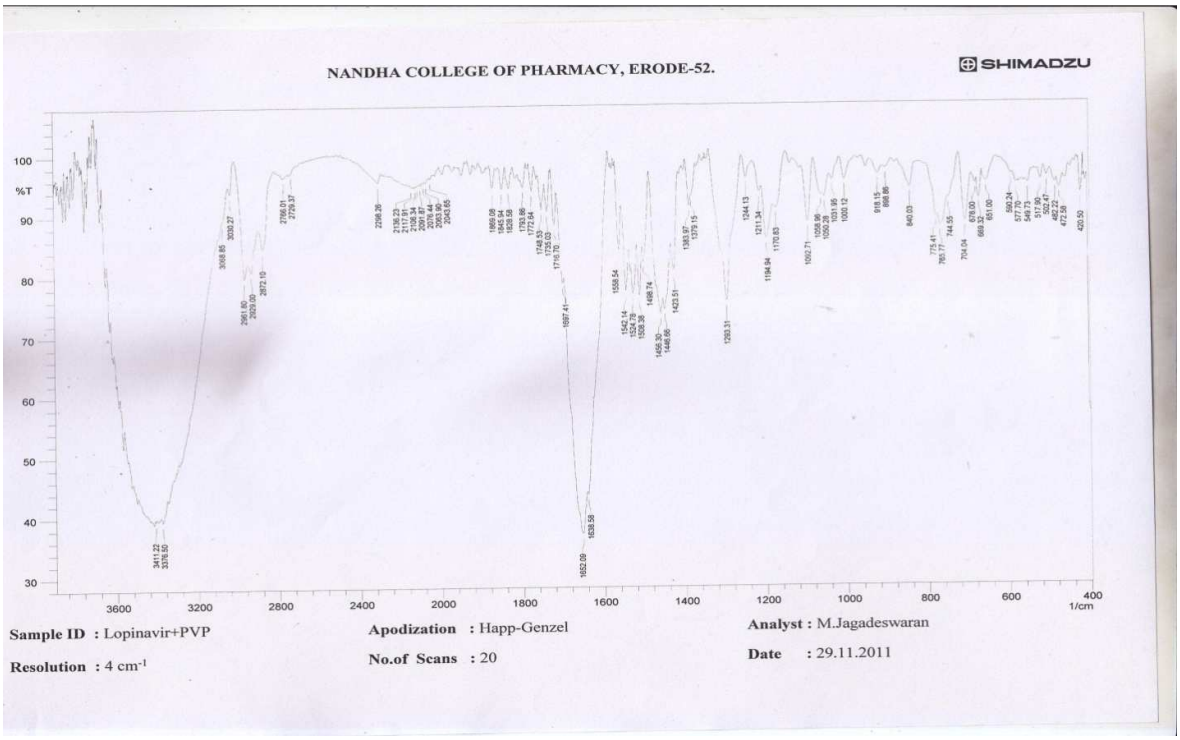


FIGURE – 9 IR SPECTRA OF MANNITOL

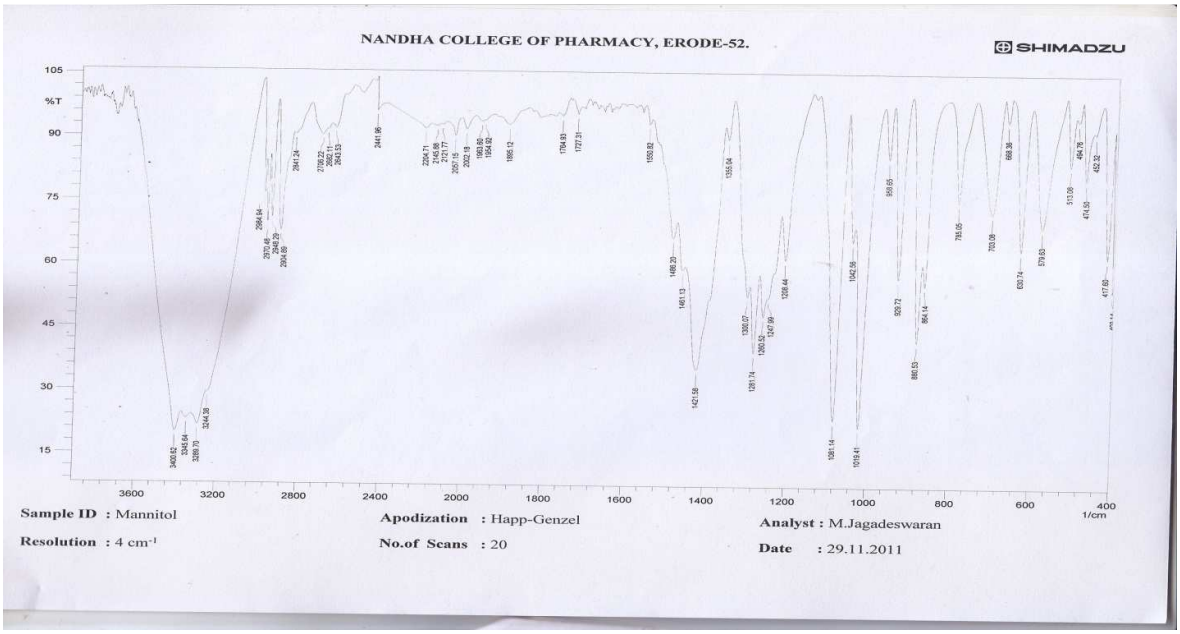


FIGURE – 10 IR SPECTRA OF UREA

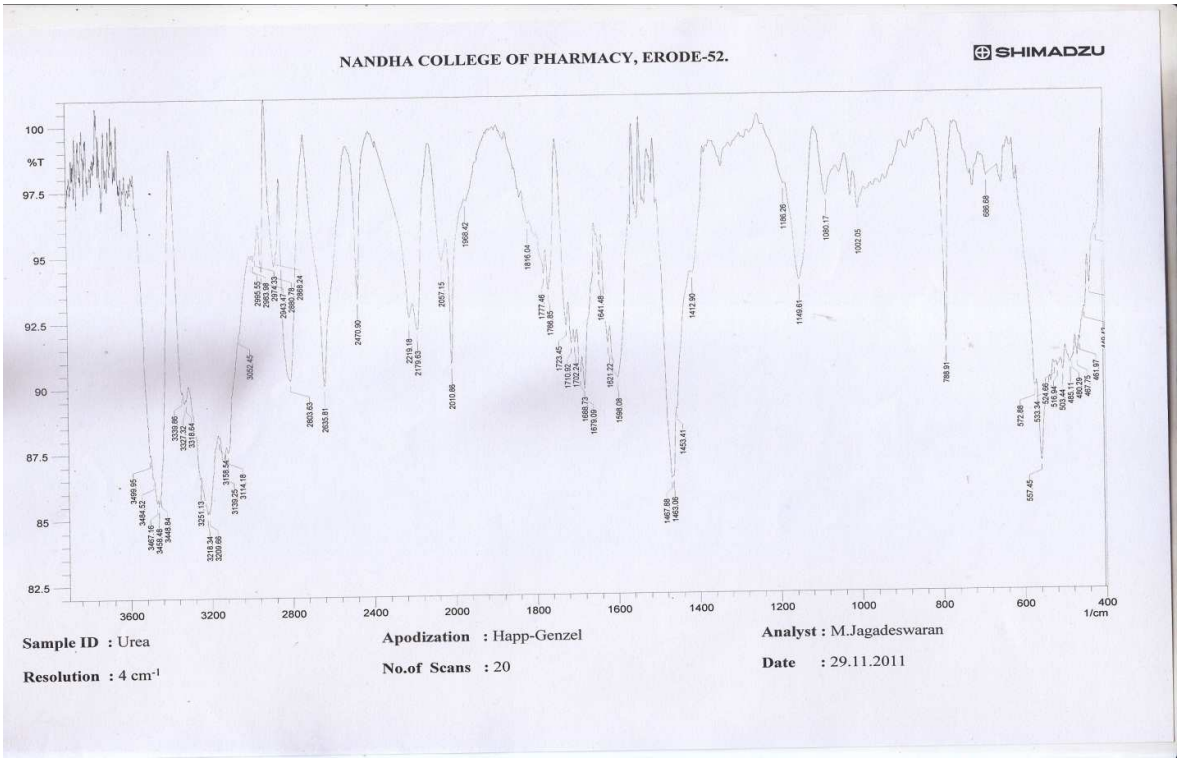


FIGURE – 11 IR SPECTRA OF SLS

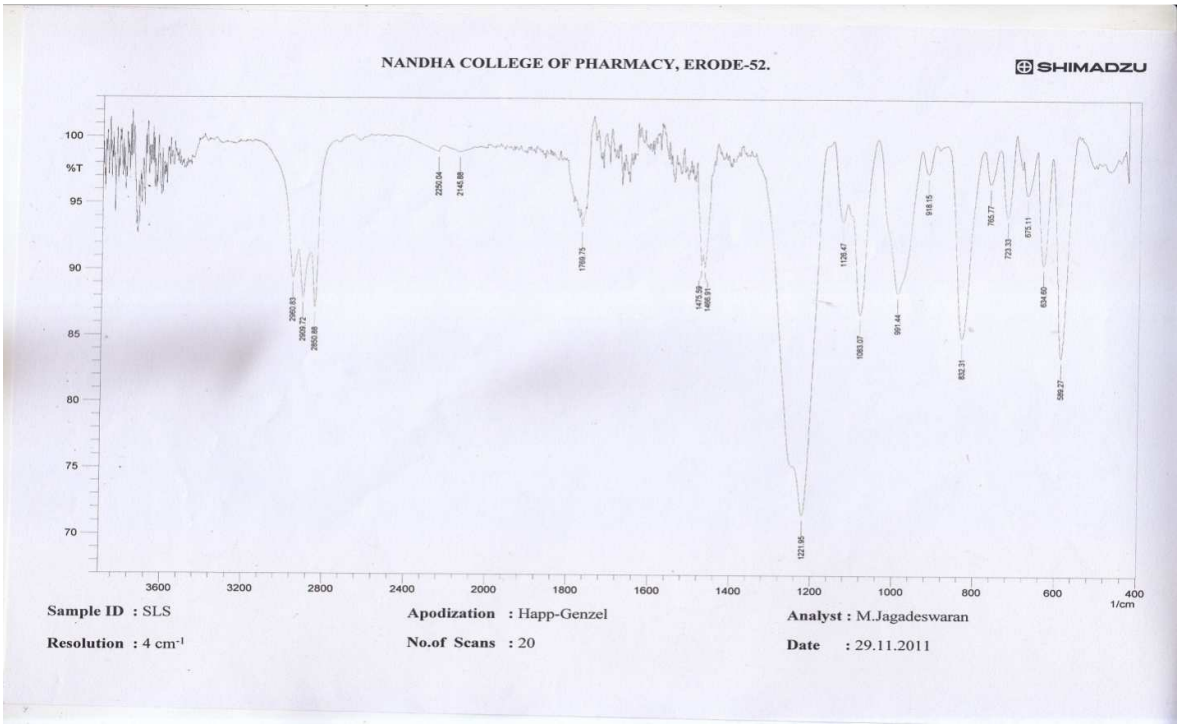


FIGURE – 12 IR SPECTRA OF LOPINAVIR WITH PVP

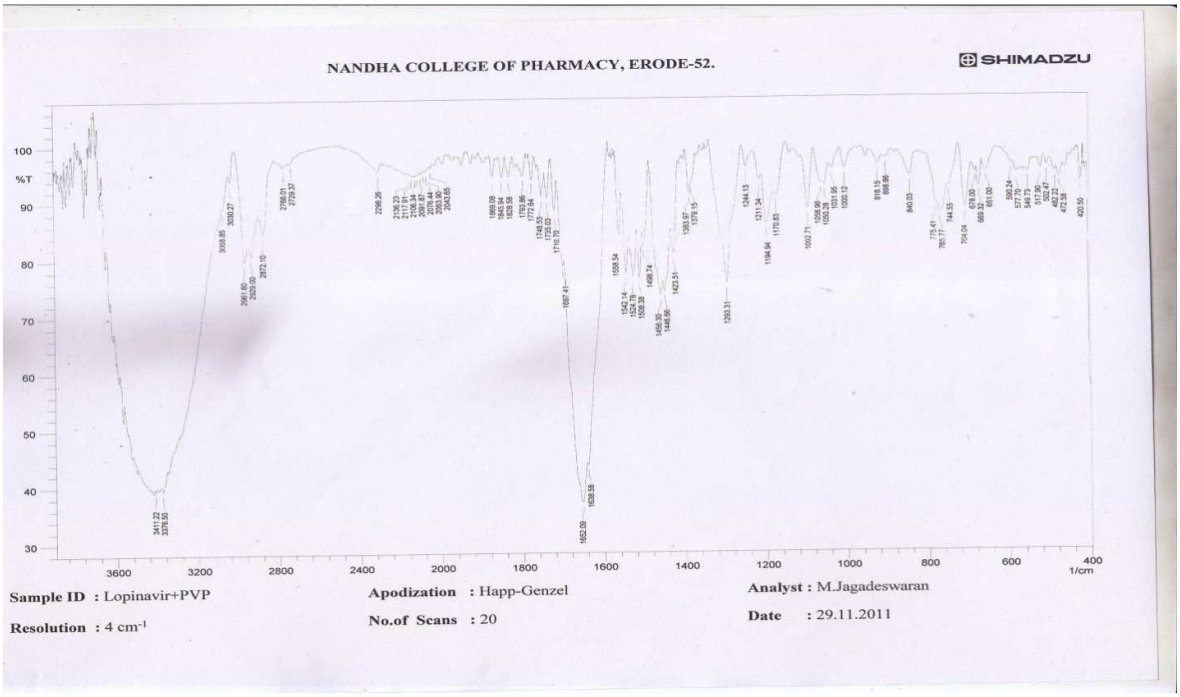


FIGURE - 13 IR SPECTRA OF LOPINAVIR WITH MANNITOL

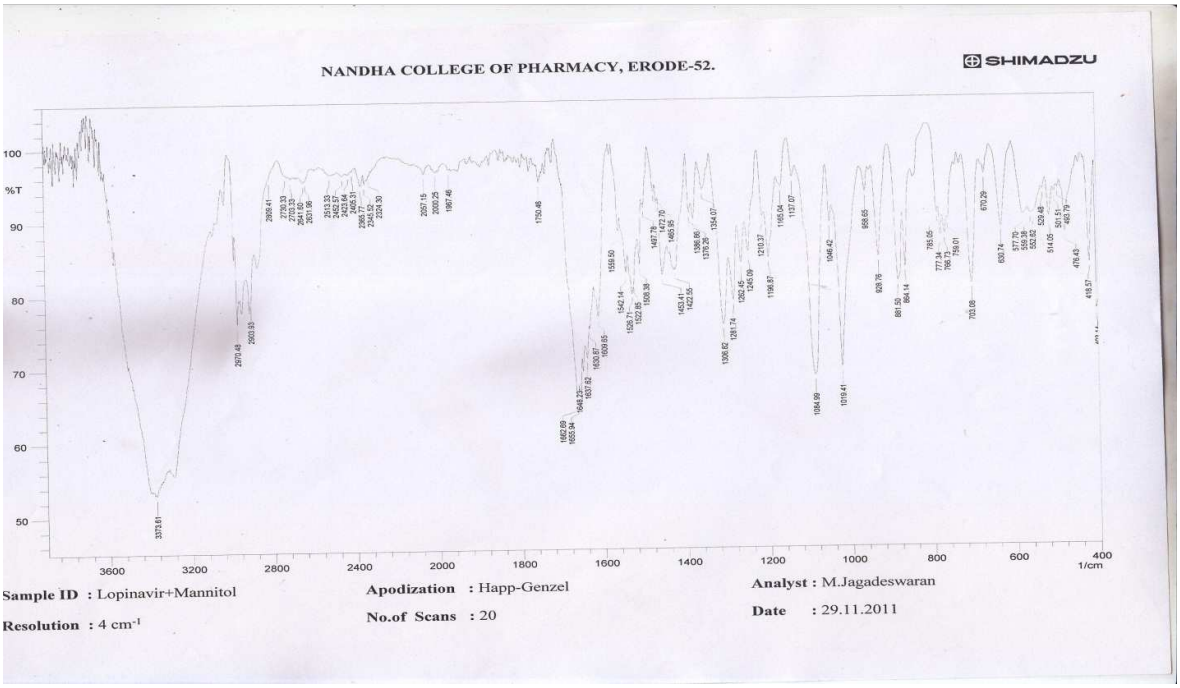


FIGURE -14 IR SPECTRA OF LOPINAVIR WITH UREA

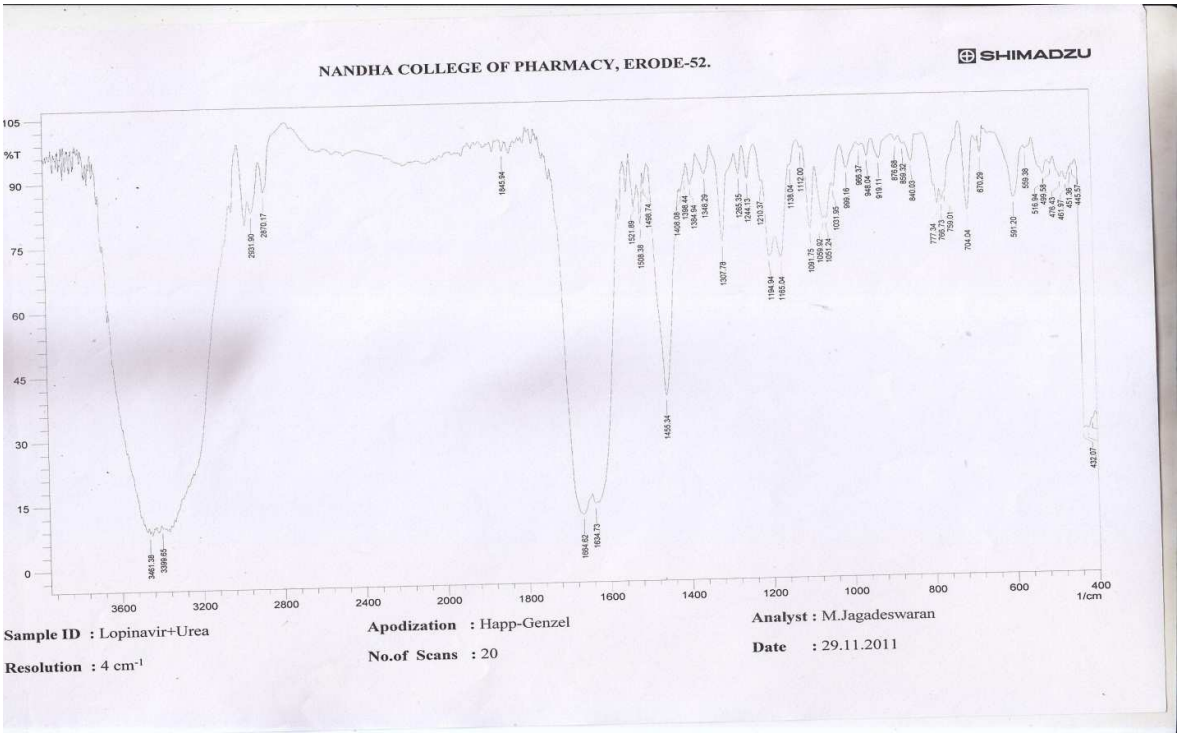
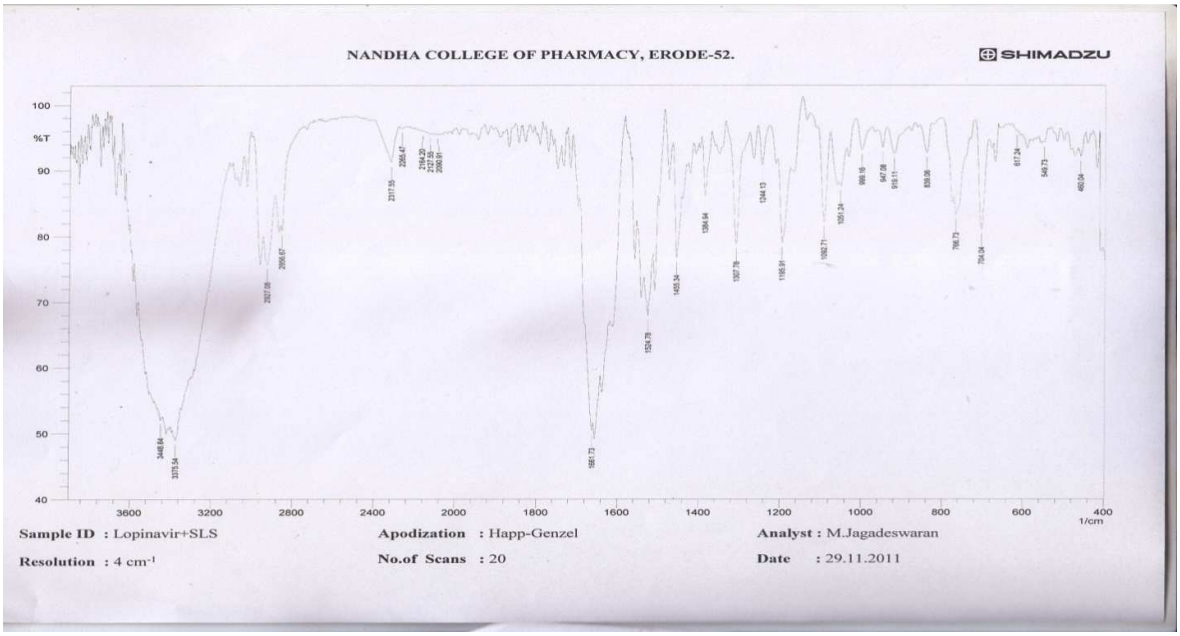


FIGURE – 15 IR SPECTRA OF OPINAVIR WITH SLS



PREFORMULATION STUDIES:

Bulk density:

The bulk density of formulations from F1-F8 was measured by the graduated cylinder. The bulk density was found in the range from 0.428 – 0.482 the results were tabulated in the table no-7.

Tapped density:

The tapped density of formulations from F1 – F8 was measured by the measuring cylinder. The tapped density was found in the range from 0.418 – 0.480 the results were tabulated in the table no-7

Angle of repose of solid dispersed Lopinavir:

Angle of repose of solid dispersed Lopinavir powders was evaluated by fixed funnel method. Acceptable range of angle of repose is 22^0 61 to 31^0 60'.all the formulations showed an angle of repose within the range as shown in table no -7 formulations F1 to F8 showed an angle of repose in the acceptable range, which indicates a good flow property.

Percentage compressibility index:

The percentage compressibility index was determined by using the bulk density and tapped density. The experimental percentage compressibility index was found to be in range of 10.56 – 19.26%. The results were tabulated in the table no -7

Percentage Drug content Estimation:

Amount of Lopinavir in formulations from F1-F8 was estimated by UV-spectroscopy and the results were found as follows:

Table: 7

Formulation code	Bulk density g/cc	Tapped density g/cc	Angle of repose	Compressibility index	DRUG CONTENT %
F1	0.428	0.435	26^0 35	15.23	88.79
F2	0.464	0.459	28^0 49	16.42	78.14
F3	0.482	0.480	30^0 18	19.26	89.91
F4	0.423	0.418	26^0 51	15.86	86.98
F5	0.430	0.440	25^0 31	10.56	97.17
F6	0.458	0.465	29^0 58	18.64	73.99
F7	0.412	0.418	28^0 29	16.12	80.13
F8	0.473	0.463	29^0 38	18.41	75.74

EVALUATION STUDIES:

Hardness test:

Formulations was evaluated by using hardness tester .the hardness of the tablets was found in the range between 5.13 – 5.80 the results were tabulated in the following table -8

Friability test:

The tablets were evaluated by the Roche friability apparatus the acceptable range for conventional compressed tablet is not less than 0.5% - 1.0%.results are given in the Table - 8.In the above table all formulations are shows that the percentage friability ranges between 0.5% - 1.0% so all the formulations are passes the test.

Weight variation test:

The formulations are present in the range with acceptable weight variations less than 5% the results were given in the table no -8

Disintegration test:

The disintegration time of the tablets was determined and the results were tabulated in the following table no -8

Table: 8

S.no	Formulation code	Hardness kg/cm^2	Percentage friability	Weight variation	Disintegration time
1	F1	5.13	0.55 %	352±0.67	5 min 20 sec
2	F2	5.52	0.61 %	351±2.34	5 min 45 sec
3	F3	5.20	0.63 %	352±2.21	6 min 34 sec
4	F4	5.75	0.72 %	353±1.86	7 min 10 sec
5	F5	5.15	0.59 %	350±3.90	6 min 15 sec
6	F6	5.62	0.65 %	351±1.77	6 min 50 sec
7	F7	5.28	0.68 %	352±2.03	7 min 45 sec
8	F8	5.80	0.74 %	353±1.92	7 min 55 sec

IN VITRO DRUG RELEASE STUDY:

The release data obtained for F1-F8 formulations were tabulated in the following tables.

Table - 9: In-vitro release of F1-F8 Formulations of Lopinavir solid dispersion.

Time (min)	Percentage drug released									
	Pure Drug	Marketed Drug	F1	F2	F3	F4	F5	F6	F7	F8
5	2.26	3.54	6.65	4.07	5.43	3.26	6.79	5.29	7.87	3.93
10	8.34	9.13	13.48	9.53	8.99	6.94	9.54	12.12	14.3	7.9
15	12.37	22.6	21.36	19.5	17.16	17.16	18.56	21.03	22.77	19.96
20	15.27	40.78	43.89	35.4	37.88	38.37	39.54	39.5	46.06	41.11
30	19.34	51.83	61.55	50.3	53.1	51.04	65.35	46.3	61.57	58.77
45	26.79	64.8	76.35	63.2	70.6	63.41	89.81	58.8	80.46	73.58
60	29.52	75.13	87.22	70.7	81.4	68.22	98.09	71.6	90.97	81.86

In vitro drug release studies reveal that there is marked increase in dissolution rate of Lopinavir from all the solid dispersions when compared to pure drug itself. The increase in dissolution rate is in the order of PVP>MANNITOL>UREA>SLS. The dissolution rate of Lopinavir in solid dispersion was strongly dependent on the relative concentration of the carrier. As the concentration of the carrier in the solid dispersion increased, the dissolution rate also increased. Formulation containing 1:4 ratio of Drug: PVP (F5) showed the best release with a release of 98.09% as compared to 29.52% with the pure drug.

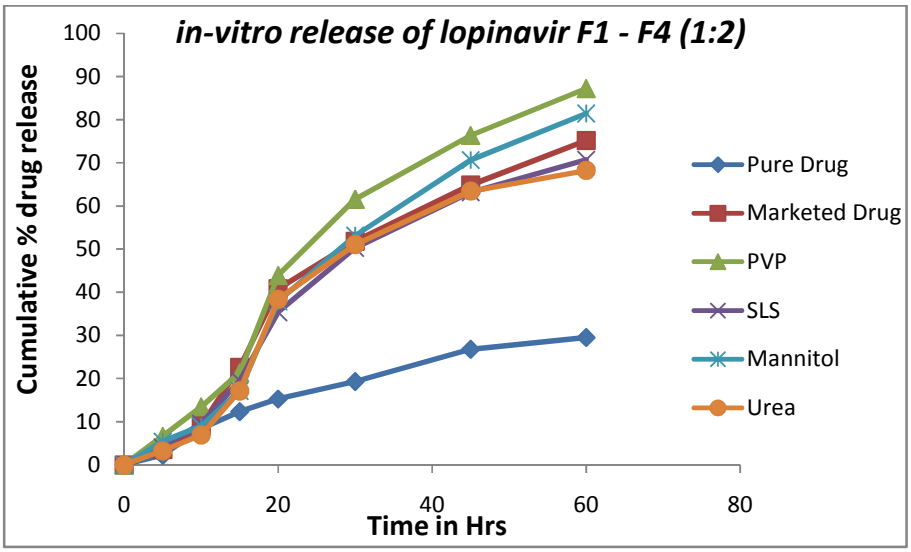


Fig 16: *In-Vitro* Drug Release of LopinavirF1-F4 (1:2)

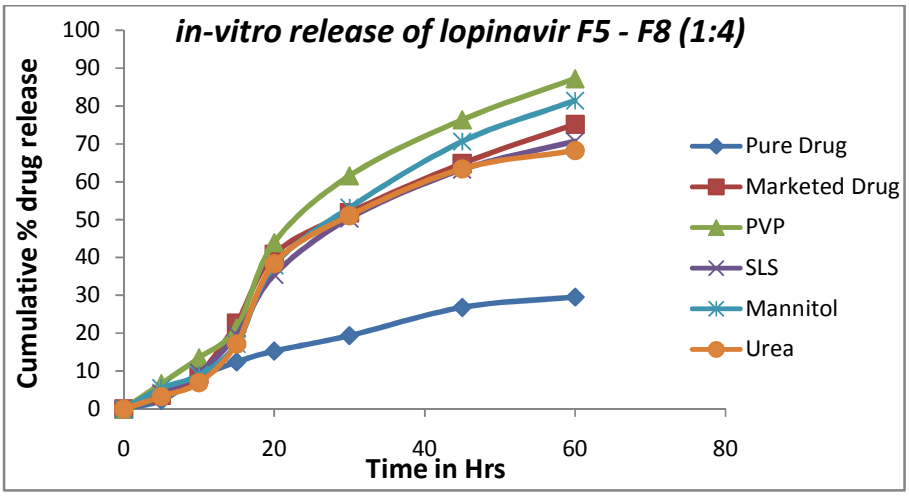


Fig 17: *In-Vitro* Drug Release of LopinavirF5-F8 (1:4)

Stability Studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. Stability studies of optimized formulation (F1 and F8) of Lopinavir tablets were placed on plastic tubes containing desiccant and stored at conditions, such as at room temperature, oven temperature (40±2ºC and 75 ± 5%) and refrigerator (2-8ºC) for a period of 3 month. The tablets were evaluated for Mucoadhesive properties and *in vitro* drug release after 2, 4 and 6 Results obtained were compared with data obtained for zero time at room temperature, oven (40±2ºC and humidity 75 ± 5%) and refrigerator condition.

TABLE -10

Parameters	1st month		2nd month		3rd month	
	RT	**40 °C**	**RT**	**40 °C**	**RT**	**40 °C**
Uniformity of weight	351	350	354	352	352	352
Hardness	5.23	5.87	6.28	5.33	5.19	5.01
Friability	0.51	0.47	0.27	0.54	0.67	0.66
% drug content (%)	98.33	97.77	98.40	96.90	98.28	97.37
Disintegration test (in mins)	6.20	5.42	5.50	6.12	6.24	5.36
Cumulative % release	98.11	98.17	97.56	98.08	97.67	98.32

SUMMARY

Solubility of drug molecule is a significant factor that affects the dissolution rate and bioavailability. According to biopharmaceutical classification Lopinavir belongs to class II drug, acting as an antiretroviral drug of the protease inhibitor class. The major problem associated with this drug is its poor bioavailability because of its insolubility in water and reduced dissolution rate. So in order to improve the drug solubility the drug must be formulated as conventional tablets by solid dispersion technique using different polymers.

Dissolution is the rate limiting step for poorly water soluble drugs. Lopinavir is one such drug. The use of Solid dispersion technique has increased the dissolution rate of the drug by 30-65%. The solid dispersions of Lopinavir were successfully formulated by solvent evaporation method using carriers like PVP, SLS, mannitol, and urea. In-vitro release studies reveal that there is marked increase in the dissolution rate of Lopinavir from all the solid dispersions when compared to the pure Lopinavir itself. Using all four polymers 8 different formulations are prepared using the ratio 1:2 and 1:4 All the eight formulations are then subjected to various characterization studies like, *FT-IR*, tablet evaluation studies, *in-vitro* drug release studies, and stability studies etc.

Preformulation study is carried out, bulk density, tapped density, Angle of repose, percentage compressibility was found out and all values are within the acceptable limit. The dissolution studies indicating that solid dispersion showing maximum cumulative percentage drug release compared to unprocessed drug. Tablet evaluation tests like hardness (5.13 – 5.80kg/cm^2), Friability test (0.5% - 1.0 %.), weight variation, disintegration was complies with IP standards. *In-vitro* drug release studies shows release rate was in the order of F5>F7>F3>F1>F8>F6> F4> F2. The increase in dissolution rate is due to the presence of carrier and the order was found to be PVP>mannitol>urea>SLS. Thus, if we formulate the poorly water soluble drugs like Lopinavir as solid dispersions the dissolution rate of drug can be increased markedly and hence higher plasma levels can be achieved.

CONCLUSION

In the present research work an attempt was made to develop solid dispersion Lopinavir by solvent evaporation method for improving the solubility and bioavailability of drug. From the experimental findings, it is concluded that:

- Polyvinyl pyrrolidone is the better polymer than urea, SLS and Mannitol and is not producing any interaction with drug when compared with other formulations.
- The percentage drug content in all formulations was found in the range of 73.99 to 97.17 %.
- All the solid dispersion showing better saturation cumulative drug release compared to pure Lopinavir.
- The *in-vitro* drug release studies shows that all the formulation releasing maximum amount of drug within 60 min and formulation F5 showing maximum drug release.
- The optimum drug to polymer ratio was found to be in F5 (1:4), depending on *in-vitro* drug release studies. There is a significant increase in drug release with increase in drug to polymer ratio.
- The stability studies showed that the remaining drug content is within the limits at different temperature and humidity levels.

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Certificates

Declaration

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