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A REVIEW ON SOLID DISPERSION CONTAINING PHOSPHOLIPID

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Abstract:
The oral solubility of poorly aqueous soluble drugs endures the major challenging feature in pharmaceutical formulation. There are more than 60-70 % of the drugs suffers low aqueous solubility, which can be dramatically increased by solid dispersion. One or more active pharmaceutical ingredient is dispersed in a solid carrier to improve their dissolution and bioavailability is called solid dispersion. Phospholipid based solid dispersion is a novel formulation which is used to enhance solubility and drug release of poor aqueous soluble drugs. Phospholipids are derived from different sources such as natural and synthetic, and have the magnificent biocompatibility and particular amphiphilicity. Due to their special characteristic they are used in drug delivery system to intensify solubility and dissolution. Phospholipids have the ability to enhance the penetration across the cell membrane to deliver active drug substance which results to increase bioavailability. The present article summarized the solid dispersion types, methods, phospholipid types and their application in drug delivery system

Keywords:*Solid Dispersion, Bioavailability, Phospholipid, Application*

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INTRODUCTION:

The most common and preferred route of administration is oral route due to the ease and comfortable delivery of drug. Swallowing the medication is most preferred mode for administration of drug as per the patient's convenience. The patient chooses the oral mode of administration over other route such as parenteral route(1). Drug having low solubility in water are still great provocation in prosperous formulation of therapeutic products because of their low oral bioavailability(2).The drugs are distinguished in biopharmaceutical classification system according to their solubility and permeability. It seems over 70% of drugs or active ingredients are belongs to BCS classII which is poor water soluble drug (2).

The mechanism by which the solubility and dissolution of drugs can be increased is the reduction in particle size of drug from crystalline to amorphous(3). For enhancement of solubility and dissolution of poor water soluble drugs, there are various methods available such as liquisolid, in which dissolve drug is absorbed over insoluble carrier, add surfactant, micronization, nanocrystalisation, salification, co-crystallisation, cyclodextrine inclusion, micelle solubilisation, and encapsulation of nanoparticles(2). But solid dispersion is most optimistic method for formulation of poor aqueous soluble drug because of its ease of formulation, optimization and reproducibility(4).

Dispersion is defined as a technique in which a material is diffused in other molecules or continues phase.This can be categorised in different ways such as their size and state of dispersed matter. Here, Solid dispersion are the diffusion of one or more pharmaceutical active ingredient or drug in an inert carrier at solid state produced by solvent evaporation, spray drying, melting method, lyophilisation or other methods(2).The drug or API in solid dispersion method can be dispersed in crystalline or unformed particles while the carrier can be in crystalline or unformed state. Several publications found in google search engine on solid dispersions which dominant properties of solid dispersions such as enhancing the solubility and dissolution rate of less aqueous-soluble drugs. These advantages comprise reducing particle size, enhancing wettability and porosity, improving solubility by changing the crystalline nature of drug into amorphous (4).

Solid dispersion containing phospholipid formulation is one of the most promising methods to enhance the solubility, dissolution and bioavailability of less aqueous soluble drug. The phospholipid is encapsulated into drug particle which helps to change crystalline nature to amorphous nature of drug.

Phospholipids are one of the types of lipids that contributes major component of all cell membranes. This constitutes lipid bilayers by their amphiphilic characteristic. The structure of phospholipid molecules usually consisted of two hydrophobic fatty acid 'tails' and hydrophilic 'heads' consisting of phosphate group and joined together due to a glycerol molecule. The hydrophilic head group constructed with simple organic molecules like "choline, ethanolamine or serine". The phospholipid first identified in 1847 by French analyst and pharmacist as a consequence in biological tissue was lecithin, andphosphatidylcholine, in the egg yolk of chicken (fig. 1).

Phosphatidylcholine (PC) from egg yolk was the primarily identified phospholipid. The various phospholipids are derived such as phosphatidic acid (PA)(phosphatidate), phosphatidylethanolamine PE (cephalin), phosphatidylcholine PC (lecithin), phosphatidylserine PS (5).Phosphatidylcholine PC or lecithin is common term which is used to nominate yellow brownish fatty substance available in animal or plant tissue linked of phospholipids, phosphoric acid, triglyceride, and glycolipids. Lecithin is comfortably removed from sources like soybeans, eggs, milk, marine sources, rapeseed, cottonseed and sunflower chemically by using hexane, ethanol, etc. Lecithin has emulsification and emollient characteristics. Lecithin from egg and soybean exploits an important part in drug delivery(5, 6).

The drug delivery system using Phospholipid (PL) is one of the most encouraging approaches for enhancing oral bioavailability. Phospholipids are biodegradable, biocompatible as well as having an amphiphilic characteristic that allows PLs arranged each other as lipid bilayers when deposit in water, the hydrophobic tails bunch up against each other and the hydrophilic head-group interfacing the water on both sides. PLs are considered as most suitable excipients for low aqueous soluble drugs. Solid PL loaded formulations (solid dispersion) have attracted increasing application since they have various advantages over other PL containing formulations for oral drug delivery. One of its advantages is that they may have improved as well as enhance physical and chemical stability during storage. The additional advantage is that they (the powder) can be used in formulations of solid dosage forms with comparatively straightforward preparation processes(7).Phospholipids have been extensively utilized to prepare liposomal, ethosomal and other Nano formulations of topical,

oral and parenteral drugs for the reasons like increased solubility, bio-availability and reduced toxicity and increased permeability betweencell membranes.The SD loaded with Phospholipid is not only produced homogeneous distribution of drug in solid state but also stabilized the unstable drug by oxidation and hydrolysis(6).

Several review articleshas published to describe the SD techniques and applications. In present review, a compendious survey on the applications of solid dispersion and lipid based dispersion for enhancement of dissolution and bioavailability of poorly aqueous soluble drugs. This article summarizes the formulation development, SD application and preparative techniques of solid dispersion. In addition, the other dispersion methods are also described, such as lipid based dispersion and applications of solid dispersion containing phospholipids for enhancement of dissolution and bioavailability of poorly aqueous soluble drugs.

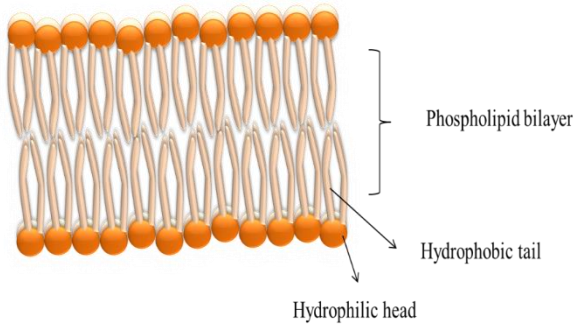

Fig: 1 phospholipid bilayer structure(7)

Types of solid dispersions:

1) Eutectic mixture
2) Solid solution
3) Amorphous precipitation in crystalline carrier
4) Glass solution and suspension

1. Eutectic mixture:

The eutectic mixture plays a significant role in preparation of solid dispersion which isa keystone of this approach to enhance bioavailability of poorwater soluble drug. A simple eutectic mixture composed of two compounds which are entirely compatiblein the liquid form and shows limited miscibility in solid state (Fig. 2) (1, 8).

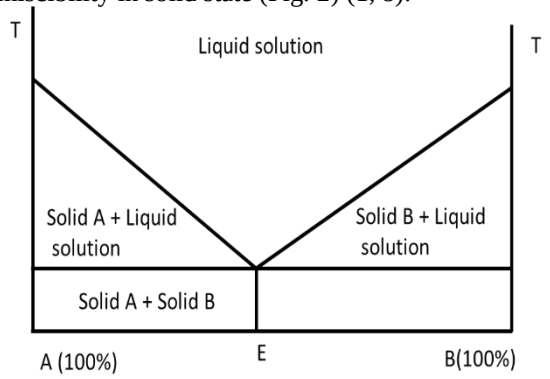

Fig 2: Eutectic mixture

When a mixture of A and B dissolved in E and cooled, both A and B component simultaneously crystalized. Solid eutectic mixtures are usually formulated by fast cooling of a solution of the two compounds which produce physical mixture of very fine crystals of the two components(3, 9).

2. Solid solution:

Solid solutions are corresponding to liquid solutions which consist just one phase despite the number of components. Solid solutions are used to reduce the grain size of the drugs to its molecular dimension. Solid solutions of drugs with poor aqueous solubility are dissolved in a carrier which have good aqueous solubility are used to improve the bioavailability. Solid solutions are categorized according to their miscibility (continuous or discontinuous) and the way of distribution insolvents (substitutional or interstitial)(3, 10).

Solid solution can generally be classified according to the extent of miscibility between the two components or the crystalline structure of the solid solution(1, 3).

a) Continuous solid solution
b) Discontinuous solid solution
c) Substitutional solid solution
d) Interstitial solid solution

a) Continuous solid solution

In this system, the two components are soluble or mixable at solid form in all proportions (Fig3).No established continuous solid solutionhas been shown to enhance the dissolution properties, even though it is theoretically possible. It is visible that a rapid dissolution rate would be acquired if the drug were present as a small constituent. However, the small amount of soluble carrier is existence in thecrystalline lattice of the poor aqueous drugs may also cause an improved dissolution rate than the pure drug with same granular size(10).

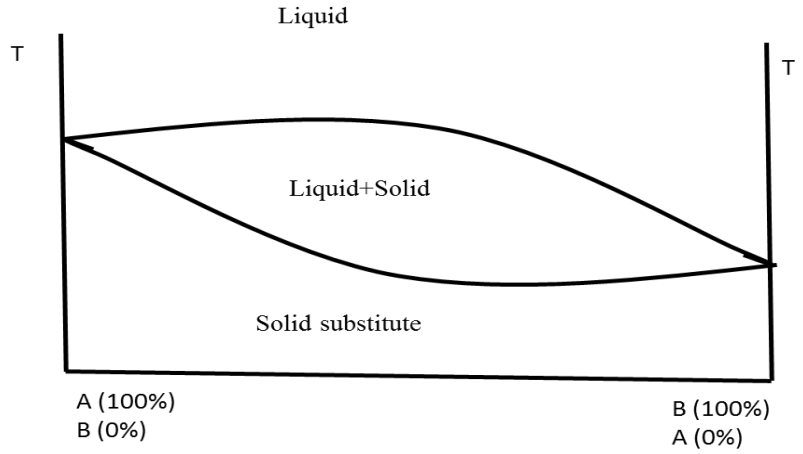

Fig 3: Continuous solid solution

b) Discontinuous solid solution

In discontinuous solid solution, shows the divergence to continuous, solid solution which shows the limited solubility of each compound in the other compound Fig 4. A and B shows the regions of true solid solutions. Each component is having the ability of dissolving the other ingredient to a certain degree exceeding the eutectic temperature. It should be considered that below a definite temperature, the correlative solubilities of the two components start decrease. Due to practical deliberations it has been reported in Goldberg et al 1966(10) that the term solid solution should only be applicable when the correlation solubility of the two components exceeds 5%(1, 3, 11).

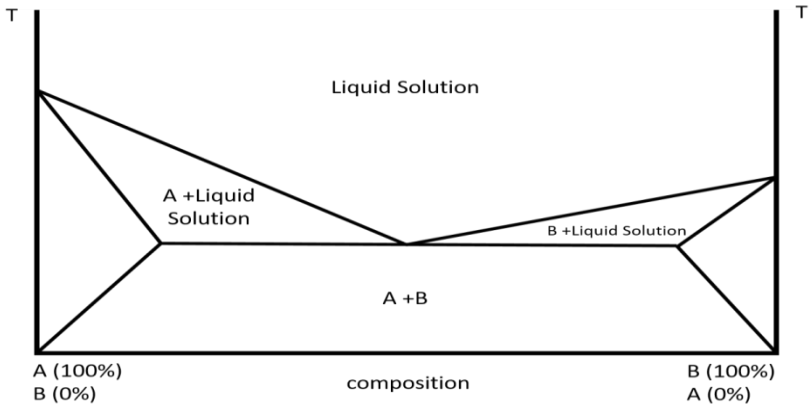

Fig 4: Discontinuous Solid Solution

c) Substitutional solid solution:

Substitutional solid solutions have a crystal like structure, in which the solute particle can eithercompetent into the interstices in the middle of solvent particleorsubstitute for solvent particle in the crystal lattice this is depicted in Fig. 5. Solute atom size nearly similar to solvent atom, due to similar size solute atoms live in empty site in solvent atom. Replacement of molecules is only feasible whenthe size of the solute atom varies by not more than 15% with the solvent molecules(3).

d) Interstitial solid solution

When the solute atoms live in the interstitial spaces in the lattice of the solvent is called as interstitial solid solution. The figure (Fig 6) shows the solute interstitially incorporated into solvent crystal lattice by occupying into the space between solvent particles. It generally forms only a discontinuous solid solution. The size of the solute is critical in order to fit into the interstices. It was found that the size of solute should less than 20% then the solvent to form interstitial solid solution, and also the volume of the solute should not more than 20% of solvent(3,8).

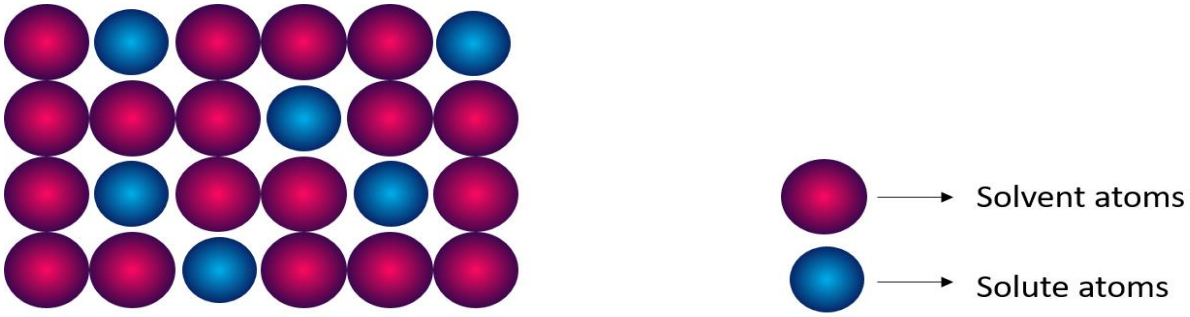

Fig 5: Substitutional solid solution:

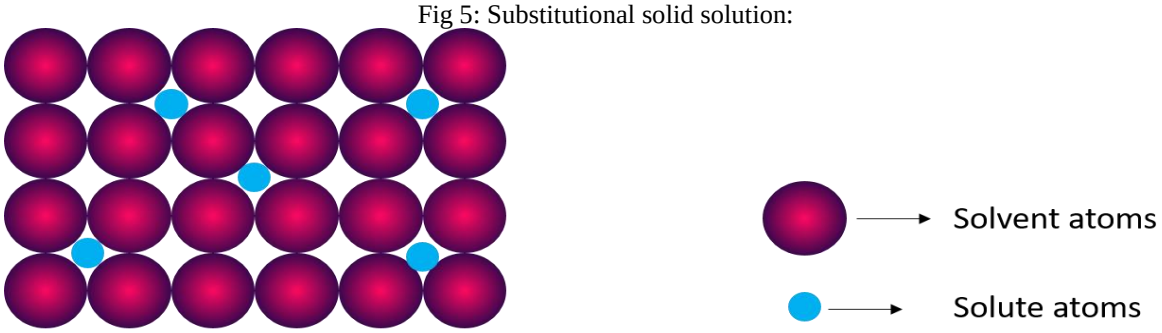

Fig 6: Interstitial solid solution

3) Amorphous precipitation in crystalline carrier :

Amorphous precipitation comes when drug precipitates out in amorphous form in the inert carrier.Thedrug produced by amorphous precipitation generally shows the higher dissolution rate than the analogous crystalline nature of drug. It is hypothesis that a drug with high super cooling property has more affinity to solidify as an amorphous form in the presence of a carrier, therefore amorphous precipitation is acutely observed. This is same as simple eutectic mixtures but only variation is that amorphous form of drug is precipitated out (1, 3).

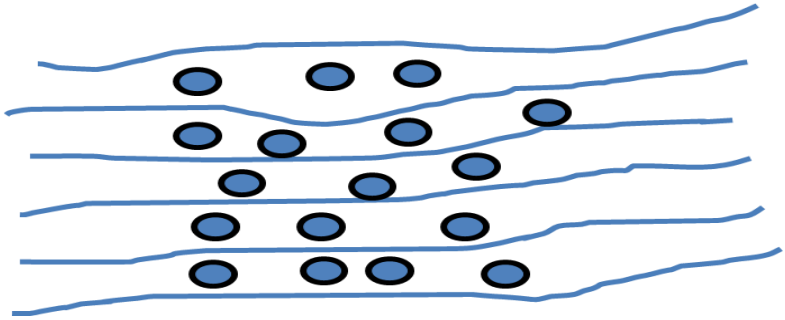

Fig 7: Amorphous precipitation in crystal carrier

4) Glass solution and suspension:

Glass solutions are homogeneous glassy system in which drug solubilises into the matrix of glassy or vitreous carrier. Glass suspensions are amalgam in which precipitated particles are dispersed in glass solvent. Lattice energy is significantly lower in glass solution and suspension. The glassy state is generally obtained by sudden quenching of the melt. It is categorised by transparency and brittleness under the glass transition temperature (Tg).

Methods of preparation of solid dispersion

1. Spray drying method
2. Lyophilisation or Freeze drying method
3. Melting method
4. Hot melt extrusion method
5. Supercritical fluid method
6. Solvent evaporation
7. Melt agglomeration
8. Use of surfactant

1. Spray drying method

In early 1920s the Spay drying method was first used to manufacture milk powder. Now spray drying discovers great utility in pharmaceutical industries because of fast drying and other characteristics such as fine particle size and shape of the final product. This is one of the rapidly used techniques for formulation of solid dispersion.

Spray drying is a process by which liquid product is sprayed very finely in a hot gas to obtain a powder (product) rapidly. The mostly used gas is air and nitrogen gas is rarely used. The initial liquid to be feed into sprayer can be a suspension or a solution or an emulsion. Spray draying produced a very fine particles (10 to100µm) or large particles (2-3 mm) depending upon starting feeding material. In addition,spray drying method is 30-40 times more economical in comparison to freeze drying (11).

The process of spray drying method includes, atomization, droplet-hot air contact, evaporation of droplet water and dry product-humid air separation. There are many atomizer used in spray drying such as pneumatic atomizer, pressure nozzle, two fluid nozzle and sonic nozzle. Liquid atomization in small droplet can be obtained by high pressure and centrifugation. The purpose of this step is to maximize heat transfer between hot air and feed liquid. The choice of atomizer is depend upon the liquid and final product characteristics. During atomization droplet-hot air contact takes place which initiate the drying process. The liquid is sprayed at same direction to a hot air flow, and the temperature of hot air is typically at 150-220 ºC which enhance the evaporation. Dry product-humid air separation done through the cyclone placed outside of spray dryer. The large particles are redeemed at the base of drying chamber while fine particles are pass through cyclone where separated from humid air(12).

2. Freeze drying method:

Freeze drying is also called as lyophilisation. Freeze drying monopolize transfer of heat and mass to and from the product. This is alternative technique to solvent evaporation. Lyophilisation is a mixing of drug and carrier in a common solvent, allow for primary drying which leads to sublimation to obtain a lyophilized dispersion. Lyophilisation is extensively used in pharmaceutical industries to enhance stability and long term storage stability(8).

The process of freeze drying consists of several stages such as pre-treatment, freezing, primary drying and secondary drying. Pre-treatment is treating, formulating and adding a component to increase stability in the product before or prior to freezing and decreasing the high vapour-pressure or enhancing the surface area. In many occasion the decision to pre-treat the product is on the basis of theoretical information of freeze drying(13).

Freezing is the most typical process where most of solvent specially water is evaporated from solute to form ice. Therefore, the solute part becomes a highly concentrated which called 'freeze concentrate'. After completion of freezing process, the freeze concentrate contain only 20% of water(w/w)or not more than 1% of water in the solution before ice formation. This process takes several hours. The next process of freeze drying is primary freeze. During primary dying the chamber pressure is lowered (milli bar range), shelf temperature is raised and supply enough heat to the product for the ice to sublime. In the primary drying process the pressure of chamber is enough lower than the vapour pressure of ice, and ice is evaporated from product to condenser by sublimation and crystalline the product onto the condenser plate at -50 ºC. In drying phase about 95% of water sublimed, and this stage is longest drying stage, it take several days. The purpose of secondary drying is to remove unfrozen water molecules, because the ice was eliminated in the primary drying process. In secondary drying phase raised the temperature above the primary drying, can even be above 0 ºC (32 ºF), which break any physicochemical interaction that have formed between water molecules and material (13, 14).

3. Melting / Fusion method

This is the easy method of preparation of dispersion, in the melting and fusion method the physical mixture of drug and water soluble carrier is melted directly under the heating. After melting the drug-carrier mixture, solidify the mixture quickly in an ice bath under the magnetic stirrer. The final mixture in crushed to powder and sieve. Then this mixture is placed onto the metallic plate such as stainless steel plate or ferrite plate and allows the flow of air or water onto the other side of plate.The super saturation of drug and solute found by quenching, which gives the finest dispersion of crystallites as compare to simple eutectic mixture. In many cases drug or carrier may decompose by increasing the temperature, it may also cause evaporation of volatile drug or evaporation of volatile carrier. To overcome these problems heat the physical mixture in sealed container of under vacuum(13).

4. Hot melt extrusion method

The process of hot melt extrusion was primarily used in 1930. Hot melt extrusion is mostly utilized in rubbers and plastic industries for the production of plastic bags, pipes and sheets. Hot melt extrusion is recently used in pharmaceutical industries, researchers found that this technique enhance the dissolution property of the less water soluble drugs, therefore, this is used to enhance the dissolutionof the poor water soluble drugs(15).

Extrusion is the process in which preparation of thick semi-solid paste convert into uniform extrude like shape by forcing it in between dies under certain condition. Extruder is usually made up of

two parts such as conveying system and die system. The conveying system is allowed to equal distribution of material or dispersive mixing and transfer the material from hopper to dies and the die system moulds the material into desired or required shape. Various types of extruder have common feature such asFeeding of hoppers, Conveying system flow of material between dies, and collect the material from dies exits(16, 17).

5. Supercritical fluid method

The supercritical fluid technique is also known as anti-solvent technique, where carbon dioxide is rapidly used as an anti-solvent for the solute but as an organic solvent. Many acronyms are used by the author's such as gas anti-solvent, supercritical anti-solvent, micronization process and compressed fluid anti-solvent.

Supercritical anti-solvent process is to spraying of the solution composed of solute and organic solvent onto a continuous supercritical phase. Carbon dioxide is widely used as anti-solvent because it have several advantages over other such as it is easily remove after completion of process from the polymeric material, and not harm the patient even fraction of carbon dioxide entrapped inside the polymer. By decreasing the melting temperature of dispersed active agents, supercritical fluid used to reduce the temperature of dispersion process (1, 18, 19).

6. Solvent evaporation method

The solvent evaporation method is widely used in the formulation of solid dispersion. In this method solvent is evaporated from the solution and dry product will be obtained. By increasing temperature and reduced pressure solvents are removed by evaporation. The fast solvent evaporation required the large amount of processing fluid. Solvent evaporation process at small scale is easy to operate, sanitise and improved or equal size distribution as compare to other mixing process.

Solvent evaporation process consists of four steps such as dissolution, emulsification, extraction and harvesting of dried product. Dissolution of pharmaceutical active compound in organic solvent, active compounds is dispersed in organic solvent stir till it completely dissolves in solvent. The extraction of solvent by increasing temperature and reduce pressure which leads to evaporation of solvent. The final step is harvesting or collection of dried products(20, 21).

7. Melt agglomeration method

Melt agglomeration is one of the methods of solid dispersion in which binder is used as a carrier. Melt agglomeration is prepared by three ways such as, in heated excipient add the molten carrier and drug solution. In theheating mixture of drug and excipient adding molten carrier,Heating a mixture containing drug, carrier and excipients below or above the melting point of carrier.

The rotary processor is the alternative technique for melt agglomeration or even rotary processor is preferable technique for this method because rotary processor is easy to control the temperature and integrate higher binder content in agglomerates. The characteristic of binder, types, particle size of binder and method of preparation are critical parameter which can affect the preparation of solid dispersion. Since these parameter can affect the dissolution rate, agglomerate size, agglomerate formation and growth of agglomerates. Melt agglomerate can be prepare by melt in procedure (which is describe above) and spray on procedure, in spray on the molten carrier is sprayed on mixture of drug and excipient. But melt in procedure is preferred because it gives high dissolution rate and homogenous distribution in comparison of spray on procedure(4, 13).

8. Use of surfactant

Uses of surfactant are conventional method of preparation of solid dispersion. The addition of surfactant on solid surface have the ability to modify the surface tension, surface charge, hydrophobicity and interfacial properties floatation, dispersion, flocculation, wetting detergency and corrosion inhibition. Surfactants are also responsible for manifesting, solvation, glass transition temperature and decreasing the melting of drug. Polysorbate 80 or tween 80 is commonly used surfactant in preparation of solid dispersion, because of their ability to enhance dissolution and bioavailability of poorly aqueous soluble drug(19).

Classification of phospholipid:

1. Natural phospholipid

The word lecithin was come from Greek word *lekithos* which means the orange colour sticky substance separated from egg yolk. There are various definition of lecithin reported in literature's such as, from a business viewpoint lecithin mostly contain fatty acid, triglyceride, glycerophlipid and carbohydrate. From the view point of history, lecithin is a lipid which holds the phosphorous separated from brain and eggs. The scientists introduced lecithin as a PC(6).

Phospholipids are extensive spread in animal and plants. The most common natural source of phospholipid isvegetable oils (soybean, corn, cotton seed, and sunflower) and animal source (egg yolk and bovine brain). The phospholipids are derived from animal or plant required purification

before used in food or pharmaceutical industries. For example lipoid E80 contains PC, PE, fatty acid, cholesterol, lyophosphatidylcholine and water. The cost of purification and isolation of phospholipid from natural source is lower than synthetic source.

2. Synthetic phospholipid

The synthetic phospholipid can be manufactured by two ways includes, semi-synthetic and total synthetic technique. Because of separation and salvation cannot get single molecule from phospholipid. Scientist focuses on synthetic phospholipid instead of semi-synthetic phospholipid with described structure and configuration. Total synthetic method requires more reaction steps as compare to semi-synthetic method. The manufacturing of phospholipids is based on their usage and application. For instance, soya phospholipid contains more unsaturated fatty acid than egg phospholipid. Therefore to maintain the quality of soya lecithin is difficult(19, 21).

Table1: Types of phospholipids(21, 22)

Sources	Class	Phospholipid	Short form	Tg
Natural	Phosphatidyl choline's	Egg Phosphatidylcholine	EPC	-5 TO -15
		Soy Phosphatidylcholine	SPC	-20 TO -30
		Hydrogenated soy Phosphatidylcholine	HSPC	52
Synthetic source	Phosphatidyl choline's	Dilauroyl Phosphatidylcholine	DAPC	-
		Dimyristoyl Phosphatidylcholine	DMPC	23
		Dipalmitoyl Phosphatidylcholine	DPPC	41
		Distearoyl Phosphatidylcholine	DSPC	55
		Dioleoyl Phosphatidylcholine	DOPC	-22
Synthetic source	Phosphatidyl Glycerol's	Dimyristoyl Phosphoglycerol	DMPG	23
		Dipalmitoyl Phosphoglycerol	DPPG	41
		Distearoyl Phosphoglycerol	DSPG	55
		Palmitoyl oleoyl Phosphoglycerol	POPG	-18
Synthetic source	Phosphatidyl Ethanolamine's	Dimyristoyl Phosphoethanolamine	DMPE	50
		Dipalmitoyl Phosphoethanolamine	DPPE	60
		Distearoyl Phosphoethanolamine	DSPE	-
		Dioleoyl Phosphoethanolamine	DOPE	-16
Synthetic source	Phosphatidic acids	Dimyristoyl Phosphatidic Acid	DMPA	-
		Dipalmitoyl Phosphatidic Acid	DPPA	-
		Distearoyl Phosphatidic Acid	DSPA	-
Synthetic source	Phosphatidyl Serine's	Dimyristoyl Phosphatidylserine	DMPS	38
		Dipalmitoyl Phosphatidylserine	DPPS	51
		Dioleoyl Phosphatidylserine	DOPS	-10

Phospholipid containing solid dispersion is novel approach for improving or enhancing dissolution and bioavailability of less water soluble drugs. There are many research article have been published on phospholipid loaded solid dispersion, some of them are included in this review article (Table 2). The purpose of this table is to show which types of phospholipid are used, method of solid dispersion and the outcomes of that article.

Table 2: Phospholipid loaded solid dispersion

Drugs	Phospholipid	Solid Dispersion Method	Findings	References
Fenofibrate	Soya lecithin-Phosphatidylcholine	Freeze drying	The formulation increased the drug dissolution and Improving oral bioavailability of fenofibrate in rat	Shi 2015 et al(23)
Cyclosporine	Dimyristoyl Phosphatidylcholine (DMPC)	Kneading Method	The suitability of DMPC as a carrier for enhancement of dissolution of Cyclosporine by Kneading method	Zidan 2008 et al(24)
Celecoxib	Egg-Lecithin Phosphatidylcholine (Lipoid E80)	Freeze drying	No clear observation was found between the enhancement of celecoxib solubility and permeability	Fong 2016 et al(25)
Quercetine, kaempferol and isorhamnetine	Soy Phosphatidylcholine (Soy Lecithin)	Solvent Evaporation	The dissolution of Quercetine, kaempferol and isorhamnetine increased and also increased the bioavailability in rat via oral route	Chen 2010 et al(26)
Celecoxib	Egg-Lecithin Phosphatidylcholine (Lipoid E80)	Sprays drying Freeze drying	The solubility, Dissolution and bioavailability of Celecoxib is increased in spray drying method as compare to freeze drying	Fong 2015 et al(7)
Nifedipine	Egg-Lecithin Phosphatidylcholine	Solvent Evaporation	The dissolution of nifedipine was increased in rat from 6.2 mg/L to 16.3 mg/L	Law 1992 et al(27)
Ethopropazine HCL	Phospholipid (DMPC) (1,2-Dimyristoyl-*sn*-glycero-3-phosphocholine)	Solvent Evaporation Method	The X-ray Diffraction and DSC shows the loss of crystalanity which result increased dissolution of Ethopropazine HCL	Prabhu 2001 et al(28)
Ibuprofen	Phospholipone 100H	Solvent Evaporation Method	The ibuprofen containing phospholipone show improved dissolution behaviour and Bioavailability increased by 2 fold	Hussain 2012 set al(29)
Various Drugs	soy-Lecithin Phosphatidylcholine (Lipoid S LPC 80)	Solvent Evaporation Method	The phospholipid have high potential to solid dispersion to enhanced oral absorption of poor soluble drug	Gautschi 2016 et al(30)
Berberine	Hydrogenated Phosphatidylcholine	Solvent Evaporation Method	The permeability and bioavailability of berberine increased but dissolution was unchanged	Shi 2015 et al(23)
Nifedipine	Dipalmitoyl-phosphatidylcholine and Dimyristoyl-phosphatdylcholine	Solvent Evaporation Method	The dissolution property of Nifedipine was improved by solid dispersion	Yamamura 1996 et al(31)
Berberine	Soy-Lecithin Phosphatidylcholine	Solvent Evaporation Method	Dissolution rate and solubility of berberine significantly increased by berberine phospholipid solid dispersion	Zhang 2014 et al(32)
	Hydrogenated soybean phospholipid	Spray drying	These phospholipid dry powder have potentially wide range of pharmaceutical application	Alves 2004 et al(33)

Application of phospholipids in pharmaceutical dosage form:

1. Liposome

Phospholipid loaded liposome is novel approach to enhance dissolution and bioavailability, liposomes have similar structure as cell membrane and also have characteristics include, biodegradable and biocompatible. Different types of liposomes are present such as ligand targeted liposome, cationic liposome, stimuli-responsive liposome and long circulating liposomes. Liposomes have several advantages including improvement of drug stability, reducing drug toxicity, control release property, tissue compatibility and delivering both hydrophilic and lipophilic drug(6, 21). In 1971, Gregoriadis et al. first used liposomes to deliver bioactive substances(34).

2. Solubility enhancer

Solubility of poorly aqueous soluble drug can be increase by phospholipid due to its particular amphiphilic and excellent biocompatible characteristics. The phospholipid increases the penetration across the cell which results to enhance the solubility and drug release. Phospholipid loaded formulations have been used to manufacture to enhance the solubility of poorly aqueous soluble drug, which penetrate the cell and enhance drug release as well as bioavailability.Fong SYK et al 2015, reported that the solubility of poor aqueous soluble drugs can be enhanced by phospholipid loaded SD(7).

3. Permeation enhancer

Phospholipids are crucial part of cell membranes in epidermis. At body temperature phospholipids are liquid-crystalline state, therefore they change and fluidize the structure of barrier layer which enhance the permeability of bioactive. The author Claudia Valente et al(35), reported the permeation of cyproterone acetate (CPA) from cream and liposomal formulation was between 2.9 and 6.8 $\mu g/m^2$within 24 hrs. By increasing phospholipid ratio the CPA permeation also increased by 2.6 fold(22).

4. Emulsion stabilizer

Phospholipids are also used to emulsify the oils and lipophilic drug toformulate oil-in-water (o/w) and water-in-oil (w/o) emulsions.Chuan chen lin, et al(36), studied the stability of formulation of curcumin loaded micro-emulsion containing phospholipid and tween 80. This formulation was not only reducingthe degradation but also improved the absorption of curcumin in aqueous solution(22).

5. Phytosomes

Phytosomes are novel complex structure which are prepared by using both natural and synthetic phospholipid viz phosphatidylethanolamine, phosphatidylcholine and phosphatidylserine. Phytosomes are manufactured by binding the herbal extract to phosphatidylcholine which enhance the dissolution and bioavailability. The reaction of phospholipid and herbal extract or polyphenolic constituent like tannins, flavonoids and terpenoids in polar solvent are produce the Phytosomes. In this formulation, the aqueous soluble phytoconstituent are engulfing into lipid molecules, which enters into systemic circulation by crossing lipid bio-membrane to enhance the absorption(22).

CONCLUSION:

Oral route of administration endures the most favourable route of administration by patients, but the solubility of poor aqueous soluble drugs still major barrier in formulation. Hence solid dispersion technique is used to enhance or improve the drug release or dissolution characteristic but also increase the bioavailability of drug. Solid dispersion also gives the physical stability and scale up manufacturing. Solid dispersion containing phospholipid has the ability to enhance solubility and drug release. Phospholipid is widely used in formulation containing poor aqueous soluble drugs due to its magnificent biocompatibility and particular amphiphilicity. There are many applications of phospholipid in drug delivery system such as liposome, micelle, solid lipid nanoparticle and phytosomes, phospholipid is also used as unique carrier in pharmaceutical formulation. Phospholipids have the ability to penetrate across lipid cell membrane to increase drug release and bioavailability.

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