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Liposomal Formulations for Improved Bioavailability of Poorly Soluble Drugs

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ABSTRACT:
Many medicines in clinical use or in development are water-insoluble and have low bioavailability (BA). Because of its biocompatibility and capacity to encapsulate hydrophobic compounds in the lipid domain, the liposomal delivery method has gained attention as one of the most notable techniques to increasing dissolution and, ultimately, absorption in the gastrointestinal (GI) tract. Due to its relatively large size, there have been various problems, including structural instability in the GI tract and low permeability across intestinal epithelia. Furthermore, despite the success of parenteral liposomes, no liposomal formulations for oral use have been approved thus far. Liposomal oral administration has resurged since the number of published studies has increased dramatically over the previous decade.

KEYWORDS: Liposomal; Polymeric micelles; Silica nanoparticles; Solubility; bioavailability; Nanotechnology

INTRODUCTION:
Poor water solubility and low medication bioavailability are two major difficulties for the pharmaceutical industry. Current studies indicate that around 40% of commercially available medications, as well as the vast majority of research therapies, have low solubility. This issue might result in reduced bioavailability and therapeutic efficacy, necessitating higher dosages to obtain the desired medicinal effect. The challenges in dissolving and releasing poorly soluble medicines have limited the bioavailability of oral solid dosage forms, which are the most extensively utilized and patient-friendly way of drug administration, impeding the development and deployment of many new chemical pharmaceuticals. Due to limited bioavailability, patients must ingest higher pharmacological dosages to achieve the required therapeutic effects. However, raising the dosage can cause greater side effects, potentially damaging patients' physical and mental health and reducing medication compliance. Low water solubility not only poses significant challenges to medical development, but it can also result in a variety of clinical issues, including variability in patient responses, difficulty maintaining a safe therapeutic index, increased costs, and the risk of toxicity or inefficacy. As a result, successfully addressing medication solubility and bioavailability has long been a focus and substantial problem in pharmaceutical and medical research. To address these challenges, nanomedicine delivery systems have developed as a new drug delivery approach, breaking down traditional bottlenecks related to drug solubility and bioavailability. [1][2]
The drug's bioavailability and the rate and volume of its absorption are largely determined by the drug's solubility, the solution, and the permeability of the gastrointestinal tract. A critical component of drug absorption following oral delivery is medicines' water solubility. When the period of dissolution is limited, the drug's solubility—the rate at which its molecule or dose form dissolves into the solution—becomes crucial. However, the drug's susceptibility to efflux mechanisms, water solubility, dissolution rate, drug permeability, and first-pass metabolism all affect how bioavailable the medication is. The quantity of solute that dissolves in a quantity of solvent is a well-defined definition of "solubility." The concentration of the solute in a saturated solution at a specific temperature is referred to as quantity. The solubility has been expressed in terms of several concentrations. [3-5]

Liposomal:
Liposomes are artificial, microscopic cells that are utilized as sustained-action delivery systems for a range of medications, vaccines, enzymes, non-enzyme proteins, genetic material, and, as of late, various dietary supplements. The medication is encased in liposomes, which eventually degrade naturally and release their contents into the bloodstream or into tissues to which they have diffusely traveled through capillary walls. Diffusional or collisional transfer to other lipid components, including lipoproteins, in the blood's lipid highway releases poorly water-soluble chemicals. According to reports, the liposome encapsulation efficiency of medications that are lipophilic is dependent on the drug's physicochemical features, including its lipophilicity.Agents that are incompatible with oral administration or that pose safety and efficacy challenges when administered orally can be introduced into the system via liposomes. Lipophilic medications have the ability to dissolve in the lipid domain of a bilayered membrane. The availability of pre-made liposomes with predetermined particle sizes and quick loading processes for medications that aren't very water soluble Liposomes are undoubtedly a helpful tool for making less water-soluble substances more soluble. A flexible and dynamic method for improving medication solubility is provided by liposomes. The safe (GRAS) status of the phospholipid components in liposomal formulations is typically viewed as the primary benefit over other carrier systems. [6][7]
Because of their biocompatibility, ability to modify their physio-chemical characteristics in accordance with their lipid content and composition, and ability to customize their surface composition, liposomes make great candidates for drug

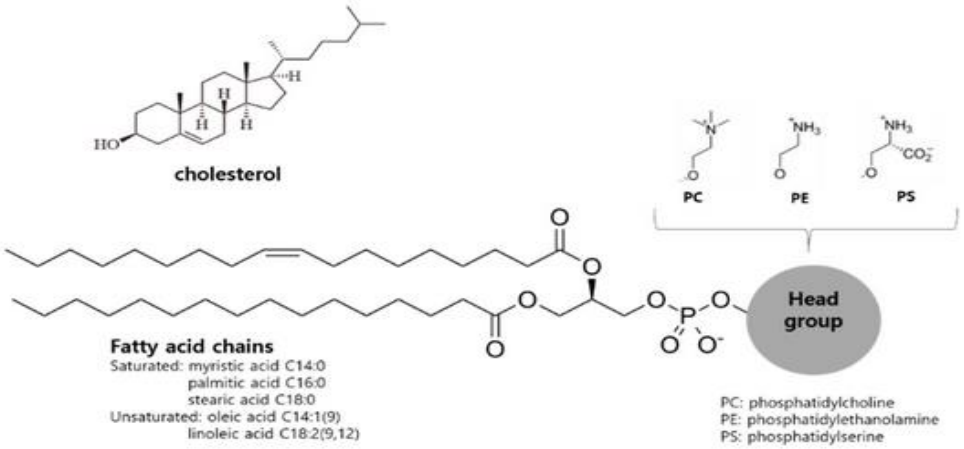
delivery. It is true that these vesicles are made of artificially created mimetic lipids around an aqueous core, or naturally occurring phospholipids. Since 2008, liposomes—which were first introduced by Gregoriad—have been the sole nanoparticles on the market. Because of the technical and practical knowledge amassed over the years, liposomes have been commercialized for a long time with a variety of classes of molecules, including doxorubicin, amphotericin B, verteporfin, cytarabine, vincristine, and inactivated hepatitis B virus. This gives liposomes an advantage over other nanocarriers. Since then, a number of businesses have been established to streamline operations and generate batches of liposomes that adhere to good manufacturing practices (GMPs). [8][9]

Phosphatidylcholine and cholesterol lipid bilayers form the enclosed vesicles known as liposomes, which have been thoroughly investigated for their potential as drug delivery systems. While hydrophobic medications can be injected into the hydrophobic lipid bilayers, hydrophilic pharmaceuticals can be loaded into the inner aqueous phase. Despite being primarily employed for parenteral administration, medication-loaded liposomes have also been investigated for possible usage as oral drug delivery methods. Oral liposomes have the potential to offer enhanced solubility of their load and defense against the harsh gastrointestinal tract environment. The most notable advantage of liposomal lipid bilayers and bio membranes is that oral absorption is greatly aided by their similarity and tiny size.For instance, it has been demonstrated that oral delivery of liposomes filled with proteins or polypeptides increases the absorption of active biomacromolecules. Oral absorption was also enhanced when tiny molecules with poor permeability were incorporated into liposomes. After liposomal encapsulation, significant improvements in bioavailability or in vivo efficacy have been noted, especially for medications that are poorly soluble in water. [10][11]

Structure of Liposomal:

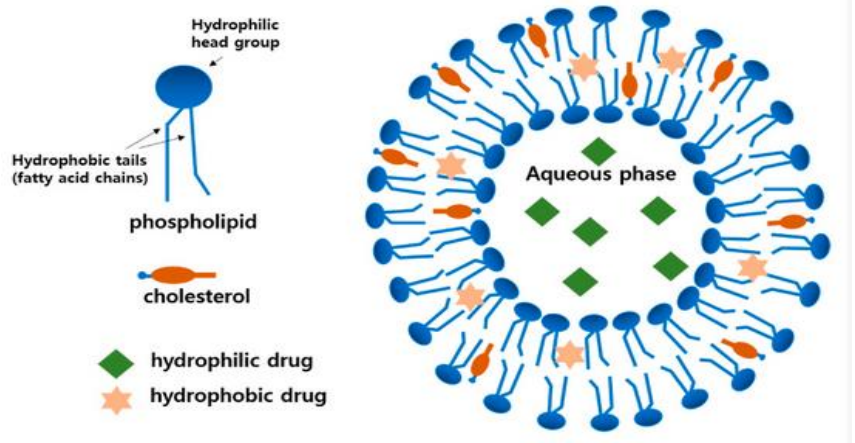
Liposomal membranes bear similarities to cell membranes consisting of bilayers of phospholipids. Because phospholipids have an amphiphilic molecular structure with hydrophilic phosphatidyl head group and hydrophobic fatty acid tails, they can spontaneously form vesicles upon hydration with aqueous media (Figure 1).

Figure 1: Structure of phospholipids and cholesterol.



Similar to how it is absorbed into the plasma membrane, cholesterol (CH) can also be readily added to the liposomal membrane to maintain the membrane and control drug release, as seen in Figure 2.

Figure 2: Structure of conventional liposome encapsulating hydrophilic and hydrophobics



Hydrophobic medications live in the lipid tail domain of the bilayer, but hydrophilic pharmaceuticals can be incorporated into the inner aqueous phase, as the structure illustrates. Liposomal membranes are fluidic, just as bio membranes, which means that the medications within the liposomes may leak out or be released. It is well known that some aspects of liposomal membrane composition, such as the presence of CH and the kind of fatty acid acyl chains in the phospholipids, affect the release rate. [12].

Formulation Techniques:
If the importance of formulation for poorly water-soluble pharmaceuticals is underestimated, it could lead to the wrong lead candidates being chosen, a longer development duration, and ultimately a significant increase in research costs. The following are some new formulation ideas that are being focused on for the delivery of medications that are poorly soluble in water:
Lipid vesicles have been discovered to be highly useful in membrane biology recently. These vesicles are also known as Bingham bodies because Bingham was the first to report them in 1965. The idea of micellar solubilization is essentially taken into account by the vesicular approach. The best candidates are poorly soluble substances that fit inside the micelle structure. Since the medicine is already soluble, these micelles absorb the lipophilic material in their lipophilic area, eliminating the requirement for the poorly soluble molecule to dissolve prior to absorption. They may be produced in big quantities and are simple to formulate.They both postpone the removal of medications that are quickly metabolized and extend the duration of the substance in the bloodstream. Numerous potential systems utilizing the vesicular method are

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REVIEW OF LITERATURE:
After examining six of these contrast agents for encapsulation in DPPG2-TSL, Hossann et al. concluded that the best contrast agent was a nonionic one with a minimal osmolality contribution. Using gadolinium-based contrast agents, two encapsulation techniques are feasible; nevertheless, it is necessary to take into account the release kinetics and signal mechanisms for both the medication and the contrast agent. Combining two groups of TSL—one containing only the contrast agent and the other containing only the medication—is one tactic. This tactic prevents osmotic effects and permits encapsulation of a greater volume of medication and contrast agent. The second tactic restricts the quantity of both components in each TSL by coencapsulating the medication and contrast agent in the same TSL. [14]
Mucoadhesive or mucus-penetrating liposomes were prepared by Chen et al. by modifying the liposomes with chitosan (CS-Lip) or Pluronic F127 (PF127-Lip), respectively. The components of the unmodified liposomes (Lip) were cyclosporin A (28:5:1), CH, and EPC. In comparison to the unmodified liposomes, the PF127-Lip enhanced Cmax and AUC0–t by 1.73 and 1.84 fold, respectively, but the chitosan-modified liposomes lowered both parameters. They conducted a stability research in both simulated intestinal fluid (SIF) and simulated gastric fluid (SGF) and found that the positively charged CS-Lip accumulated in SIF and was subsequently retained by mucus, primarily in the upper GI tract, with limited penetration. Conversely, PF127-Lip had a mucus-penetrating ability as it was stable in both SGF and SIF and was present throughout the GI tract. [15]
Ting et al. called particular attention to commercial products and specialized polymer design methodologies that can reduce the likelihood of drug recrystallization and increase the solubility of very hydrophobic medicines. The molecularly tailored polymers that make up the specifically manufactured excipients have the ability to reorganize the APIs into possible oral medications. [16]

OBJECTIVES:
1. To study of Liposomal Formulations.

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2. To study of improve bioavailability of poorly soluble drugs.
3. Study of Solubility to find different concentration of SL for preparing liposomes.

RESEARCH METHODOLOGY:
The overall design of this study was exploratory. The research paper is an effort that is based on secondary data that was gathered from credible publications, the internet, articles, textbooks, and newspapers.

RESULT AND DISCUSSION:
In order to determine the appropriate concentration of SL for liposome preparation, soluble tests were conducted. The hydrophobic nature of EFA (log P-5.4) allowed for its solubility in SL. As SL and cholesterol were the main ingredients in liposomes, it was important to figure out how much of each. Cholesterol gives the liposomal membrane its stiffness, while SL, which forms the membrane, is in charge of enhancing the drug's solubility. Since cholesterol does not increase a drug's solubility, no solubility tests including cholesterol have been conducted.

Table 1: study of Solubility

Components	Solubility (µg/ml)	Solubility enhancement ratio
Drug+water	8.45 ± 1.56	--
Drug+SL (500 mg)+water	10.32 ± 2.15	1.22
Drug+SL (600 mg)+water	11.11 ± 1.98	1.31
Drug+SL (700 mg)+water	26.52 ± 2.58	3.13
Drug+SL (800 mg)+water	26.67 ± 2.66	3.15
Drug+SL (900 mg)+water	27.82 ± 2.55	3.29

SL is soya lecithin; n=3, mean ± SD

Table 1 shows the different SL concentrations that were examined. Up to 700 mg of SL, there was a noticeable increase in the solubility of EFA. For both 800 and 900 mg of SL, there was no discernible rise in the solubility of EFA. On the basis of these findings, additional research was done to determine the ratio of cholesterol to SL in order to create blank liposomes. [17]
Drugs that are insoluble in water can be dissolved into the lipid domain of the liposomal membrane by liposomes encased in phospholipid bilayers. The structural and compositional similarities between liposomes and bio-membranes, along with their solubilizing ability and biocompatibility, have promoted the use of liposomes for non-invasive oral delivery of poorly-permeable medications. But due of the relatively large size of liposomes, there have been a number of challenges to overcome, including poor permeability across the intestinal epithelia and instability in the GI tract. It appeared that the 1980s saw a decline in liposomal oral delivery as a result of certain unsatisfactory insulin findings. Although studies related to liposomal oral delivery make up only 5–6% of all studies related to liposomes, Figure 3 illustrates how quickly the field of liposomal oral delivery has rebounded, as evidenced by the rapid increase in papers published, as indicated by the Pubmed search results. This can be attributed primarily to various advanced modification technologies.

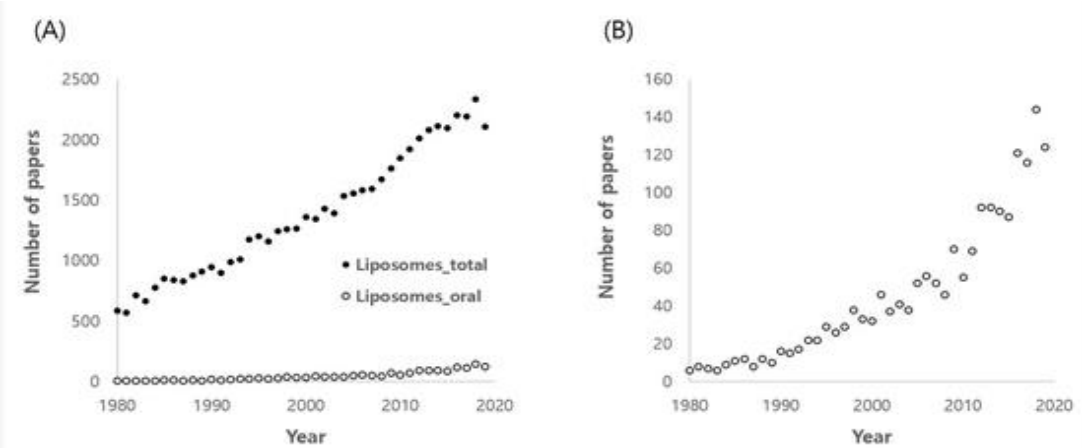

Figure 3: Comparison between Liposomaltotaland Liposomal oral

In a promising meta-analysis research, solid formulations based on phospholipids were found to be useful for enhancing BA. Liposomal delivery appears more promising for the oral delivery of hydrophobic drugs because it can solubilize poorly water-soluble drugs, protect them from GI tract degradation, and increase permeability through the epithelial cell membrane, all of which increase oral BA. However, it does not appear to improve oral BA for peptides and protein drugs to a satisfactory degree. However, the majority of published studies were limited to in vitro research, meaning that in vivo pharmacokinetic results were absent. [18]

CONCLUSION:

It has been established that the most important factor in both formulation development and therapeutic efficacy is medication solubility. One of the rate-restrictive processes for oral drug administration to attain effective concentration in systemic circulation and the ensuing pharmacological reaction is solubility. Numerous methods discussed in this study, either alone or in combination, can improve a drug's solubility and, thus, its bioavailability. More research into the creation of novel compounds and technological advancements will make formulation strategies more effective.

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