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FABRICATION AND EVALUATION OF DRUG LOADED SOLID LIQUID NANOPARTICLES FOR ORAL DELIVERY

[1]Mahewish W. Shaikh, [2]Mr. Amol G. Jadhao, [3]Mr. Taufik R. Shaikh, [4]Miss. Jayshri B. Sanap
[1]Student of B. Pharm final year, Gawande College of Pharmacy, Sakharkherda.
[2]Assitant Professor Gawande College of pharmacy, Sakharkherda (Department of Pharmaceutics),
[3]Assitant Professor Gawande College of pharmacy, Sakharkherda (Department of Quality Assurance),
[4]Principal of Gawande College of pharmacy, Sakharkherda (Department of Pharmacology).
Gawande College of pharmacy, Sakharkherda (Department of Pharmaceutics), At. Post: Kalambeshwar, Tq. Mehkar, Dist. Buldana-443304.

Abstract:
The past few decades have seen significant advances in drug delivery technologies. Oral drug delivery is not only the largest and the oldest segment of the entire drug delivery market; it is also the fastest growing and the most preferred route for drug administration. “Nano” word comes from the Greek word nano which means dwarf. Nano means it is the factor of 10^{-9} or one billionth. Solid lipid nanoparticles (SLNs) are emerging as alternative carriers to colloidal systems, for controlled and targeted delivery. These are in submicron size range (50–1000 nm) and are made up of biocompatible and biodegradable materials capable of incorporating lipophilic and hydrophilic drugs. This review mainly deals with the preformulation factors, novel methods of preparation, characterization, evaluation and their applications for improving bioavailability, site-specific delivery, local action, etc. The main objective of the present investigation was to incorporate CC into triglycerides, to get solid lipid matrices to improve the oral bioavailability by exploiting the intestinal lymphatic transport. Further, to understand the pharmacodynamic effect of CC-SLNs in animal models. Oral administration is a delivery system that is suitable for widespread clinical application. However, apomorphine administered orally was not successful because of the rapid degradation in the gastrointestinal (GI) tract and first-pass effect, resulting in bioavailability of 1.7%.

Keywords: Solid Liquid Nanoparticles (SLNs), Nanoparticles, Evaluation of (SLNs), High pressure homogenization, Ultrasonication /high speed homogenization, Solvent evaporation Method.

INTRODUCTION:

The past few decades have seen significant advances in drug delivery technologies. Oral drug delivery is not only the largest and the oldest segment of the entire drug delivery market; it is also the fastest growing and the most preferred route for drug administration. Because a large number of recently developed chemical entities have poor aqueous solubility, many formulation approaches, such as salt formation, co-solvent, size reduction, complexation and lipid-based drug delivery systems have been evaluated to increase their bioavailability[1]. Solid lipid nanoparticles (SLNs) are emerging as alternative carriers to colloidal systems, for controlled and targeted delivery. These are in submicron size range (50–1000 nm) and are made up of biocompatible and biodegradable materials capable of incorporating lipophilic and hydrophilic drugs. The general structure of SLNs is shown in Figure 1. SLNs combine the advantages of different colloidal carriers, for instance like emulsions and liposomes, these are physiologically acceptable and like polymeric nanoparticles, controlled

release of drug from lipid matrix can be anticipated. Additional advantages include lack of coalescence after reaching to room temperature (following their preparation or during their storage) and better physical stability. Since mobility of the incorporated drug molecule is drastically reduced in SLNs, there would not be any appreciable drug leakage from the particles. In recent years, much work has been focused in the development of SLNs as delivery systems for anticancer drugs, peptides, genetic material, cosmetics, etc. This review mainly deals with the preformulation factors, novel methods of preparation, characterization, evaluation and their applications for improving bioavailability, site-specific delivery, local action, etc [2]. Solid lipid nanoparticles (SLNs) are at the harbinger of the quickly developing field of nanotechnology with several potential applications in drug delivery and research It is the principal approach for the production of SLNs by a high-speed stirring method utilizing lipid microparticles, a hot surfactant solution obtaining an emulsion by high-pressure homogenization or micro emulsification[34]. Candesartan cilexetil (CC) is an ester prodrug of candesartan, a non-peptide angiotensin II type 1 (AT1) receptor antagonist, used in the treatment of hypertension and heart failure. Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from gastro intestinal tract to candesartan. The major drawback in the therapeutic application and efficacy of Candesartan cilexetil as an oral dosage form is its very low aqueous solubility and first-pass metabolism. Based on its solubility in physiologically relevant pH conditions and absorption characteristics, Candesartan cilexetil was classified in the Biopharmaceutics Classification System (BCS) as a class II drug. To overcome hepatic first-pass metabolism and to enhance oral bioavailability, lipid–based drug delivery systems like solid lipid nanoparticles can be used. These systems enhance the lymphatic transport of the lipophilic drugs and therefore increase the bioavailability. SLNs were reported as an alternative drug delivery system to traditional polymeric nanoparticles. Advantage of solid-lipid nanoparticles (SLNs) over polymeric nanoparticles is based on the lipid matrix, made from physiologically tolerated lipid components, which would decrease the potential for acute and chronic toxicity. At room temperature the particles remained in the solid state.SLNs could combine advantages of polymeric nanoparticles, fat emulsions and liposomes, i.e. controlled release just like polymeric nanoparticles, large scale production and toxicologically acceptable compare with fat emulsions and liposomes. Controlled drug delivery, enhancement of bioavailability of entrapped drugs via modification of dissolution rate and/or improvement of tissue distribution and targeting of drugs were reported by using SLNs in various application routes. So far, no reports were published describing the role of SLNs on pharmacodynamic effects. The main objective of the present investigation was to incorporate CC into triglycerides, to get solid lipid matrices to improve the oral bioavailability by exploiting the intestinal lymphatic transport. Further, to understand the pharmacodynamic effect of CC-SLNs in animal models[3]. Oral route is the most preferred route for drug administration due to greater convenience, less pain, high patient compliance, reduced risk of cross-infection, and needle stick injuries. Major portion of the drug delivery market is occupied by oral drug delivery systems. However, oral drug delivery is continuously looking into newer avenues due to realization of the factors like low drug solubility, poor gastrointestinal (GI) absorption, rapid metabolism, high fluctuation in the drug plasma level, and variability due to food effects. These factors may cause disappointing in vivo results leading to failure of the conventional delivery systems [24]. SLN offer unique properties such as small size, large surface area, high drug loading, and interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals[27]. In today's drug development world, combinatorial chemistry, high-throughput screening, and genomics have provided a technologic platform that produces a large number of new chemical entities (NCE) with therapeutic potential each year. The pharmaceutical drug delivery market is also expected to grow from $1048.1 billion in 2015 to $1504.7 billion by 2020, with a compound annual growth rate of 7.5%[28]. Delivery of drugs to the brain is a major challenge due to the presence of the blood–brain barrier. Successful delivery across the blood–brain barrier (BBB) has only been achieved in some cases, e.g. through the use of prodrugs. To reach therapeutic drug level in the brain, nanoparticulate systems as drug carriers with sufficiently high loading capacity and small particle size, which can bypass the Reticulo Endothelial System (RES system), are being looked into as suitable delivery systems [29]. Great progress has been made in the treatment of a variety of diseases by using drug delivery systems including solid lipid nanoparticles (SLN). SLN are colloidal drug carrier systems. They are very much like nanoemulsions, differing in lipid nature. The liquid lipid used in emulsions is replaced by a lipid solid at room temperature in SLN including highmelting point glycerides or waxes. They are increasing in signifi cance as alternative drug carriers to polymeric nanoparticles. Controlled drug delivery, enhancement of bioavailability of entrapped drugs via modifi cation of dissolution rate and/or improvement of tissue distribution and targeting of

drugs by using SLN have been reported in various application routes: Parenteral (intravenously, intramuscularly or subcutaneously, Oral, Rectal, Opthalmic, Topical (in cosmetics and dermatological preparations)[30].

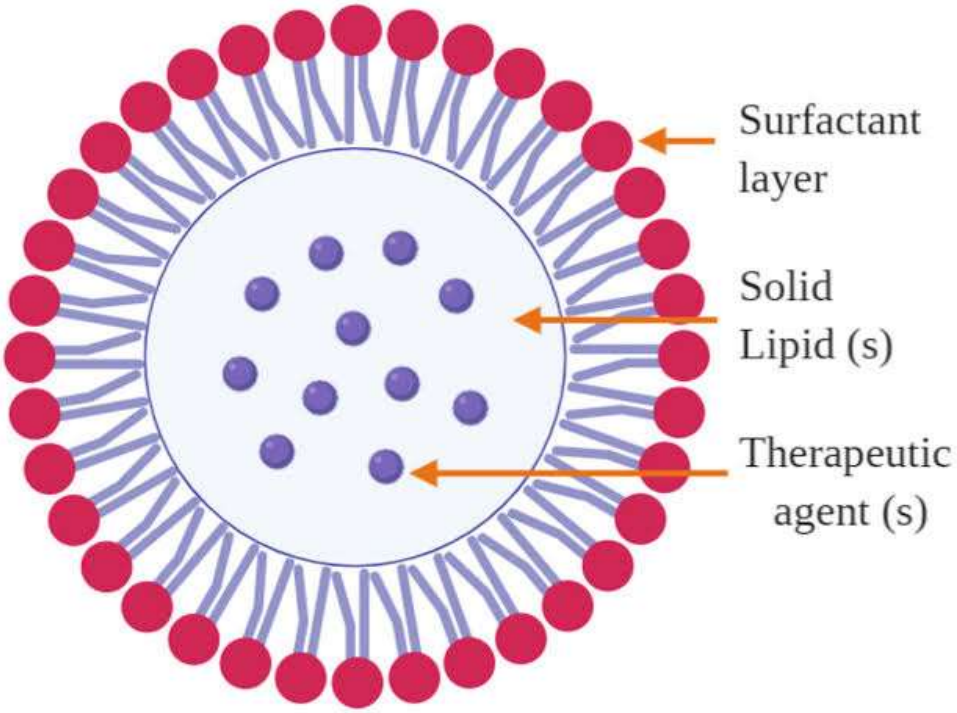

Fig 1: General Structure of Solid Lipid Nanoparticle

In the present scenario, oral drug delivery is continuously looking into newer avenues due to realization of the factors like poor drug solubility and/or absorption, rapid metabolism, high fluctuation in the drug plasma level and variability due to food effect which are playing major role in disappointing in vivo results leading to failure of the conventional delivery system[12]. Colloidal particles ranging in size between 10 and 1000 nm are known as nanoparticles. They are manufactured from synthetic/natural polymers and ideally suited to optimize drug delivery and reduce toxicity[22].In recent years it has become more and more evident that the development of new drugs alone is not sufficient to ensure progress in drug therapy. Exciting experimental data obtained in vitro are very often followed by disappointing results in vivo. Main reasons for the therapy failure include:

- Insufficient drug concentration due to poor absorption, rapid metabolism and elimination (e.g. peptides, proteins). Drug distribution to other tissues combined with high drug toxicity (e.g. cancer drugs).
- Poor drug solubility which excludes i.v. injection of aqueous drug solution.
- High fluctuation of plasma levels due to unpredictable bioavailability after peroral administration, including the influence of food on plasma levels (e.g. cyclosporine)[13].

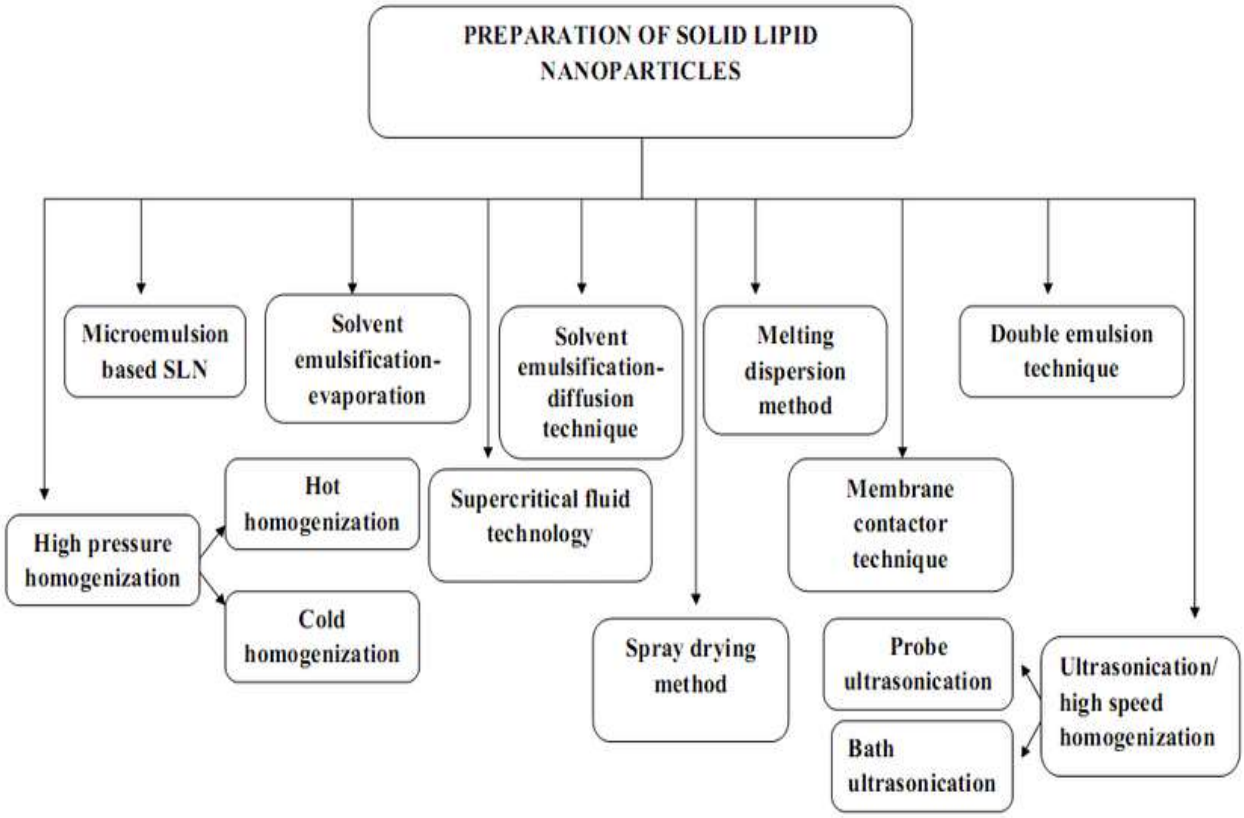

Fig 2: Methods of preparation of solid lipid nanoparticles

The first generation of lipid nanoparticles was introduced as solid lipid nanoparticles (SLN). SLN have been intensively studied as drug delivery systems for several routes of administration such as peroral, parenteral, dermal, and topical delivery. The crystallinity of solid lipids affects the release properties of the SLNs derived. Directly after the formation of SLN, lipids partially crystallize in high-energy modifications with many imperfections in the crystal lattice. When a polymorphic transition to low-energy modification takes place during storage, the incorporated drug may be expelled from the lipid matrix. To overcome drug expulsion during storage, use of blends of lipids that do not form a highly ordered crystalline arrangement is needed[14]. Oral drug delivery is the simplest and major route for the treatment of many diseases, in particular, for cardiovascular or cerebral diseases. However, approximately 30% of selling medicines and 40% of new chemical entities (NCEs) entering development programs showed too low aqueous solubility or oral bioavailability to bring about satisfactory therapeutic efficacy[16]. Iron oxide nanoparticles offer valuable benefits in the in vivo biomedical applications due to their size-dependent superparamagnetism and nontoxic, metabolizable nature Superparamagnetic iron oxide nanoparticles are clinicallyused as contrast media in magnetic resonance imaging, and extensivelyevaluated for manyapplications such as magnetic drug delivery, cell tracking, hyperthermia[31]. Huge advances in understanding these events can potentially be gained by investigating cell migration in vivo. In particular, the goal of noninvasive imaging of cell migration, and specifically of genetically engineered stem and progenitor cells, has long been sought. Traditionally, cells have been followed by technically challenging and invasive chamber models using intravital microscopy or by using flow cytometry analysis of fluorescently labeled cells recovered from excised tissues[32]. Sunscreen products are widely used by adults and children to prevent sunburn, photoaging, and skin cancer. They are routinely applied to the arms and face for everyday protection or to larger body surface areas during swimming and beach-related activities. In addition, many cosmetics and hair products contain sunscreens, which often results in the daily application of sunscreens without the user making a conscious decision to use a sunscreen[33]. Solid lipid nanoparticles (SLNs) are at the harbinger of the quickly developing field of nanotechnology with several potential applications in drug delivery and researchIt is the principal approach for the production of SLNs by a high-speed stirring method utilizing lipid microparticles, a hot surfactant solution obtaining an emulsion by high-pressure homogenization or micro emulsification[34]. Colloidal drug carriers such as liposomes and nanoparticles can be used to improve the therapeutics index of both established and new drugs by modifying

their distribution, thus increasing their efficiency and/or reducing their toxicity. This is because the drug distribution then follows the carrier, rather than depending on the physicochemical properties of the drug. [18]

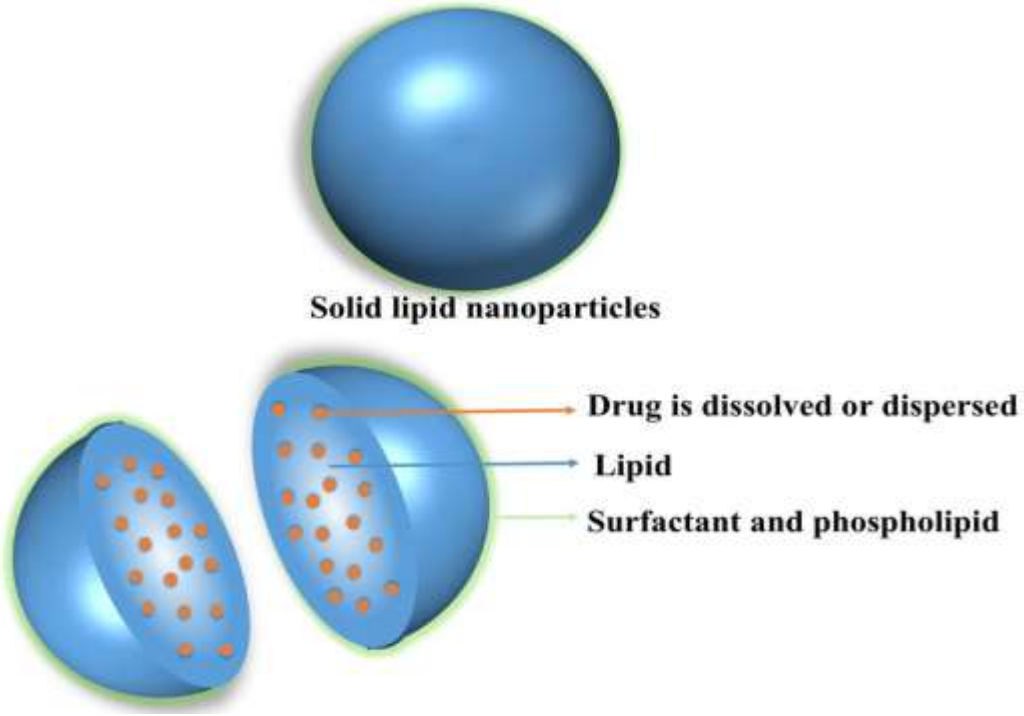

Fig 3: General structure of solid lipid nanoparticle (SLN) loaded with drug

Advantages of SLN's:

SLNs offer many benefits in comparison to other colloidal carriers which include:

1. Improved solubility and bioavailability of lipophilic drugs.
2. Provide long-term stability against environmenal degradation.
3. Surface modification can be easily done.
4. Controlled release of active drug through lipid matrix.
5. Excellent biocompatibility of excipients used for SLNs.
6. Much easier to manufacture than biopolymeric nanoparticles.
7. Topical treatment of skin diseases with SLNs has the advantage that high drug levels can be achieved at the site of disease and systemic side effects can be reduced compared to oral or parenteral drug administration.
8. High drug payload.

Disadvantages of SLN's:

Some problems reported with SLNs are:

(i) Particle growth and crystallization of drugs
(ii) Unpredictable gelatin tendency
(iii) Unexpected dynamics of lipid transitions
(iv) Drug loading capacity may be limited in some cases
(v) Drug expulsion from lipids
(vi) High pressure induced drug degradation
(vii) Water content of dispersion is relatively high[23].

FACTORS TO BE CONSIDERED IN THE FORMULATION OF SLNs:

Common ingredients used in the formulation of SLNs are lipids (matrix materials), emulsifiers, coemulsifiers, and water. Charge modifiers, stealthing agents that improve long circulation time and targeting ability, are also used to meet the requirements of stability and targeting aspects[2]. Nanoemulsions are composed of nano-scale droplets of one immiscible liquid dispersed within another. In broad sense, nanoemulsions include two closely related but identical systems, which are termed "microemulsions" and "submicronemulsions". Paradoxically, microemulsions are named with a suffix "micro-" that indicates scale in the range of microns although their particle size is well below 100 nm. Submicron emulsions are originally referred to emulsions with particles of a few hundreds of nanometers and expanded to include emulsions with smaller diameters, which however are larger than 100 nm. To avoid misleading, we follow the historical naming of microemulsions, which are defined as thermodynamically stable, homogeneous (heterogeneous at molecular scale) and optically isotropic systems that comprise of a mixture of water, oils, and amphiphilic compounds. The term amphiphiles makes the definition versatile for cosurfactants, which may or may not be required for microemulsion formation. Nanoemulsions other than microemulsions have particle sizes between that of conventional emulsions and microemulsions, ranging from approximately 100 to 500 nm, and can be described as "approaching thermodynamic stability". This type of nanoemulsions have also been termed as miniemulsions, fine-disperse emulsions, submicron emulsions , unstable microemulsions and translucent emulsions. In view of the above, it appears that the thermodynamic stability instead of particle size, is the defining hallmark of microemulsion from submicron emulsions, even though the droplet sizes of the two systems may overlap[15].

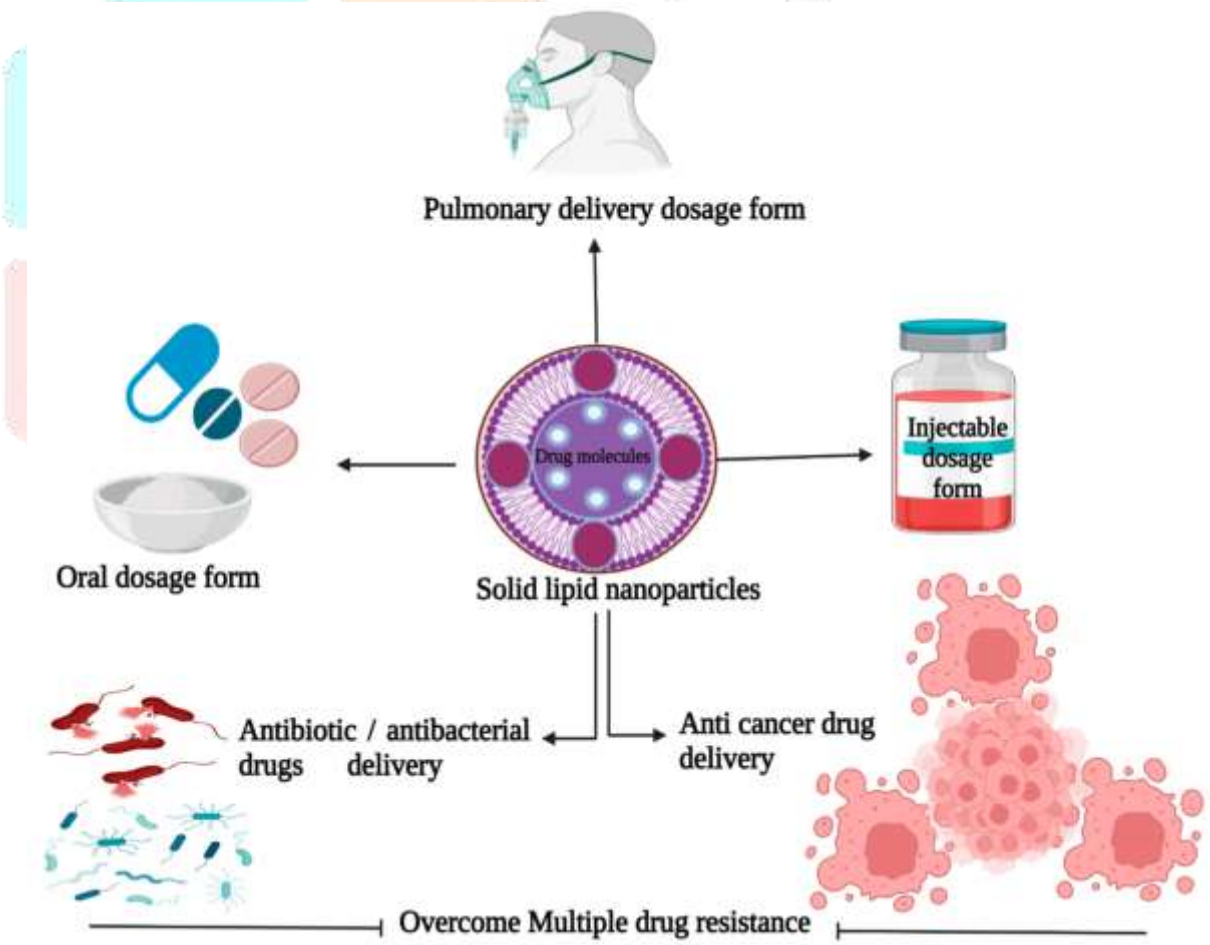

Fig 4: Perspective and Prospective on Solid Lipid Nanoparticles as Drug Delivery System.

SELECTION OF LIPIDS:

The rationale behind choosing lipid materials for developing oral pharmaceutical dosage forms had been reviewed recently. Lipid matrices used for the production of SLNs for i.v. administration should have the following appropriate properties.

1. They should be capable of producing small size particles (in the nanometer size range) with low content of micro particles (>5 m). 2. They should possess sufficient loading capacity for lipophilic and possible also hydrophilic drugs.
3. They should be suitable for sterilization by autoclaving.
4. They should be stable in aqueous dispersions, on long-term storage, or alternatively they can be lyophilized or spray dried.
5. They should be toxicologically accepted and should not leave any toxic residues from the production process (e.g. solvents).
6. They should be biodegradable [2].

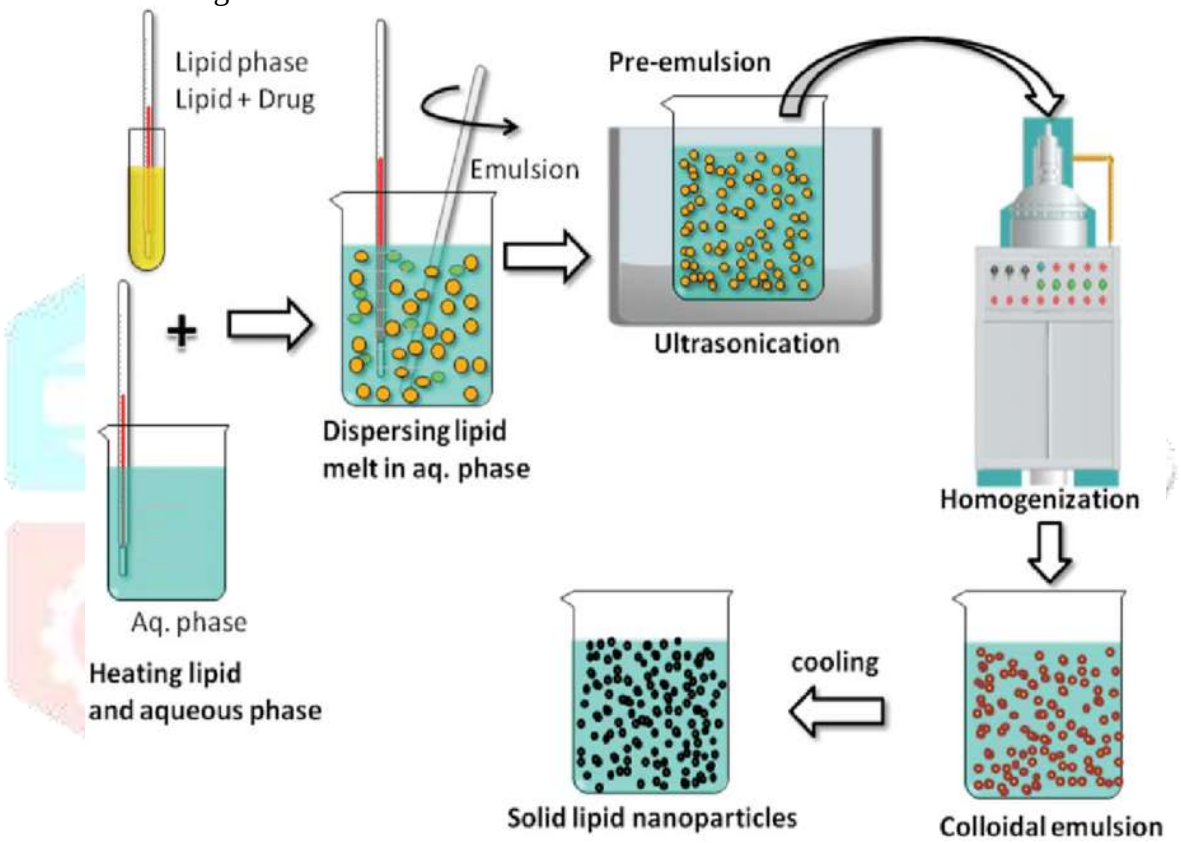

Fig 5: Schematic depiction of various steps involved in the preparation of Solid Lipid nanoparticles by hot homogenization technique.

Compositions of lipid nanoparticles that are exclusively based on physiological compounds avoid the toxological problems often described for polymeric nanoparticles. Lipids such as tristearin, tripalmitin, trilaurin, hard fat or cetyl palmitate have been used for the production of lipid nanoparticles[4]. Most of the published papers on solid lipid nanoparticles (SLN) suspensions report on particles formulated with glyceride matrix material and stabilized with blockpolymers or phospholipids.Glycerides are triglycerides or partial glycerides and, with respect to the fatty acid composition, monoacidic or polyacidic However, waxes and paraffins can be used as core materials as well. Waxes can be defined as simple esters of fatty acids with alcohols. In contrast to glycerides, the alcohol represented is not glycerol. Waxes may contain free hydroxy groups within the molecule (e.g. hydroxyoctanosyl hydroxystearate) or free fatty acid functions (e.g. beeswax). Besides differences in chemical composition, glyceride and wax bulk material feature different physical properties[5]. "Nano" word comes from the Greek word nano which means dwarf. Nano means it is the factor of 10^{-9} or one billionth. Nanoparticles are sub nanosized colloidal structures composed of synthetic and semi synthetic polymers. The continuous quest towards physical stability improvisation of liposomes resulted in to development of solid core nanoparticles as drug carriers. The rationale behind the development and use of nanoparticles is,

1) To decrease the toxicity and occurrences of adverse drug reactions.
2) Better drug utilization.
3) Controlling the rate and site of drug release.
4) Provide a more predictable drug delivery system.
5) Providing greater convenience and better patient compliance.
6) The therapeutic effectiveness of drug i.e. the overall pharmacological response of drug per unit dose is enhanced.
7) They are reproducible.
8) They can be freez dried so can be obtained in the dry form.
9) Non toxic and biodegradable[6].

The Biopharmaceutics Classification System (BCS) is not only a useful tool for obtaining waivers for in vivo bioequivalence studies but also for decision making in the discovery and early development of new drugs. It is because BCS is based on a scientific framework describing the three rate limiting steps in oral absorption.The three necessary steps for a drug to be absorbed are, release of drug from dosage forms, maintenance of dissolved state throughout gastrointestinal (GI) track, and permeation of drug molecules through GI membrane into hepatic circulation. There is a fourth step, i.e. enterohepatic metabolism that influences the systemic availability as well as release of metabolites into the systemic circulation[7].

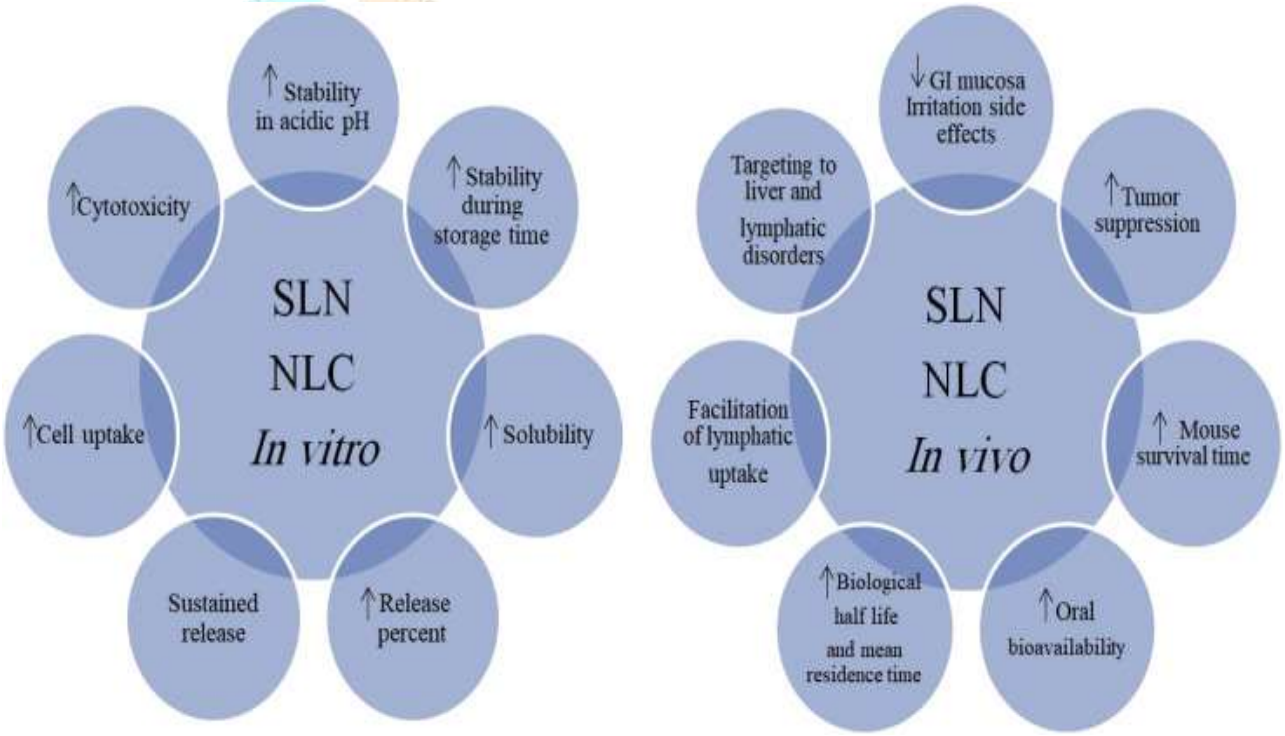

Fig 6: Solid lipid nanoparticles and nanostructured lipid carriers in oral cancer drug delivery.

Release of peptides – Digestion of SLNs and NLCs:

In vitro drug release tests generally show a sustained release of encapsulated peptides from lipid-based carriers. However, a burst effect is often noted and is attributed to absorption of peptide at the surface of the particles (Gallarate et al., 2011; Hu et al., 2004; Martins et al., 2009; Yang et al., 2011). Bernkop-Schnürch and Jalil have recently shown that, in the case of SEDDS, the sustained release effect observed is proportional to the partition coefficient of the drug between the lipophilic phase and the release medium (Bernkop-Schnürch and Jalil, 2018). This postulate can be extrapolated to the release of drugs from SLNs. The observed burst effect from nanoparticles could be due to the rapid diffusion of the hydrophilic peptide from the lipid core due to its positive partition coefficient. Then drug release is controlled by the rate of digestion of the carrier by lipases[26] .In recent years, the development of new drug alone is not sufficient to provide the base for the progress in drug therapy and the in-vitro data obtained from various experiments are very often followed by disappointing results in vivo due to following reasons.

a) Poor absorption, rapid metabolism and elimination lead to insufficient drug concentration at the specific site.
b) High fluctuation of the plasma levels due to unpredictable bioavailability after peroral drug administration.
c) Poor drug solubility[19].

Oral administration is a delivery system that is suitable for widespread clinical application. However, apomorphine administered orally was not successful because of the rapid degradation in the gastrointestinal (GI) tract and first-pass effect, resulting in bioavailability of 1.7%. The oral route continues to be a challenge, even though it is the most attractive way to administer drugs. Incorporation of drugs into nanoparticles opens the perspective of enhanced and less variable bioavailability and prolonged plasma levels.Solid lipid nanoparticles (SLNs) represent an alternative drug carrier system to emulsions and polymeric nanoparticles[8].A solid lipid nanoparticle is typically spherical in shape or some time bicontionous structure with an avg. Diameter b/w 10-1000 nm. In SLN drug is encapsulated in lipid matrix which is stabilised by using surfactant or co-surfactant or by using mixture of surfactant. Combination of surfactants prevents particles agglomeration more efficiently. Lipid used in SLN preparation are triglyceride i.e. Tristearin, Monoglyceride i.e. Glycerol Monostearate, steroids and wax's. There are various methods which uses different types of precursors for the preparation of solid nanoparticles. These precursors provide intermediates to the obtain nanoparticles of desired size. Precursor chosen for the preparation of SLN depends on size of particle which we want to obtain. Some precursors like emulsion, micro emulsion produce SLN whereas some precursors and methods produce SLM (solid lipid micro particles). Various solvents used during preparation of precursor which removed completely at final step of SLN formation which is important from toxicological point of view[17]. Natural products have been used as a source of cosmetics, food, and traditional medicines for thousands of years. In addition, plant-derived products are rich in a variety of secondary metabolites, such as terpenoids, alkaloids, and phenolic compounds. Supercritical fluids have been successful as solvents in extraction processes and this can be attributed to their unique tunable physical properties, such as changeable density, liquid/gas-like viscosity and high diffusivity[20].

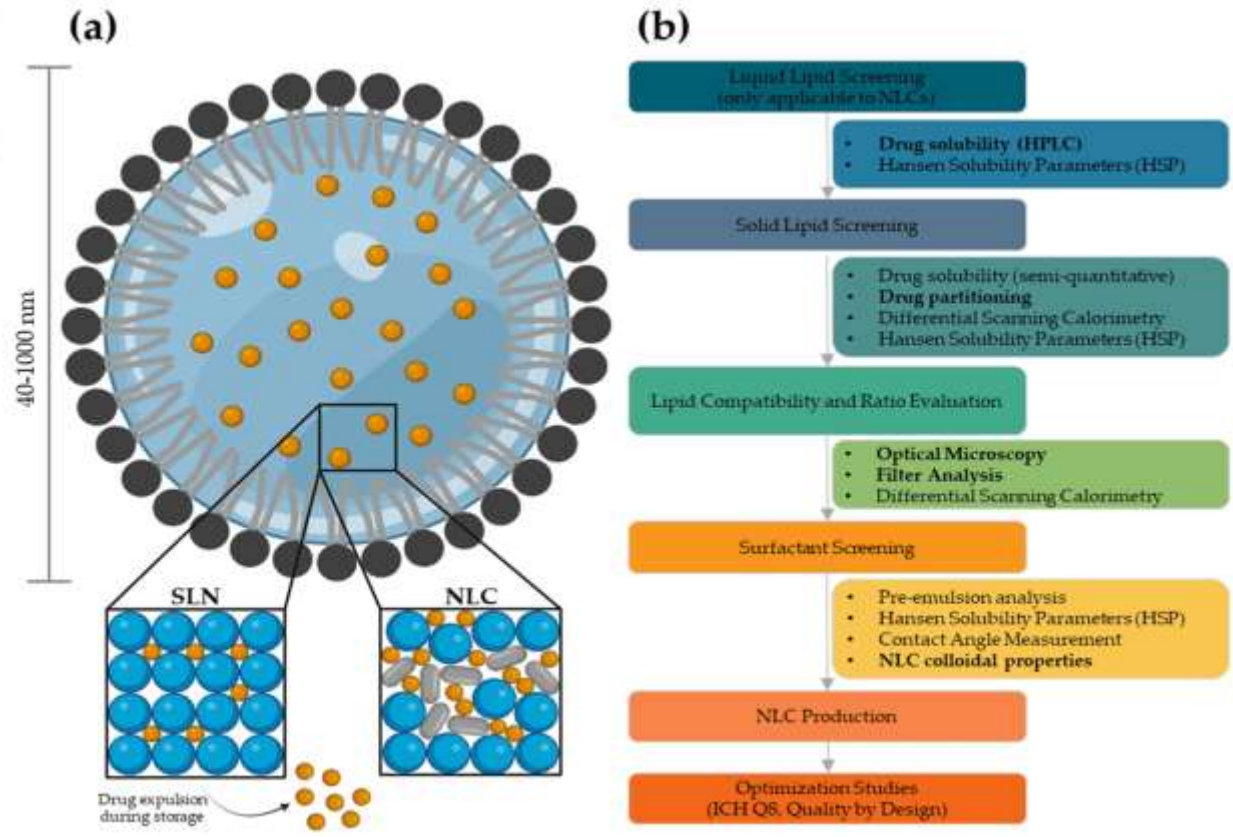

Fig 7: A Stepwise Framework for the Systematic Development of Lipid Nanoparticles.

ROLE OF THE STOMACH AS A DIGESTIVE ORGAN:

Muscle contractions of the stomach-particularly peristalsis against a closed pylorus and the squirting of fat through a partially opened pyloric canal-produce the shear forces sufficient for emulsification. Potential emulsifiers that can function in the acid milieu of the stomach include peptic digests of dietary proteins, complex polysaccharides, and membrane derived phospholipids. Enzymatic hydrolysis of triglycerides also begins in the stomach (43-45), and since triglyceride is stored for 2-4 hours, 30% of the total dietary triglyceride may be digested[21]. Breast cancer is one of the most frequently occurring cancers in women and the second leading cause of cancer deaths in women. However, since 1989, the breast cancer morality rate has decreased 1.8% per year, due to improvements in breast cancer prevention as well as treatment. Lymph node metastasis leading to locoregional relapses is one of the decisive factors in the treatment efficiency, since lots of lymph nodes are present around the breast, especially in armpits. A 50–60% of the breast cancer patients were detected to suffer from lymph node metastases in armpits. Even after the surgical operation, lymph node metastases are still a serious problem.

Instrument:

A spectrophotometer (UV-2201, Shimazu, Japan) was used to quantitate the drug in solution. HPLC (Agilent 4890, HP Co., USA) was used to quantitate the drug in plasma or tissues. A rotary evaporator (ZFQ85A, Medical Instrument Co., Shanghai, China) and a probe sonicator (250W, Ultrasonic Cell Pulverizer, JY88-II, Xinzhi Scientific Instrument Institute, Ningbo, China) were used for preparation of SLN. Laser particle sizer (Mastersizer 2000, Malvern, UK), and a transmission electron microscope (JEM-100SX, Electron Co., Japan) were used to characterize the SLN. Cryogenic Ultracentrifuger (L8-80M, Beckmann, USA), Freeze-Dryer (type 2040, Snijfers Scientific Ltd., Holland), a 60Co- radiator (Agricultural Institute of Sichuan, China) and a microbalance (Sartorius, Germany) were also used[25].

MATERIALS AND METHODS:

MATERIALS:

Materials Solid lipids:

Softisanw 100, softisanw 142, softisanw 154, witepsolw H35 (Condea, D-Witten), cetyl palmitate (Caelo, D-Hilden). Softisanw lipids consist of a triglyceride mixture of natural, saturated, even-numbered and unbranched fatty acids with a chain length from C10 to C18. Softisanw 100 and 142 have melting points of 33.5–35.5 8C and 42–44 8C, respectively. They are also specified as 'hydrogenated coco-glycerides' whereas softisanw 154 with a melting point of 53–58 8C is specified as 'hydrogenated palm oil'. Witepsolw H35 is a half synthetic suppositories base obtained from coconut oil with a melting point of about 35 8C. In contrast, cetyl palmitate is a mixture of esters, containing C14–C18 acids and alcohol components with a melting point of approximately 54 8C. Emulsifiers: phospholiponw 90G (Phospholipid, D-Ko¨ln), containing at least 90% phosphatidylcholine, polysorbate 80 (Unigema, B-Everberg), poloxamer 188 (Synopharm, DBarsbu¨ttel). Solvents: acetone, ethanol, ethylacetate, methanol, isopropanol, 85% glycerol (Sigma-Aldrich, D-Seelze), bidistilled water. Devices: single-use syringe injectw, injection needle stericanw 0.40 £ 12 mm (Braun, D-Melsungen), paper filter B 90 mm (Schleicher & Schnell, D-Dassel).

Preparation of LNP:

LNP were prepared by a modified solvent injection technique. The lipids were dissolved in a water-miscible solvent and a water-miscible solvent mixture (1–-100 mg/ml) and then rapidly injected through an injection needle into a stirred (330 rev./min) aqueous phase with or without surfactant. The resulting dispersion was then filtered with a paper filter in order to remove any excess lipid.

Particle size measurement:

The size distribution of the LNP was investigated by photon correlation spectroscopy (PCS) using a Zetasizer 3 (Malvern, D-Herrenberg) modified with a He/Ne laser model 127 (Spectra Physics, USA, Mt. View, CA). The different systems were investigated at an angle of 908 in a measuring cell AZ 10 tempered at 293 K. Each sample was diluted with filtered bidistilled water until the appropriate concentration of particles was achieved to avoid multiscattering events and measured with a sample time of 30 ms for 10 min in serial mode. Each measurement was performed in triplicate and both the particle z-average diameter and polydispersity index (PI) were determined.

Transmission electron microscopy (TEM):

Samples were shock-frozen in melting nitrogen at 63 K between two flat gold holders. The frozen samples were fractured at 173 K in a BAF 400 instrument (Balzers, DWiesbaden). Shadowing was performed with

platinum/ carbon (2 nm) at 458 and with pure carbon at 908 for replica preparation. After cleaning with a chloroform/methanol mixture (1:1), the replicas on uncoated grids were viewed using a transmission electron microscope EM 300 (Philips, D-Kassel).

Differential scanning calorimetry (DSC):

Measurements were performed on a calorimeter DSC 220C connected to a disc station 5200H (Seiko, J-Tokyo). Approximately 15 mg of the dispersion or 0.039 mg of bulk material were accurately weighed in an aluminium crucible and fused on cold. The probes were measured against an empty reference crucible in a temperature range of 5–75 8C at a heating rate of 5 8C/min.

Viscosity measurement:

The dynamic viscosity of the aqueous phase was varied by the addition of 10%, 20%, 30% and 50% (v/v) glycerol. The viscosity of the aqueous phase was determined with an Ubbelohde viscometer (Schott, D-Hofheim) with an instrument constant k ¼ 0:009615. Previously, the density was determined with a digital densitometer (Anton Paar, AGraz). [9]

Membrane contractor method:

The present study investigates a new process for the preparation of SLN using a membrane contactor, to allow large scale production. The lipid phase is pressed, at a temperature above the melting point of the lipid, through the membrane pores allowing the formation of small droplets. The aqueous phase circulates inside the membrane module, and sweeps away the droplets forming at the pore outlets. SLN are formed by the following cooling of the preparation to room temperature. The influence of process parameters (aqueous phase and lipid phase temperatures, aqueous phase cross-flow velocity and lipid phase pressure, membrane pore size) on the SLN size and on the lipid phase flux is investigated. Also, vitamin E loaded SLN are prepared, and their stability is demonstrated[10].

EVALUATION OF SOLID LIQUID NANOPARTICLES (SLNs):

1. High pressure homogenization (HPH):

It is a reliable and powerful technique, which is used for the first time for production of SLNs. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (over 1000 Km/h). Very high Shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5-10% lipid content is used but up to 40% lipid content has also been investigated. HPH is of two types-hot homogenization and cold homogenization. In both cases, a preparatory step involves the drug incorporation into the bulk lipid by dissolving or dispersing the drug in the lipid melt.

Hot Homogenization:

Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device (Ultra-Turrax). The quality of the final product is affected by the quality of pre-emulsion to a large extent and it is desirable to obtain droplets in the size range of a few micrometers. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures also accelerate the degradation rate of the drug and the carrier. The homogenization step can be repeated several times. The primary product is a nanoemulsion due to the liquid state of the lipid which on cooling at room temperature leads to solid particles. Due to the small particle size and the presence of emulsifiers, lipid crystallization may be highly retarded and the sample may remain as a super cooled melt for several months.

Cold Homogenization:

In contrast, the cold homogenization is carried out with the solid lipid and represents, therefore, a high pressure milling of a suspension. Effective temperature control and regulation is needed in order to ensure the unmolten state of the lipid due to increase in temperature during homogenization. Cold homogenization has been developed to overcome the following three problems of the hot homogenization technique.

1. Temperature-induced drug degradation able equipment.
2. Drug distribution into the aqueous phase during homogenization.
3. Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts pressure.

The first step is same as in hot homogenization which includes the solubilization or dispersing of the drug in the melt of the bulk lipid. In general, compared to hot homogenization, larger particle sizes and a broader size distribution are observed in cold homogenized samples.

Ultra Sonication And High Speed Homogenization:

SLNs are also prepared by ultrasonication or high speed homogenization techniques. For smaller particle size combination of both ultrasonication and high speed homogenization is required. It reduces shear stress but has some disadvantages like potential metal contamination, physical instability like particle growth upon storage. In this probe sonicator or bath sonicator is used.

Solvent evaporation method:

The lipophilic material is dissolved in a water-immiscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by giving the nanoparticles of 25 nm mean size. The solution was emulsified in an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure (40–60 mbar).

Solvent emulsification diffusion method:

The particles with average diameters of 30-100 nm can be obtained by this technique. Voidance of heat during the preparation is the most important advantage of this technique. In this technique lipid is, are generally dissolved in the organic phase in water bath at50 °C and used an acidic aqueous phase in order to adjust the zeta potential to form coacervation of SLN, and then easy separation by centrifugation. The SLN suspension was quickly produced. The entire dispersed system can then be centrifuged and re-suspended in distilled water.

Supercritical fluid method:

This is a relatively new technique for SLN production and has the advantage of solvent-less processing. There are several variations in this platform technology for powder and nanoparticle preparation. SLN can be prepared by the rapid expansion of supercritical carbon dioxide solutions (RESS) method. Carbon dioxide (99.99%) was the good choice as a solvent for this method.

Microemulsion based method:

Gasco and co-workers developed SLN preparation techniques which are based on the dilution of microemulsions. By stirring at 65-70°C an optically transparent mixture is obtained which is typically composed of a low melting fatty acid (stearic acid), an emulsifier (polysorbate20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), co-emulsifiers(sodium monooctylphosphate) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. Typical volume ratios of the hot microemulsion to cold water are in the range of1:25 to 1:50. The dilution process is critically determined by the composition of the microemulsion. According to the literature, the droplet structure is already contained in the microemulsion and therefore, no energy is required to achieve submicron particle sizes. The hydrophilic co-solvents of the microemulsion play a similar role in formation of lipid nanoparticles as acetone for formation of polymer nanoparticles.

Double emulsion based method:

Warm w/o/w double microemulsions can be prepared in two steps. Firstly, w/o microemulsion is prepared by adding an aqueous solution containing drug to a mixture of melted lipid, surfactant and co-surfactant at a temperature slightly above the melting point of lipid to obtain a clear system. In the second step, formed w/o microemulsion is added to a mixture of water, surfactant and cosurfactant to obtain a clear w/o/w system. In case of SLNs production, they have to be stable for few minutes, the time between the preparations of the clear double microemulsions and its quenching in cold aqueous medium, which is possible to achieve.

Precipitation technique:

Solid lipid nanoparticles can also be produced by a precipitation method which is characterized by the need for solvents. The glycerides will be dissolved in an organic solvent (e.g. chloroform) and the solution will be emulsified in an aqueous phase. After evaporation of the organic solvent the lipid will be precipitated forming nanoparticles.

Film ultrasound dispersion:

The lipid and the drug were put into suitable organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is formed, then the aqueous solution which includes the emulsions was added. Using the ultrasound with the probe to diffuser at last, the SLN with the little and uniform particle size is formed.

Solvent injection technique:

It is a novel approach to prepare SLN, which has following advantages over other production methods like use of pharmacologically acceptable organic solvent, easy handling and fast production process without technically sophisticated equipment. It is based on lipid precipitation from the dissolved lipid in solution. In this technique the solid lipid was dissolved in water-miscible solvent (eg. ethanol, acetone, isopropanol) or a water miscible solvent mixture. Then this lipid solvent mixture was injected through an injection needle into stirred aqueous phase with or without surfactant. The resultant dispersion was then filtered with a filter paper in order to remove any excess lipid. [10]

Oral administration:

Advantages and drawbacks Oral administration is the preferred route for drug delivery. It is patient-friendly, painless and easy for self-medication. Compared to parenteral delivery, it suppresses risk of disease transmission, reduces cost and increases patient compliance. It allows flexible and controlled dosing schedule. It is particularly convenient for chronic therapy. Oral bioavailability of drugs is strongly influenced by their properties. Solubility and permeability are two important parameters for their absorption via passive diffusion. The Biopharmaceutic Classification System defines four categories of drugs based on their solubility and their permeability[11]. The drug delivery system using solid lipid nanoparticles (SLN) came into being about two decades ago and since then lot of work has been done in this field SLN for oral drug administration are specifically used to target the uptake of the drug by lymphatic system which prevents its first pass metabolism. Lymphatic uptake of drugs follow two routes which include transcellular transport through the enterocyte and phagocytosis of the drugs by Mast cells of payer's patches lining the intestinal mucosa[35].

CONCLUSION:

In conclusion, this studied provided several interesting findings about drug loaded nanoparticles prepared by solvent diffusion or precipitation method. Extension to other living and controlled polymerization systems will open up a wider route to functionalized surfaces for promoting the fabrication of new types of nanoparticles that could be used in many targeted drug actions. With regard to the targeting issues, the importance of physiological barriers, on the fate and activity of these nanoparticles with respected to their biodegradability/bioerodibility was also stated. These nanomaterials form the building blocks for new bottom-up approaches to materials assembly for a range of used. Such materials also received attention because of their intrinsic size dependent properties and resulting applications. Different methodology provided a simple and convenient route to a variety of building blocks for assembling materials with novel structure and function in nanotechnology. The nontoxic excipients and sophisticated material engineering of SLNs tailor the controllable physicochemical properties of the nanoparticles for GI penetration via mucosal or lymphatic vehicle. So the greatest capability for its applicability to various classes of drug delivery and chronic diseases in the future.

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