European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 7, Issue 07, 2020

Solid Lipid Nanoparticles In Obesity Management

Keerti Bhardwaj*, Iqbaljit Kaur[1], Tamanna[1], Satendra Kunwar[2]

[1]*Department of Pharmaceutics, Lovely School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, 144411*

[2]*Shambhunath Institute of Pharmacy, Uttar Pradesh Technical University, Allahabad, Uttar Pradesh, 211012*

ABSTRACT

Obesity is the lifestyle disorder which is becoming very common with the passage of time due to the unhealthy lifestyle followed by us resulting into fat accumulation and abnormal increase in body weight which ultimately leads to many other fatal diseases. The drugs proposed by FDA for the treatment and management of obesity are administered through different routesto exhibit their effective pharmacological action but these drugs are having either poor solubility or poor permeability due to which an achieving an effective bioavailability is a challenge. Solid lipid nanoparticles are the lipid based nano-carriers which facilitates the drug to reach into the systemic circulation. Solid lipid nanoparticles carry the drug in their lipidic medium increasing the permeability through the phospholipid bilayer. The approach is empowered by articulating from conventional to lipid-based nano-carrier formulation and in addition, specific amendment in the functional components. The enhanced solubility and therefore the bioavailability results into dose reduction which also lowers the risk of side effects due to drug toxicity or due to higher doses.

1. INTRODUCTION

To Solid Lipid Nanoparticles

The Solid Lipid Nanoparticles (SLNs) were innovated in the year 1991 as a substitute approach for conventional colloidal carriers such as liposomes, polymeric microparticles, emulsions and polymeric nanoparticles. Since then the drug delivery system has drawn so much attention of the researchers for the intravenous route of application as it can act as the perfect substitute of particulate colloidal drug carrier system(Mehta *et al.*,2016).

The solid lipid nanoparticle system comprises of the nanosized range spherical solid-lipid particles. The average size of the diameter of these nanoparticles ranges from 10 to 1000 nanometers. These particles are dispersed into water or any other aqueous surfactant solution. The SLNs are made of the hydrophobic core of lipid which remains solid at room temperature and has the phospholipid monolayer coating over it. The hydrophobic solid core consists of the drug which is dispersed or dissolved into the solid matrix of the lipid and the phospholipid

hydrophobic chains gets embedded into this solid lipid matrix. This system has the capacity to carry both hydrophilic as well as hydrophobic drugs and diagnostics in itAnand *et al.*, 2017.

The solid lipid nanoparticles consist of the combined properties of fat emulsion, liposomes and polymeric nanoparticles. They possess several advantages such as non-toxic nature, better bioavailability, chemically stability from hydrolysis, biodegradability, coalescence, physical stability and efficient lipophilic drug carrier.The main difference between the liposomes and the lipid emulsion is that the basic structure of lipid emulsion consists of a neutral hydrophobic oil core covered with a amphiphilic lipid monolayer while the liposomes comprises of the amphiphilic phospholipid bilayer as outer covering and has aqueous chamber inside [Flegal *et al.*, 2010*;* Gasco *et al.*, 1993; Gohla *et al*., 2001] The solid lipid nanoparticles can be administered through many routes as shown in Fig. 2.1 and their *in-vivo* activity depends on these routes of administrations.

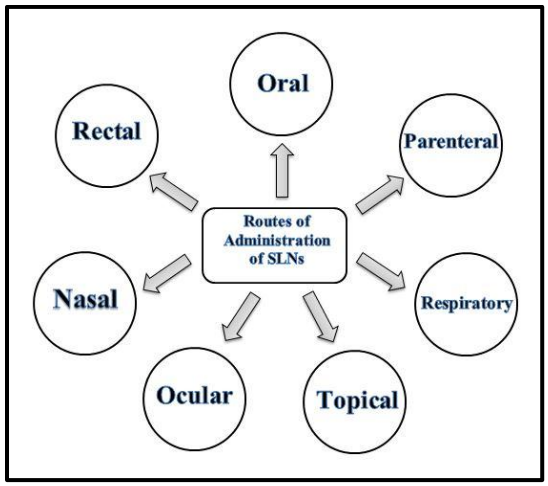


Fig. 2.1 Routes of administration of SLNs

Advantages of SLNs

- SLNs exhibits much better stability and gives better scope of upgradability as than that of the liposomes
- The lipid matrix of the SLNs consists of the physiological lipid which lowers the risk of either acute or chronic toxicity.
- The SLNs possesses long term and high physical as well as chemical stability.
- The manufacturing of SLNs is comparatively easier than the preparation of bipolymeric nanoparticles.
- The SLNs have good control upon the release kinetics of the entrapped active component.
- SLNs are capable of improving the bioavailability of the incorporated bioactive compound.
- The solid lipid nanoparticles provide chemical stability to the labile encapsulated component.

- The solid lipid nanoparticles do not need any different raw materials than the emulsions. Therefore, they are easy and manageable to manufacture.
- The large-scale production of SLNs is possible.
- The functional compound of SLN can be achieved at higher concentrations.
- The solid lipid nanoparticles are suitable to undergo lyophilisation, if needed.

Methods of preparation of SLNs

There are several production methods through which we can achieve the solid lipid nanoparticles at large scaleproduction [Shah*et al*., 2011; Shick*et al*., 1998; Shidhaye*et al*., 2008]. Some of these approaches which are adopted in this work are:

- High pressure homogenisation
- Hot high pressure homogenisation
- Cold high pressure homogenisation
- Microemulsion
- Ultrasonication
- Solvent evaporation

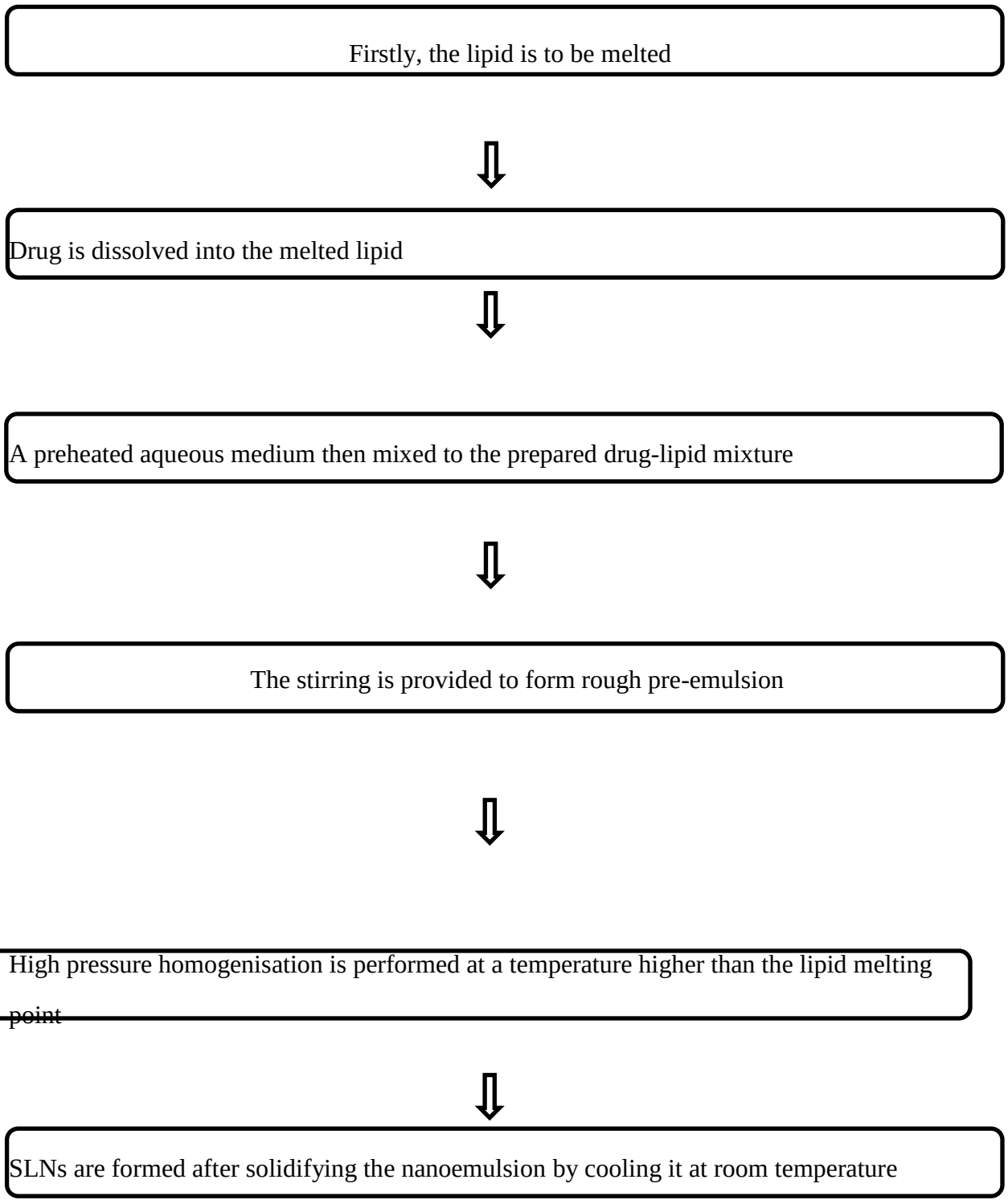
2. HIGH PRESSURE HOMOGENISATION

High Pressure Homogenisation (HPH) is an influencial and reliable technique for the preparation of solid lipid nanoparticles. In this approach, the high-pressure homogenizers thrust the liqiuid at a very high pressure of 100-2000 bar through a slender gap of few microns range size. This elevates the fluid to very high velocity of more than 1000 Km/h at a small distance. The very high shear stress and cavitation forces produced by these conditions leads to the size reduction of particles till submicron range (Ahlin*et al.*, 19988).

At first, the HPH technique was adopted for the formulation of solid lipid nano-dispersions. However, the quality of the dispersion was often compromised due to the micro size range of the particles.

The HPH technique is carried out by two general approaches of hot high pressure homogenisation and cold high pressure homogenisation working on the same theory of mixing the drug into the bulk amount of meltedsolid lipid.

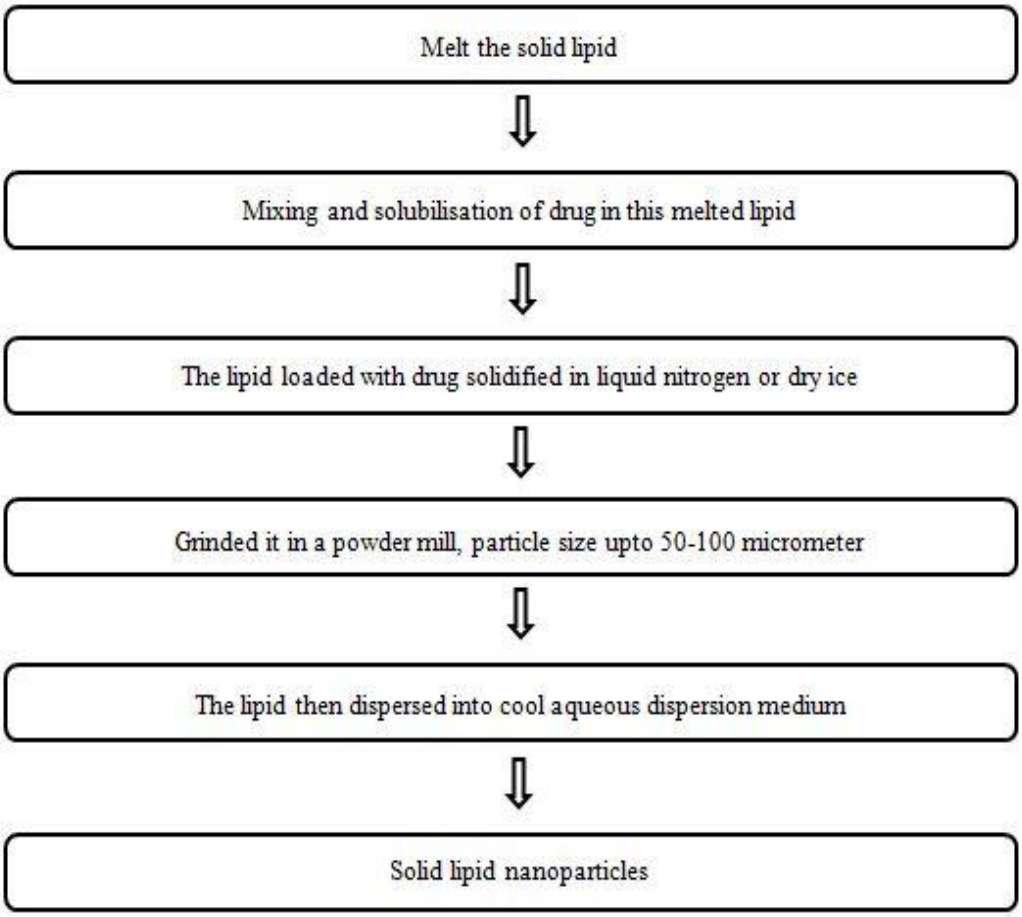
Hot High Pressure Homogenisation



The desired drug which is to be encapsulated into the nanostructured lipid carriers, was firstly dispersed or dissolved either into the melted lipid which was solid at the room temperature or into the mix of an oil and a solid lipid after melting. Now, in the process of hot homogenization,

the hot lipid melt having the dissolved drug would be dispersed into a hot surfactant solution with continuous and vigorous stirring. The temperature must be maintained 5-10 °C more than the solid lipid melting point orthe melting point of whole lipid mix. Now this pre-emulsion should be treated under the high pressure homogenizer regulated to the temperature same as earlier and the rotations are adjusted at 500 bars for three rotations and at 800 bars for two rotations. The technique in mainly applied in case of hydrophobic and poorly soluble drugs. Since, the operating time and heat exposure time is short, some heat sensitive or thermolabile drugs can also be safely handled. But this techniques is not useful in case of hydrophilic drug incorporation into SLNs as the higher fraction of drug content in water at the time of homogenization will lead to low entrapment efficiency.

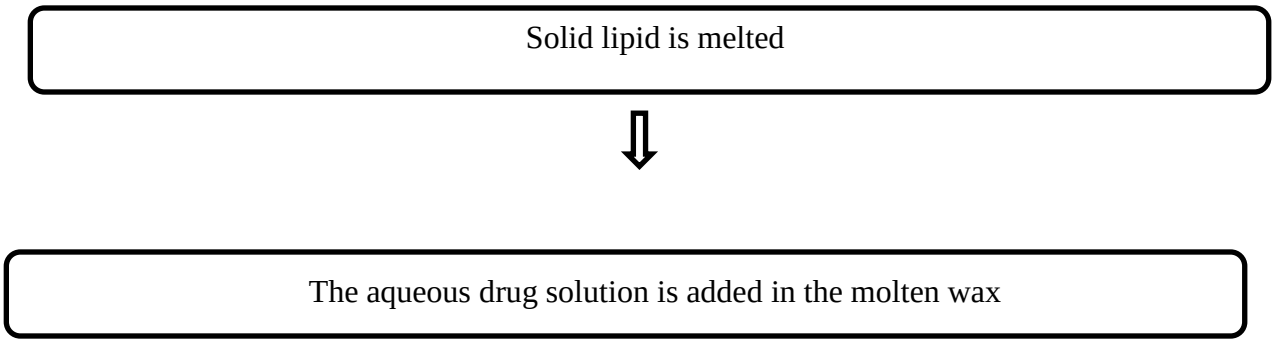
Cold High Pressure Homogenisation

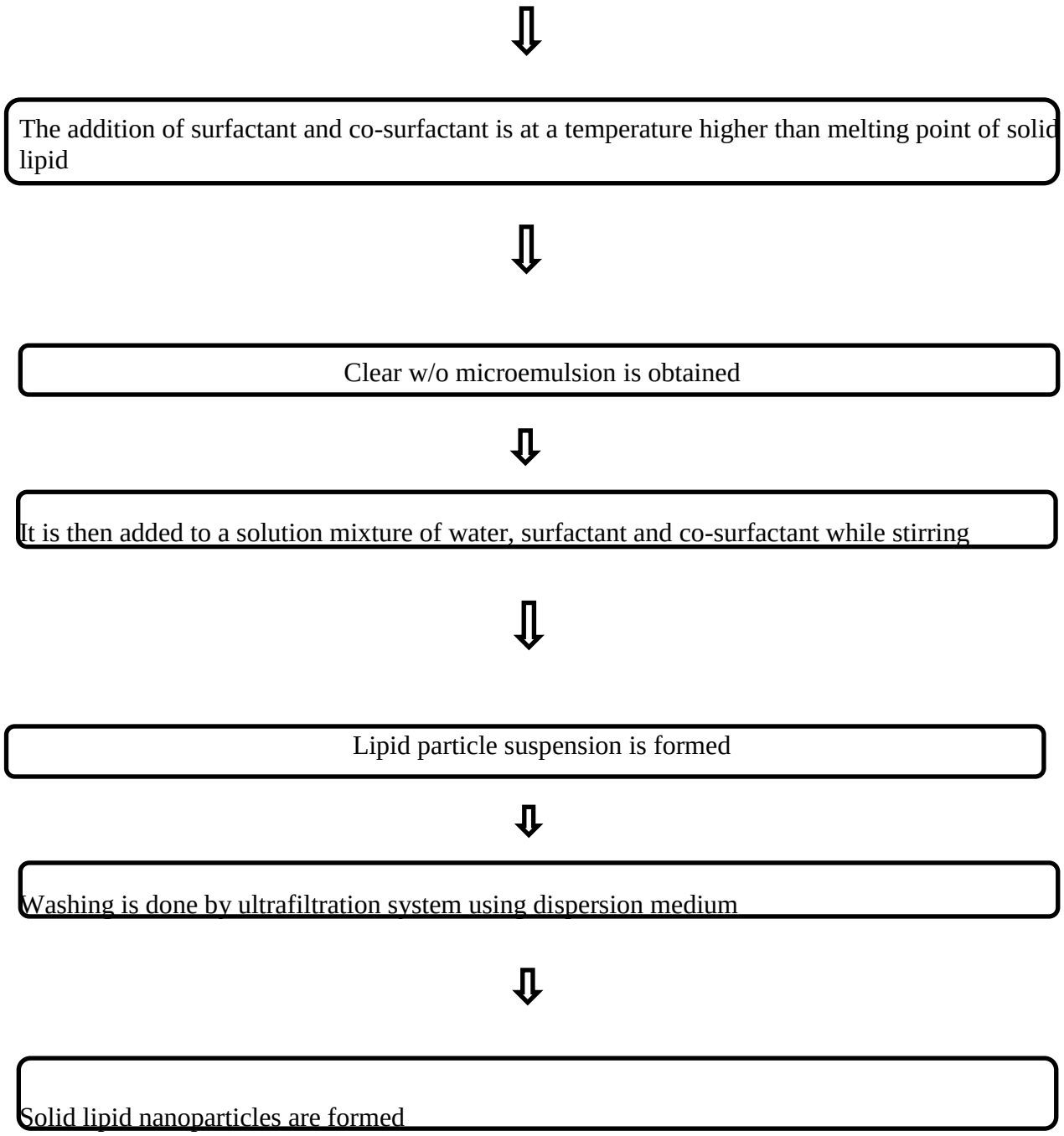


The initial step of cold high pressure homogenization is nearly same as that of the hot high pressure homogenization, that is, dispersion or solubilisation of drug into the pre-melted solid lipid or to the mix of oil and a melted solid lipid. Dry ice is used to promptly cool the prepared mixture, liquid nitrogen may also be used in this aspect. The resulting solid product of SLN loaded with the drug was milled with the help of ball mill or mortar pestle up to the size of 50-100 micron and these milled microparticles then added into the cool emulsifier solution. The makes the pre-suspension. Followed by pre-suspension which is exposed under the HPH at or below 25°C where the hollow point process gets introduced strongly on the pre-suspension and breaks the microparticles further to the desired solid lipid nanoparticles. This technique reduces the lipid melting and thus lowers the risk of drug loss of hydrophilic nature into the aqueous phase [Cavalli*etal.*, 2002; Ekambaram*et al.*, 2012; Eldem*etal.*, 1991]. A different approach can also be applied to ensure the minimum hydrophilic drug loss into the aqueous phase is by substituting the water with any other media for example, oil or PEG 600 in which the drug would be less soluble. The polydispersity index and particle size of product obtained from the cold HPH technique is more as that of the hot HPH technique. The cold HPH technique decreases the heat exposure time for the drug but does not avert it completely since the heat is applied for the melting of the solid lipid in the initial step as well as the high-pressure homogenization also generated heat during its vigorous cycles, that is, 10-20°C elevated temperature in each cycle. Mostly, 3-5 rotational cycles at 500-1500 bars are enough to produce desired solid lipid nanoparticles. Any increase in the number of rotational cycles or shear in homogenization may lead to the larger particle size of the product caused by the high kinetic energy among the particles [Parhi et al, 2010].

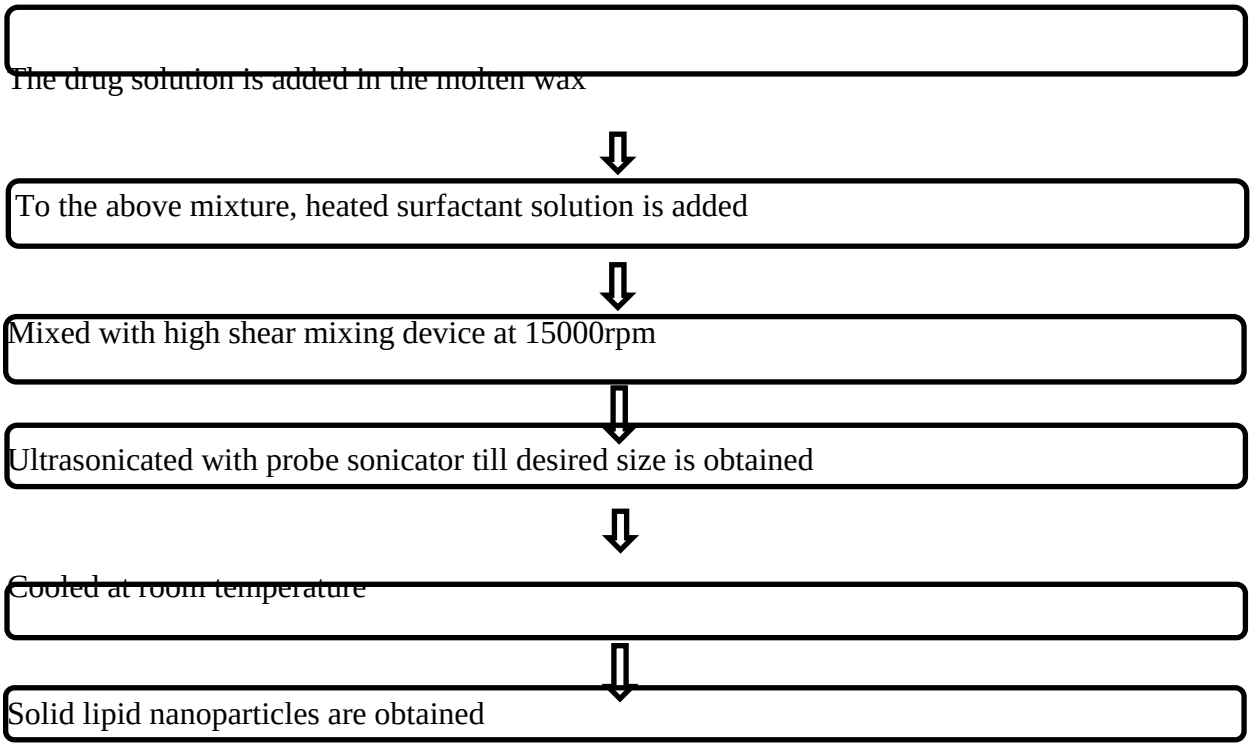
Microemulsion based SLNs

The principle of the technique depends upon the microemulsion dilution process. The microemulsion is composed of two different phases, that is, one inner phase and one outer phase (o/w microemulsions). An optically transparent mixture was prepared containing a fatty acid with low melting point such as stearic acid, an emulsifier like polysorbate 20, a co-emulsifier for example butanol and water. This mixture is then stirred continuously at 65-70°C temperature. Then this hot mixture is mixed into cold water having temperature 2-3°C during stirring. The rapid change in the temperature helps in fast lipid crystallisation and prevents the risk of accumulation. The presence of lipid content in the microemulsion is comparatively less as that of the HPH formulations because of the dilution step.



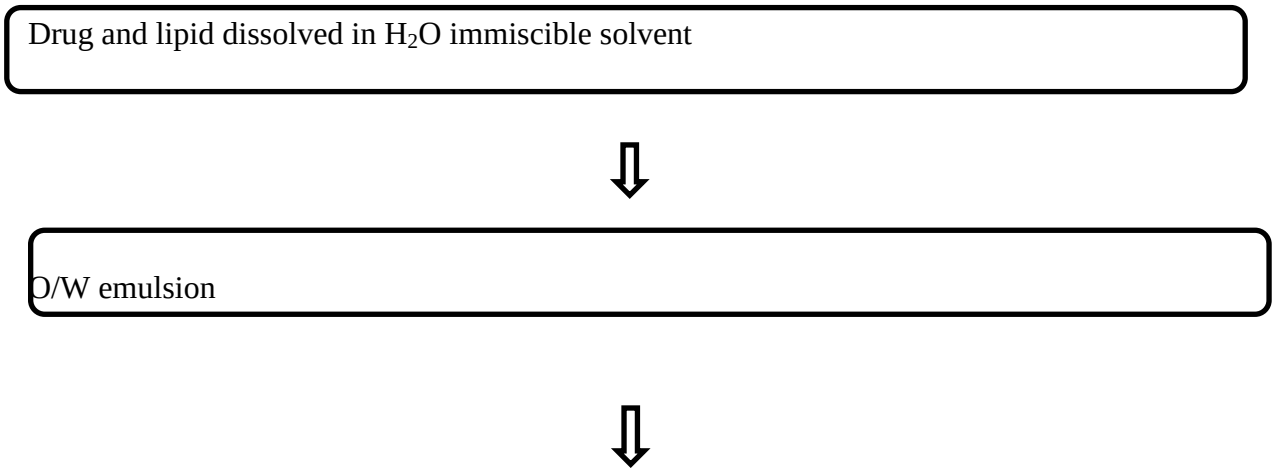

The addition of surfactant and co-surfactant is at a temperature higher than melting point of solid lipid
Clear w/o microemulsion is obtained
It is then added to a solution mixture of water, surfactant and co-surfactant while stirring
Lipid particle suspension is formed
Washing is done by ultrafiltration system using dispersion medium
Solid lipid nanoparticles are formed

3. ULTRASONICATION



4. SOLVENT EVAPORATION

The lipophilic drug and the hydrophobic material are mixed in a non-polar solvent like cyclohexane, chloroform, toluene etc. and then emulisified in a water phase during high speed homogenization. For the enhanced efficiency of the emulsification, the rough or coarse emulsion is passed through the micro fluidizer immediately [Jain *et al*.1997; Lander*et al.*, 2000; Lau*et al.*, 2006]. The organic solvent gets evaporated during stirring at reduced pressure and room temperature leads to lipid precipitates of SLNs.



Solvent gets evaporated and leaves behind the SLNs

5. OBESITY MANAGEMENT

The common causes of obesity are:

- ✓ Excessive food intake
- ✓ Less or no physical activity
- ✓ Genetics: The genetic factor is one of the common obesity causes. Not much can be done regarding that other than regular exercise and controlled diet. The family history of hypothyroidism, diabetes, hypertension etc. may also result into obesity.
- ✓ High carbohydrate and fatty diet
- ✓ Medications: Some medications play significant role in weight gain such as diabetic treatments, steroid hormones, psychotropic medications, antihypertensive drugs, contraceptives, protease inhibitors and antihistamines. The drug-induced obesity comes with further risks of enrooting hyperlipidemia, hypertension, type II diabetes along with poor compliance to medications.
- ✓ Mental illness: Psychological factors like stress, depression, anxiety may results into eating disorders also known as stress eating or comfort eating which eventually displayed as obesity.
- ✓ Lifestyle: The modernized lifestyle with more mechanized work and ease of technology results in lesser physical activity. The availability of processed food in order to make things quick and easy, the consumptions of saturated fats and synthetic food has increased tremendously leading to deposition of body fat. Lack of sleep is also one of the lifestyle factors which affects the biological cycle of the body which when gets disturbed, in order to compensate the stress body tends to produce more and more body fat.
- ✓ Diseases: Diseases like hypothyroidism, polycystic ovary syndrome, Cushing's syndrome, insulin resistance etc. may also result in obesity.

The obesity and overweight issues are greatly preventable as well as reversible. Therefore, the obesity management is possible and effective. It primarily includes physical exercise and proper healthy diet. The diet programs alone can work for a short period of time and may result into weight loss but in the long run, maintaining it can be difficult (Aronne*et al.*,2003;Carafa*et al.*,2008). Hence, the combination of low calorie diet and regular exercise must carry out for the permanent weight loss effect.

In order to reduce weight, one can:

- ✓ Limit the intake of processed food and avoid having sugar and fats.
- ✓ Switch to vegetables and fruits instead. Consume legumes, nuts, whole grains, fibres; and

- ✓ Engage one's self in regular exercise of at least 60 minutes for kids 150 minutes for an adult per week.
- ✓ Encourage yourself to opt for a scheduled day and get 7-8 hours of sleep every day to provide the much needed rest to the body.
- ✓ Try meditation to avoid stress and hypertension, especially those who suffers from depression and anxiety.

6. SOLID LIPID NANOPARTICLE FOR OBESITY MANAGEMENT

The lipid nanoparticles made with the solid matrix have emerged as an efficient carrier of drug for the enhancement of oral bioavailability and GI absorption of many poorly soluble drugs, chiefly the lipophilic ones. This system can also be used for the sustained release and are being considered and studied for their abilities to deliver the drug orally. The lipids chosen for the nanoparticles preparations should be biocompatible, biodegradable as well as physiological which minimizes the risk of toxicity associated with the polymeric nanoparticles (Lin*et al.*, 2017; Olbrich*et al.*, 2002; Pouton*et al.*, 2006). Along with that, the solid matrix results in the enhanced stability of the formulation as compared to other nano-carrier liquid preparations. Such nanoparticles preparations can be carried out using various techniques and it is easy to move up from lab scale production to industrial scale production during the process. It was observed that the solid lipid nanoparticles provide improved drug entrapment efficiency as well as bioavailability and oral absorption were also enhanced in the oral administration [Radte*et al*., 2005; Ramteke*et al.*, 2012; Schwarz*et al.*, 1994].

The drugs having problems related to their solubility and bioavailability are intended to be delivered through any novel delivery system to overcome the shortcomings and get the desired therapeutic effect on the body. The various techniques involved in enhancing the properties of drug involve precipitation, micronization, nanonization, and use of surfactants or drug coating.

Other than these conventional methods, active attempts are being made to upgrade the drug efficacy by encapsulating the drug into suitable nano carriers as drug delivery systems. The efficacious implementation of nanoparticles as drug delivery system depends on upon various factors such as penetration capacity of the system through a number of physiological as well as anatomical barriers, the sustained release of their constituents and their ability to remain stabilized in nanometer size range also [Siekmann*et al*., 1996; Speiser*et al.*, 1990; Yang*et al.*, 1999]. However, the shortage of the variety of safe polymers, which could get the regulatory approval along with the high cost of the available polymers have made it more difficult for the application in nanoparticles formulation for clinical medicines.

To conquer these limitations, lipid has been used in place of polymers to act as a delivery system, especially in case of lipophilic active constituents and these lipid-based nanoparticles are known as the Solid-Lipid Nanoparticles (SLNs) which are drawing more and more attention of the researchers.

The lipid matrix made in the SLNs are prepared by the physiologically tolerated fat content which results in the decrease in the potential risk of chronic or acute toxicity which can occur in case of polymeric nanoparticles. Therefore, it can be concluded that solid-lipid nanoparticles have the combined advantages of various delivery systems such as the low toxicity of liposomes

and fatty emulsions and are capable of providing sustained release occurred because of the solid matrix just like the polymeric nanoparticles and can exhibit targeted drug delivery if administered parenterally.

7. CONCLUSION

The SLNs are considered to be the favourable systems of drug delivery in advanced era of submicron-sized emulsions of lipid in which the solid lipid is being used in place of the liquid lipid (oil). These solid-lipid nanoparticles exhibit several properties like nano ranged size, larger surface area, increased drug loading and the interfacial interaction of phases. These systems have the capability to enhance the therapeutic performance of the pharmaceutically active materials.

8. REFERENCES

[1] Ahlin, P., Kristl, J., & Šmid-Korbar, J. (1998). Optimization of procedure parameters and physical stability of solid lipid nanoparticles in dispersions. *Acta pharmaceutica*, *48*(4), 259-267.

[2] Anand, A., Patience, A. A., Sharma, N., & Khurana, N. (2017). The present and future of pharmacotherapy of Alzheimer's disease: A comprehensive review. *European journal of pharmacology*, *815*, 364-375.

[3] Aronne LJ., Segal KR., 2003. Weight gain in the treatment of mood disorders. J Clin Psychiatry. 64(Suppl 8),22–29.

[4] Carafa, M., Marianecci, C., Salvatorelli, M., Di Marzio, L., Cerreto, F., Lucania, G., & Santucci, E. (2008). Formulations of retinyl palmitate included in solid lipid nanoparticles: characterization and influence on light-induced vitamin degradation. *Journal of Drug Delivery Science and Technology*, *18*(2), 119-124.

[5] Cavalli, R., Gasco, M. R., Chetoni, P., Burgalassi, S., & Saettone, M. F. (2002). Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin. *International journal of pharmaceutics*, *238*(1-2), 241-245.

[6] Ekambaram, P., Sathali, A. A. H., & Priyanka, K. (2012). Solid lipid nanoparticles: a review. *Sci Rev Chem Commun*, *2*(1), 80-102.

[7] Eldem, T., Speiser, P., & Hincal, A. (1991). Optimization of spray-dried and-congealed lipid micropellets and characterization of their surface morphology by scanning electron microscopy. *Pharmaceutical research*, *8*(1), 47-54.

[8] Flegal KM., Caroll MD., Ogden CL., 2010. Prevalence and trends in obesity among US adults, 1999-2008. JAMA 303(3), 235-241.

[9] Gasco, M. R. (1993). *U.S. Patent No. 5,250,236*. Washington, DC: U.S. Patent and Trademark Office.

[10] Gohla, S. H., & Dingler, A. (2001). Scaling up feasibility of the production of solid lipid nanoparticles (SLN). *Die Pharmazie*, *56*(1), 61-63.

[11] Jain, N. K. (1997). Controlled and novel drug delivery CBS publishers & distributors. *Daria Gang, New Delhi*, 101-127.

[12] Lander, R., Manger, W., Scouloudis, M., Ku, A., Davis, C., & Lee, A. (2000). Gaulin homogenization: a mechanistic study. *Biotechnology progress*, *16*(1), 80-85.

[13] Lau DC., Douketis JD., Morrison KM., Hramiak IM., Sharma AM., Ur E., April 2007. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children summary. CMAJ. 176 (8), S1–13.
[14] Lin CH., Chen CH., Lin ZC., Fang JY., 2017. Recent advances in oral delivery of drugs and bioactive natural products using solid lipid nanoparticles as the carriers.Journal of Food and Drug Analysis. Volume 25, Issue 2, Pages 219–234.
[15] Mehta, C. M., Srivastava, R., Arora, S., & Sharma, A. K. (2016). Impact assessment of silver nanoparticles on plant growth and soil bacterial diversity. *3 Biotech*, *6*(2), 254.
[16] Olbrich, C., Gessner, A., Kayser, O., & Müller, R. H. (2002). Lipid-drug-conjugate (LDC) nanoparticles as novel carrier system for the hydrophilic antitrypanosomal drug diminazenediaceturate. *Journal of drug targeting*, *10*(5), 387-396.
[17] Parhi, R., & Suresh, P. (2010). Production of solid lipid nanoparticles-drug loading and release mechanism. *J Chem Pharm Res*, *2*(1), 211-27.
[18] Pouton CW., 2006. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. Eur J Pharm Sci. 29, 278-87.
[19] Radte M., Souto EB., Muller RH., 2005. Nanostructured Lipid Carriers: a novel generation of solid lipid drug carriers. Pharm Technol Eur. 17(4), 45-50.
[20] Ramteke, K. H., Joshi, S. A., & Dhole, S. N. (2012). Solid lipid nanoparticle: A review. *IOSR J. Pharm*, *2*(6), 34-44.
[21] Schwarz, C., Mehnert, W., Lucks, J. S., & Müller, R. H. (1994). Solid lipid nanoparticles (SLN) for controlled drug delivery. I. Production, characterization and sterilization. *Journal of Controlled Release*, *30*(1), 83-96.
[22] Shah Chandni, V., Viral, S., & Umesh, U. (2011). Solid lipid nanoparticles: a review. *Current Pharma Research*, *1*(1), 351-68.
[23] Shick SM., Wing RR., Klem ML., McGuire MT., Hill JO., Seagle H., April 1998. Persons successful at long-term weight loss and maintenance continue to consume a low-energy, low-fat diet. J Am Diet Assoc. 98(4), 408–13.
[24] Shidhaye SS., Vaidya R., Sutar S., Patwardhan A., Kadam VJ., 2008. Solid lipid nanoparticles and nanostructured lipid carriers-innovative generations of solid lipid carriers. Curr Drug Deliv. 5(4), 324-31.
[25] Siekmann, B., & Westesen, K. (1996). Investigations on solid lipid nanoparticles prepared by precipitation in o/w emulsions. *European journal of pharmaceutics and biopharmaceutics*, *42*(2), 104-109.
[26] Speiser, P. (1990). Lipidnanopellets als Trägersystem für Arzneimittel zur peroralen Anwendung. *European Patent EP*, *167825*, 0167825.
[27] Yang S., Zhu J., Lu Y., Liang B., Yang C. 1999. Body distribution of camptothecin solid lipid nanoparticles after oral administration. Pharmaceutical Research, 16(5), 1-7.