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A REVIEW ON POLYMERIC NANOPARTICLES (PN) WITH SPECIAL EMPHASIS ON LYCOPENE AS PROTOTYPE

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ABSTRACT

Drug absorption from the GI tract can be limited by a variety of factors most significant contributor being poor aqueous solubility and poor permeability of the drug molecule. When administered an active agent orally it must first dissolve in gastric and / or intestinal fluids before it can permeate the membrane of the GIT to reach systemic circulation. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agent include ; enhancing of solubility and dissolution rate of poorly water soluble drugs. Lycopene has attracted considerable attention as a natural chemo preventive agent through various properties including its potent antioxidant properties. Hence, this review primarily focuses on solubility enhancement of lycopene and methods for development of polymeric nanoparticles.

Keywords: Nanoparticles; Lycopene; Solubility Enhancement

INTRODUCTION

Carotenoids

Oxidative stress is an important contributor to the risk of chronic diseases. Dietary guidelines recommended increased consumption of fruits and vegetable to combat the incidence of human diseases such as cancer, cardiovascular disease, osteoporosis and diabetes .Fruits and vegetable are good sources of antioxidant phytochemical that mitigate the damaging effect of oxidative stress. Carotenoids are a group of phytochemical that are responsible

for different colours of the foods. All carotenoids are tetra terpenoids, meaning that they are produced from 8 isoprene units and contain 40 carbon atom. Carotenes are valuable preventive medicines, too. Research shows that who eat a lot of foods rich in beta –carotene carotenoids with the greatest vitamin A value are less likely to develop lung cancer **[1]**. Carotenoids are fat soluble food component that are categorized as either xanthophyll's (oxygen containing carotenoids) or carotenes (hydrocarbon carotenoids) according to their chemical composition .most xanthophyll's are found in green leafy vegetables and nearly all carotenes are found in yellow vegetable. The most important carotenoids are α-carotene, β – carotene, β-ceyptoxanthin, lutein, lycopene, zeaxanthin violaxanthin, and neoxanthin. The first six carotenoids can normally be found in human plasma, an indication of their bioavailability **[2]**. Carotenoids have linked with various health benefits, such as improvement of visual function , prevention of cardiovascular diseases , and lower the risk of pigmentation abnormalities. Carotenoids can serve several important function in human beings. The most widely studied and well –understood nutritional role of carotenoids is their provitamin-A activity. Lycopene, the hydrocarbon carotenoid that gives tomatoes their red colour, particularly effective at quenching the destructive potential singlet oxygen. Lutein and zeaxanthin (xanthophylls) are accumulated in the macula lutea in the eye. The presence of these two carotenoids reflects their close relationship with age –related macular degeneration there is epidemiological evidence that lycopene reduces the incidence of prostate cancer **[3]**.

Lycopene:

Lycopene has attracted considerable attention as a natural chemo preventive agent through various properties including its potent antioxidant properties. Inhibition of cancer cell proliferation and decreased lipid oxidation. Number of epidemiological studies have demonstrated that high dietary intake of Lycopene is associated with reduced risk of prostate cancer.

Lycopene is a highly lipophilic carotenoids (C Log p= 17.6) with the poor aqueous solubility, and previous studies have predicted that Lycopene will display solubility rate limited absorption characteristics. Hence formulation approaches which enhance solubility of Lycopene within the gastrointestinal tract (GIT) are considered crucial to increasing oral absorption. A number of formulation approaches have been utilised to enhance

solubility of poorly soluble drug in GIT such as particle size reduction, or modification of crystal habit to enhance dissolution **[4]**.

Solubility

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution as at a certain temperature and in qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as the parts, percentage, molarity, volume fraction, and mole fraction.

Drug solubility is the maximum concentration of the drug solute dissolve in the solvent under specific condition of temperature, pH and pressure. The drug solubility in saturated solution is a static property where as the drug dissolution rate is dynamic property that relates more closely to the bioavailability rate. The solubility of a drug is described in various descriptive terms which is based on the amount of the drug dissolved in solvent **[5]**.

1.2.1 Mechanism of Solubility

The process of solubility depends on the bonding between solute and solvent. The bonding is generally dipole interaction, London forces, hydrogen bonding, and ionic bonding.

Generally following three steps are involved in solubilisation **[6]**.

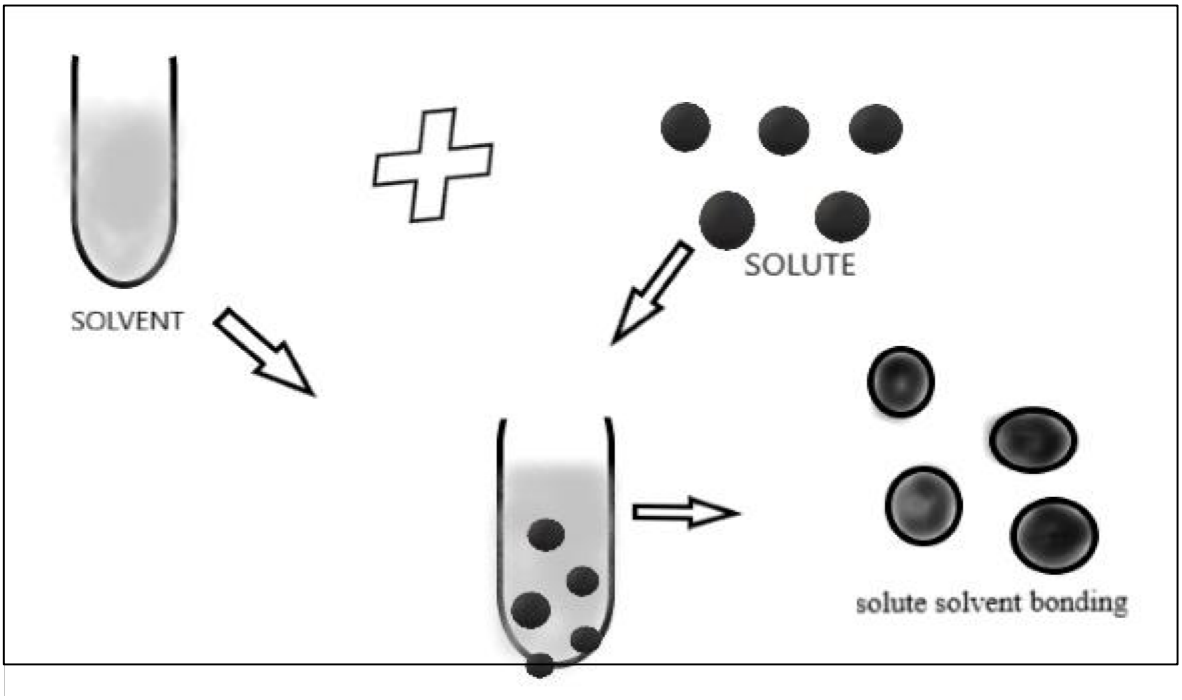

Figure 1.1: Steps of Solubilisation

Factor Affecting Solubility

1. Temperature
2. Pressure
3. Molecular size
4. Polarity
5. Effect of salt form.

Importance of Solubility

Solubility is one of the significant parameters to attain a preferred concentration of drug in systemic circulation for providing a therapeutic response. Oral intake is the most suitable and frequently employed route of drug delivery owing to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. The oral bioavailability depends on several factors including aqueous solubility drug permeability, dissolution rate, first pass-metabolism and susceptibility to efflux mechanism **[7]**.

Need of Solubility

Drug absorption from the GI tract can be limited by a variety of factors most significant contributor being poor aqueous solubility and poor permeability of the drug molecule. When administered an active agent orally it must first dissolve in gastric and / or intestinal fluids before it can permeate the membrane of the GIT to reach systemic circulation. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agent include ; enhancing of solubility and dissolution rate of poorly water soluble drugs **[8]**. The BCS is a scientific framework for classifying a drug substance base on its aqueous solubility and intestinal permeability. As for BCS class II & IV drug rate limiting step is drug release from the dosage form and solubility in gastric fluid and not the absorption , so increasing the solubility in turn increase the bioavailability for BCS class II & IV drugs **[9]**.

Approaches to Enhance Solubility

Poor aqueous solubility leads to poor dissolution and ultimately poor oral bioavailability. The enhancement of solubility of poorly water- soluble drugs remains one of the most challenging aspects of drug development. Some aspects such as complexation, solubilisation, solid dispersion and particle size reduction have commonly been used to increase solubility, dissolution rate and thereby oral absorption and bioavailability of such drug. The chief objective of a formulator is to design and formulate a dosage form processing optimum therapeutic efficacy of drug, economical production on large scale and prolonged shelf

life of the drug. Drugs with optimum intrinsic solubility or dissolution rate pose no problem, while poorly soluble drugs are challenge to the formulator to be appropriately dispensed. Different techniques have been developed. The methods employed to enhance the drug solubility can be summarized as follows.

Solid Dispersion

The term solid dispersion refers to a group of solid products consisting of at least two different components. Generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Chiou defined solid dispersion as "the dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredient could exist in finely crystalline, solubilized, or amorphous states". Sekiguchi first developed the concept of solid dispersion to enhance absorption of poorly water-soluble drugs. It involved the formation of eutectic mixtures of drug with water- soluble carries by melting of their physical mixtures, and once the carriers dissolved, the drug precipitated in finely divided state in water.

1.3.1 Classification of Solid Dispersion

A. According to molecular arrangement.

1. **Simple Eutectic mixture.**

Solid solution:

According to their miscibility.

- Continuous solid solution
- Discontinuous solid solution
- According to the way in which the solvate molecules are distributed in solvent

I. Substitution crystalline solid solution

II. Interstitial solid solution

III. Amorphous SDs

2. Glass solution

3. Amorphous precipitation in crystalline.

B. According to carriers used.

1. Crystalline carrier (first generation)

e.g.: Urea, Sugars, and Organic acids.

2. Polymorphic carrier (second generation)

e.g.: PVP, HPMC, PEG etc.

3. Surface active self-emulsifying carriers (Third generation)

e.g.: poloxamer 408, Tween 80 etc. **[10]**

Advantages of Solid Dispersion.

II. Particles with reduced particle size increased surface area

III. Particles with improved wettability.

IV. Particles with high porosity.

V. Particles in amorphous state

Disadvantages of Solid Dispersion.

I. Instability
II. By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place resulting in reduction of drug solubility
III. Difficulty in handling because of tackiness.

Limitation of Solid Dispersion

I. Physical and chemical stability of drugs and vehicles
II. Method of preparation
III. Reproducibility of solid dispersion into dosage form
IV. Scale-up of manufacturing processes
V. Poor predictability of solid dispersions behavior **[10]**

1.3.5. Techniques for Preparation of Solid Dispersion

Many methods are used for the preparation of solid dispersion systems and some of them are enlisted as follows:

- Fusion/Melting method
- Solvent method
- Melting solvent method (melt evaporation)
- Melt extrusion method
- Lyophilization techniques
- Melt agglomeration process
- Use of surfactants
- Electro spinning
- Super critical fluid technology
- Kneading method
- Co-grinding method

Solvent Method

The method involves preparation of a solution containing both matrix material and drug in a common volatile solvent followed by the evaporation of the solvent at either room temperature or elevated temperature with/without vacuum. It results in a solvent free film which is further dried to constant weight.

Lyophilization Techniques

It is molecular mixing technique where the drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. An advantage of this method is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion and the risk of phase separation is minimized as soon as the solution is can vertex into glass or a glassy substance.

Melt Agglomeration Process

This technique has been used to prepare solid dispersion in which the binder acts as a carrier. Solid dispersions are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a

dispersion of drug in molten binder on the heated excipient (spray-on procedure). Instruments like rotary processor is preferable for high melt agglomeration as it is easier to control temperature and higher binder content can be incorporated in the agglomerates. Melt-in method gives a higher dissolution rates than the spray-on method with PEG 3000, poloxamer 188 and gelucire 50/13.

Use of Surfactants

Adsorption of surfactant on solid surface modifies their hydrophobicity, surface charge, and also controls other interfacial properties such as flocculation/dispersion, floating, wetting, solubilisation, corrosion inhibition and enhanced oil recovery. Use of surfactants results in solvation/ plasticization, reduction of melting active pharmaceutical ingredient, glass transition temperature and combined glass transition temperature of solid dispersion.

Characterization of Solid Dispersion

The physical nature of SD can be characterized by various methods. Single method is not sufficient to furnish the complete information rather a combination of two or more techniques is needed

- Thermal analysis
- X-ray diffraction method
- Spectroscopic method
- Modulated temperature differential scanning calorimetric
- Environmental scanning electron microscopy
- Dissolution testing
- Dissolution rate method
- Microscopic method
- Thermodynamic method
- Solubility Study

POLYMERIC NANOPARTICLES (PN)

The polymeric nanoparticles (PNPs) are prepared from biocompatible and biodegradable polymers in size between 10-1000 nm where the drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation nanoparticles, Nano spheres or Nano capsules can be obtained. Nano capsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while Nano spheres are matrix systems in which the drug is physically and uniformly dispersed **[11]**. PNPs are promising vehicles for drug delivery by easy manipulation to prepare carriers with the objective of delivering the drugs to specific target, such an advantage improves the drug safety **[12]**. Polymer-based nanoparticles effectively carry drugs, proteins, and DNA to target cells and organs. Their nanometer-size promotes effective

permeation through cell membranes and stability in the blood stream. Polymers are very Convenient materials for the manufacture of countless and varied molecular designs that can be integrated into unique nanoparticle constructs with many potential medical applications **[13]**.

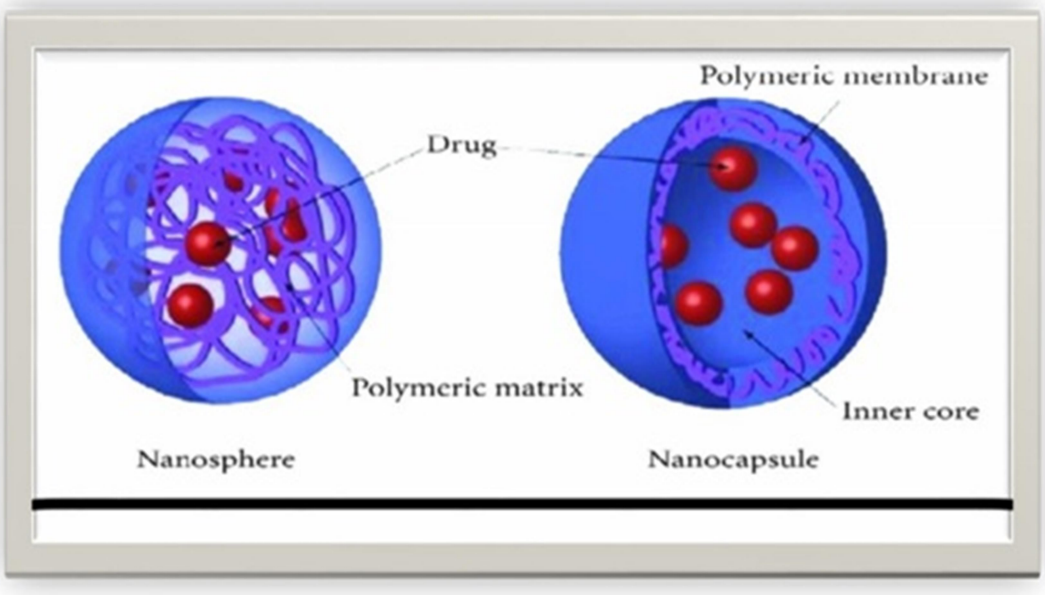

Figure 1.2: Differences between Nano Sphere and Nano capsule

There are many advantages of using polymeric nanoparticles in drug delivery

- Increases the stability of any volatile pharmaceutical agents, easily and cheaply fabricated in large quantities by a multitude of methods.
- They offer a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness.
- Delivers a higher concentration of pharmaceutical agent to a desired location.
- The choice of polymer and the ability to modify drug release from polymeric nanoparticles have made them ideal candidates for cancer therapy, delivery of vaccines, contraceptives and delivery of targeted antibiotics.
- Polymeric nanoparticles can be easily incorporated into other activities related to drug delivery, such as tissue engineering.
- Non-toxic, biodegradable and biocompatible **[14]**.

Mechanism of Drug Release

The polymeric drug carriers deliver the drug at the tissue site by any one of the three general physico-chemical mechanisms.

- By the swelling of the polymer nanoparticles by hydration followed by release through diffusion.
- By an enzymatic reaction resulting in rupture or cleavage or degradation of the polymer at site of delivery, there by releasing the drug from the entrapped inner core.
- Dissociation of the drug from the polymer and its dead sorption/release from the swelled nanoparticles **[15]**.

1. Methods for Preparation of Nanoparticles From Dispersion of Preformed Polymer

Dispersion of drug in preformed polymers is a common technique used to prepare biodegradable nanoparticles from these can be accomplished by different methods described below.

- Solvent evaporation
- Nano precipitation
- Emulsification/solvent diffusion
- Salting out
- Dialysis
- Supercritical fluid technology (SCF)

2. Methods For Preparation of Nanoparticles From Polymerization of Monomers

- Emulsion
- Mini emulsion
- Micro emulsion
- Interfacial polymerization
- Controlled/Living radical polymerization(C/LRP)

3. Ionic Gelation Or Coacervation Of Hydrophilic Polymers

1. Solvent Evaporation Method

Solvent evaporation method is one of the most frequently used methods for the preparation of nanoparticles. This method involves two steps (first is emulsification of the polymer solution into an aqueous phase and second is evaporation of polymer solvent, inducing polymer precipitation as Nano spheres). This method is based on the solubility of polymer and hydrophobic drug since both polymer and hydrophobic drug are dissolved in an organic solvent (dichloromethane, chloroform or ethyl acetate) which is also used as the solvent for dissolving the. Mixture obtained from polymer and drug solution is then emulsified in an aqueous solution. This aqueous solution contains surfactant or emulsifying agent to form oil in water (o/w) emulsion. Once the stable emulsion forms, the organic solvent is

evaporated either by continuous stirring or by reducing the pressure.

2. Salting Out Method

Method involves the separation of a water-miscible solvent from aqueous solution via a salting-out effect. It's based on the on the separation of a water miscible solvent from aqueous solution via a salting-out effect. During the initial process polymer and drug are dissolved in a solvent which is subsequently emulsified into an aqueous gel containing the salting out agent and a colloidal stabilizer. Various types of salting out agents (electrolytes, such as magnesium chloride and calcium chloride, or non-electrolytes such as sucrose) and colloidal stabilizer (such as polyvinyl pyrolidone or Hydroxy ethyl cellulose) have been used.

3. Solvent Displacement/Precipitation Method

In this method preformed polymer is precipitated in an organic solution and organic solvent is diffused in the aqueous medium. Diffusion of organic solvent can be achieved in the presence or absence of surfactant. Semi polar water miscible solvent such as acetone or ethanol can be used to dissolve the polymers, drug, and or lipophilic surfactant. After their complete dissolution, solution is then poured or injected into an aqueous solution containing stabilizer under magnetic stirring. Nano particles are formed immediately by the rapid solvent diffusion. This step is followed by the removal of solvent from the suspensions under reduced pressure.

3. Emulsions-Diffusion Method

This is another widely used method to prepare nanoparticles. The encapsulating polymer is dissolved in a partially water-miscible solvent (such as propylene carbonate, benzyl alcohol), and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. Subsequently, the polymer-water saturated solvent phase is emulsified in an aqueous solution containing stabilizer, leading to solvent diffusion to the external phase and the formation of Nano spheres or Nano capsules, according to the oil-to-polymer ratio. Finally, the solvent is eliminated by evaporation or filtration, according to its boiling point **[16]**.

1.5.5.Characterization of Polymeric Nanoparticle

1. Measurement of particle size and zeta potential

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for routine measurements of particle size. PCS (also known as dynamic light scattering) measures the fluctuation of

the intensity of the scattered light which is caused by particle movement. This method covers a size range from a few nanometres to about 3 microns. PCS is a good tool to characterize nanoparticles, but it is not able to detect larger micro particles **[17]**. The measurement of the zeta potential allows for predictions about the storage stability of colloidal dispersion **[18]**. In general, particle aggregation is less likely to occur for charged particles (high zeta potential) due to electric repulsion. However, this rule cannot strictly be applied for systems which contain steric stabilizers, because the adsorption of steric stabilizers will decrease the zeta potential due to the shift in the shear plane of the particle **[19]**.

2. Drug loading and encapsulation efficiency measurement

Entrapment efficiency (% EE) is expressed as fraction of drug incorporated into formulations relative to the total amount of drug used. Determination of % entrapment efficiency is an important parameter in case of polymeric nanoparticles as it may affect the drug diffusion. EE is determining the free drug (non-encapsulated) by UV method **[19]**.

3. Drug Release :

In Vitro Method:

I. Dialysis Tubing

The polymeric nanoparticles dispersion is placed in prewashed dialysis tubing which can be hermetically sealed. The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at specific time interval, centrifuged and analysed for the drug content using suitable method such as UV Visible spectrophotometry, HPLC. The maintenance of sink condition is essential.

II. Reverse Dialysis

In this technique a number of small dialysis bags containing 1 mL dissolution medium are placed in polymeric nanoparticles dispersion. The polymeric nanoparticles are then displaced into dissolution medium. The direct dilution of polymeric nanoparticles is possible with this method; however the rapid release cannot be quantified using this method.

III. Franz Diffusion Cell

The polymeric nanoparticles is placed in donor chamber of Franz diffusion cell fitted with a cellophane membrane. The dispersion is then dialyzed against a suitable diffusion medium at room temperature; the samples are withdrawn from the diffusion medium at suitable intervals and analysed for the drug content with the help of UV Visible

spectrophotometry, HPLC. In this method sink condition were maintained **[20]**.

CONCLUSION

In this informative review, information has been compiled from various studies across the world on polymeric nanoparticles and their development with special emphasis has been given for solubility enhancement and lycopene as prototype.

REFERENCES

[1] Rebecca LJ, Sharmila S, Das MP, Seshiah C. Extraction and purification of carotenoids from vegetables. J. Chem. Pharm. Res. 2014; 6(4): 594-8.

[2] Brabletz S, Brabletz T. The ZEB/miR-200 feedback loop—a motor of cellular plasticity in development and cancer?. EMBO reports. 2010 Sep; 11(9): 670-7.

[3] Lau JL, Dunn MK. Therapeutic peptides: Historical perspectives, current development trends, and future directions. Bioorganic & medicinal chemistry. 2018 Jun 1; 26(10): 2700-7.

[4] Faisal M, Saquib Q, Alatar AA, Al-Khedhairy AA, Hegazy AK, Musarrat J. Phytotoxic hazards of NiO-nanoparticles in tomato: a study on mechanism of cell death. Journal of hazardous materials. 2013 Apr 15; 250: 318-32.

[5] Jambukiya VV, Parmar RB, Dudhrejiya AV, Tank HM, Limbachiya VD. Enhancement of Solubility and Dissolution Rate of Poorly Water Soluble Drug by Using Modified Guar Gum. Asian J Pharm Technol. 2013 Mar 28; 3(1): 25-30.

[6] Godse SZ, Mohini S, Patil SM, Saudagar RB. Techniques for solubility enhancement of Hydrophobic drugs: A Review. Journal of Advanced Pharmacy Education & Research Oct-Dec. 2013; 3(4).

[7] Jadhav SB, Singhal RS. Pullulan-complexed α-amylase and glucosidase in alginate beads: Enhanced entrapment and stability. Carbohydrate polymers. 2014 May 25; 105: 49-56.

[8] Patil MS, Godse SG, Saudagar RB. Solubility enhancement by various techniques: An overview. World journal of pharmacy and pharmaceutical sciences. 2013; 2(6): 4558-72.

[9] Bothiraja C, Pawar AP, Dama GY, Joshi PP, Shaikh KS. Novel solvent-free gelucire extract of

Plumbago zeylanica using non-everted rat intestinal sac method for improved therapeutic efficacy of plumbagin. Journal of pharmacological and toxicological methods. 2012 Jul 1; 66(1): 35-42.

[10] Shrestha S, Pokhrel S, Sharma S, Manandhar M, Alam I. Formulation and evaluation of topical microemulgel loaded with terbinafine HCl microemulsion. Int J Pharm Sci Res. 2017 Nov 1; 8(11): 4716-23.

[11] Kumaresh S. Soppimath, Tejraj M. Aminabhavi, Anandrao E. Kulkarni, Walter E. Eudzinski,"Biodegradable polymeric nanoparticles as drug delivery devices", J. of Controlled Release.

[12] Shokri N, Javar HA, Fouladdel SH, Khalaj A, Khoshayand MR, Dinarvand R, Atyabi F, Nomani A, Azizi E. Preparation and evaluation of poly (caprolactone fumarate) nanoparticles containing doxorubicin HCI. Daru: journal of Faculty of Pharmacy, Tehran University of Medical Sciences. 2011; 19(1): 12.

[13] Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nano-Enabled Medical Applications. 2020 Nov 23: 61-91.

[14] Venugopal KN, Abhilash M. Study of hydration kinetics and rheological behaviour of guar gum. International Journal of Pharma Sciences and Research. 2010; 1(1): 28-39.

[15] Gaur U, Sahoo SK, De Tapas K, Ghosh PC, Maitra A, Ghosh PK. Biodistribution of fluoresceinated dextran using novel nanoparticles evading reticuloendothelial system. International journal of pharmaceutics. 2000 Jul 20; 202(1-2): 1-0.

[16] Nagavarma BV, Yadav HK, Ayaz AV, Vasudha LS, Shivakumar HG. Different techniques for preparation of polymeric nanoparticles-a review. Asian J Pharm Clin Res. 2012 Jun; 5(3): 16-23.

[17] Lippacher A, Müller RH, Mäder K. Preparation of semisolid drug carriers for topical application based on solid lipid nanoparticles. International journal of pharmaceutics. 2001 Feb 19; 214(1-2): 9-12.

[18] Kumar V, Guleria P, Kumar V, Yadav SK. Gold nanoparticle exposure induces growth and yield

enhancement in Arabidopsis thaliana. Science of the total environment. 2013 Sep 1; 461: 462-8.

[19] Jyoti K, Malik G, Chaudhary M, Sharma M, Goswami M, Katare OP, Singh SB, Madan J. Chitosan and phospholipid assisted topical fusidic acid drug delivery in burn wound: strategies to conquer pharmaceutical and clinical challenges, opportunities and future panorama. International Journal of Biological Macromolecules. 2020 May 30.

[20] Mohanpuria P, Rana NK, Yadav SK. Biosynthesis of nanoparticles: technological concepts and future applications. Journal of nanoparticle research. 2008 Mar; 10(3): 507-17.