2. LITERATURE REVIEW

- **Rahul Nair et al (2011)** formulated and characterized solid lipid nanoparticles (SLN) of hydrophilic drug Isoniazid (INH), a first line antituberculosis drug. SLN were formulated, which led to high drug entrapment efficiency. The drug solubility in the dispersion medium proved to be a crucial actor in the formulation of the SLN and enhancing the entrapment efficiency. Thus SLN can prove to be another appropriate method of drug delivery for delivering Isoniazid.\(^{[81]}\)

- **Sanjay Singh A et al (2010)** formulated solid lipid nanoparticle (SLN) of a hydrophilic drug, Zidovudine with an aim to improve the entrapment efficiency of the drug. Stearic acid was selected as the lipid and the SLN were formulated according to \(3^2\) factorial designs. w/o/w was selected as the method of formulating SLN. This work demonstrates the conceivable point of interest of unsaturated fats over triglycerides in the entrapment of hydrophilic drugs in SLN.\(^{[82]}\)

- **Kaushik M et al (2012)** formulated acelofenac SLN by solvent evaporation technique. This formulation was carried out with a view of improving the solubility of Acelofenac. Impact of the process parameters, for example, particle size; entrapment efficiency and drug release from SLN were examined. FT-IR spectra studies confirmed that there was no interaction of lipid and excipients with drug.\(^{[83]}\)

- **Soheila Kheradmandnia et al (2010)** developed strong lipid nanoparticle (SLN) that have been proposed as suitable colloidal carriers for conveyance of medications with restricted solubility Ketoprofen was selected as the model drug was formulated into SLNs prepared from a mixture of beeswax and carnauba wax using Tween 80 and egg lecithin as emulsifiers. Differential scanning calorimetry thermograms and high-performance liquid chromatographic analysis indicated the stability of nanoparticles with negligible drug leakage after 45 days of storage. It was also found that nanoparticles with more beeswax content in their core exhibited faster drug release as compared with those containing more carnauba wax in their structure.\(^{[84]}\)

- **Zhiwen Zhang et al (2012)** investigated Candesartan Cilexetil loaded solid lipid nanoparticles (CLN) were successfully developed to improve the oral bioavailability.
The pharmacokinetic results indicated that the oral bioavailability of Candesartan was obviously improved over 12-fold after incorporation into solid lipid nanoparticles. These results demonstrated that solid lipid nanoparticles have great potential for increasing oral bioavailability of lipophilic drugs such as CC.\(^{[85]}\)

- **I. Sarathchandiran et al. (2012)** presented a comprehensive review on Solid Lipid Nanoparticles & different preparation methods of SLN, Nanostructure lipid carriers, lipid drug conjugates, route of administration and applications. For each of these, the underlying scientific concepts, potential enabling technologies, and current limitations to the realization of nanotechnology applications were discussed.\(^{[86]}\)

- **Vishvajit A. Kamble et al (2010)** presented a comprehensive review on Solid Lipid Nanoparticles (SLN) as an alternative drug delivery system to colloidal drug delivery systems such as liposome, lipid emulsions. SLN are rapidly developing nanotechnology with several applications in drug delivery system, clinical medicine and other science. In this article the preparation method, characterization, route of administration of SLN, advantages, different preparation method that are suitable for large-scale production and application of SLN were discussed. Analytical techniques for characterization of SLN like photon correlation spectroscopy, scanning electron microscopy, different scanning calorimetry were also highlighted.\(^{[87]}\)

- **Umaretiya Ghanshyam et al. (2011)** formulated Solid lipid nanoparticles (SLN) were utilized for the release of Triamcinolone Acetonide (TAA) via respiratory tract for the delivery of the drug to the lung for treatment of allergic rhinitis, an excellent alternative to their per oral application, because the dose and the incidence of local and systemic side effects can be reduced. Results show a high encapsulation of the drug. The prepared formulation was also stable.\(^{[88]}\)

- **Jain Pushpendra et al. (2009)** prepared nimesulide Solid Lipid Nanoparticles (NIM-SLN), to formulate the controlled drug release and to evaluate its physiochemical characteristics. NIM-SLN were prepared by an emulsification and low-temperature solidification method. In this study an attempt was made to study the effect of individual process parameters (stirring speed and stirring time) and formulation parameters
(Lecithin concentration, drug concentration and surfactant concentration) on entrapment efficiency. [89]

- **Vandita Kakkar et al. (2012)** formulated SLN of curcumin as it showed to have low bioavailability. The results obtained showed that SLN with their improved bioavailability and permeability possess higher anti-depressant potential upon administration of a single and a much lower dose when compared to free curcumin.[90]

- **Ashay Jain et al. (2010)** formulated solid lipid nanoparticles (SLN) loaded with an anti-cancer drug doxorubicin HCl (DOX). DOX encapsulated SLN were prepared, characterized, and further mannosylated. It was concluded that the mannosylated SLN are capable to ferry bioactive selectively and specifically to the tumor sites with the interception of minimal side effects, thereby suggesting their potential application in cancer chemotherapy.[91]

- **Vobalaboina Venkateswarlu et al. (2004)** developed Solid Lipid Nanoparticles (SLN) delivery systems of Clozapine using various triglycerides (trimyristin, tripalmitin, and tristearin), soylecithin 95%, and poloxamer 188, and charge modifier stearylamine. More than 90% clozapine was entrapped in SLN. DSC and XRD analysis showed that clozapine was dispersed in SLN in an amorphous state. The release pattern of drug was analyzed and found to follow Higuchi equation.[92]

- **R.H. Muller et al (2008)** formulated Solid Lipid Nanoparticles (SLN) loaded with cyclosporine A in order to develop an improved oral formulation. It was concluded that cyclosporine was molecularly dispersed in between the fatty acid chains of the liquid-crystalline a-modification fraction of the loaded SLN.[93]

- **C. Schwarz et al (1997)** studied the protective effect of various types and concentrations of cryoprotectants (e.g. carbohydrates) freeze-thaw cycles were carried out as a pre-test. The sugar trehalose proved to be most effective in preventing particle growth during freezing and thawing and in the freeze-drying process. Changes in particle size distribution during lyophilisation could be minimized by optimizing the parameters of the lyophilisation process, i.e. freezing velocity and redispersion method. Lyophilized drug-free SLN could be reconstituted in a quality considered suitable for i.v. injection.
with regard to the size distribution. Loading with model drugs (tetracaine, etomidate) impairs the quality of reconstituted SLN. However, the lyophilisate quality is sufficient for formulations less critical to limited particle growth, e.g. freeze-dried SLN for oral administration.\textsuperscript{[94]}

- **Shuyu Xie at al. (2011)** formulated Ofloxacin-loaded SLN palmitic acid as lipid matrix and poly vinyl alcohol (PVA) as emulsifier by a hot homogenization and ultrasonication method. The physicochemical characteristics of SLN were investigated by optical microscope, Scanning Electron Microscopy, and Photon Correlation Spectroscopy. Pharmacokinetics was studied after oral administration in mice. The SLN showed sustained release and enhanced antibacterial activity in vitro. Pharmacokinetic results demonstrated that SLN increased the bioavailability of Ofloxacin. Ofloxacin was successfully incorporated into palmitic acid- SLN by a hot homogenization and ultrasonication method. SLN had a sustained-release effect and enhanced antibacterial activity.\textsuperscript{[95]}

- **Chakrapani M et al (2012)** developed Mefenamic Acid (MFA) loaded solid lipid nanoparticles (SLN). Using hydrogenated castor oil as natural lipid as it was low cost alternative to the commercial lipids used for SLN production. MFA loaded SLN were prepared by modified solvent injection method and characterized for shape, surface morphology, particle size, and drug entrapment. The drug release kinetics was analyzed for the prepared formulations and the best fitting model was ascertained. It was concluded that SLN with small particle size and controlled release for MFA from SLNs using natural lipids can be obtained by this method.\textsuperscript{[96]}

- **Soo-Jeong Lim et al (2002)** studied the poor aqueous solubility of all-trans retinoic acid (ATRA) has been a limiting factor in its clinical use. This study was undertaken to overcome the solubility limitation of ATRA by loading in SLN. The physicochemical characteristics of ATRA-loaded SLNs were investigated by particle size analysis, zeta potential measurement, thermal analysis and HPLC determination of ATRA content. No significant change was observed in the SLN-loaded concentration of ATRA and the zeta potential of SLN after freeze-drying. Taken together, SLN formulation of ATRA with similar characteristics to those of parenteral emulsions could be obtained even after freeze-drying.\textsuperscript{[97]}
Robhash Kusam Subedi et al. (2009) formulated Solid Lipid Nanoparticles (SLN) loaded with doxorubicin by solvent emulsification-diffusion method. Cell viability assay showed that properties of SLN remain unchanged during the process of freeze-drying. Stability study revealed that lyophilized SLN were equally effective (p < 0.05) after 1 year of storage at 4 °C. In conclusion, SLN with small particle size, high EE, and relatively high DL for doxorubicin can be obtained by this method.\[98\\]

Annette zur Muhlen et al (1998) developed Solid Lipid Nanoparticles (SLN) for parenteral drug administration with mean particle diameters ranging from 50 up to 1000 nm. The model drugs tetracaine, etomidate and prednisolone were incorporated (1, 5 and 10%) to study the drug load, effect of drug incorporation on the structure of the lipid matrix and the release profiles and mechanism. The results demonstrate the principle suitability of SLN as a prolonged release formulation for lipophilic drugs\[99\\]

Jameel Ahmed Mulla et al. (2009) investigated Solid Lipid Nanoparticle (SLN) of methotrexate produced by microemulsion method in an acidic aqueous system. The SLN were composed of low melting fatty acid (Glyceryl monostearate), surfactants (Egg lecithin and tween 80) and water. All the formulations were subjected to particle size analysis, zeta potential, drug entrapment efficiency and in vitro release studies. The SLN formed were in nanosize range with maximum entrapment efficiency. Formulation with 253 nm in particle size and 85.12% of drug entrapment was subjected to scanning electron microscopy (SEM) for surface morphology, differential scanning calorimetry (DSC) for thermal analysis and short term stability studies. SEM confirms that the SLNs are circular in shape. The drug release behavior from SLN suspension exhibited biphasic pattern with an initial burst and prolonged release over 24 h.\[100\\]

Volkhard Jenning et al. (2000) evaluated the potential use of solid lipid nanoparticles (SLN) in dermatology and cosmetics, Glyceryl behenate SLN loaded with vitamin A (retinol and retinyl palmitate) and incorporated in a hydrogel and o/w cream were tested with respect to their influence on drug penetration into porcine skin.\[101\\]

Elena Ugazio et al. (2002) studied the cyclic undecapeptide cyclosporine A (CyA) a potent immunosuppressive drug used in many therapies, is extremely hydrophobic.
Commercial products employ solubilising agents to improve gastrointestinal absorption. CyA Solid Lipid Nanoparticles (SLN) were prepared from warm o/w microemulsion, dispersed in cold water. The matrix chiefly consisted of stearic acid, phosphatidylcholine and taurocholate; up to 13% of CyA can be incorporated. The average diameter of CyA-loaded SLN is below 300 nm and transmission electron microscopy (TEM) analysis showed them to be spherical. In vitro release of CyA from SLNs is low. CyA-loaded SLN can be proposed for most administration routes, in particular for the duodenal route.\textsuperscript{[102]}

- Jian You et al. (2007) investigated hydrophilic and temperature-induced degradation drug, Vinorelbine Bitartrate (VB)-loaded Solid Lipid Nanoparticles (SLN) prepared by a cold homogenization technique. The physicochemical properties of the SLN, with various lipid compositions, drug content and altered homogenizing times, were investigated. The physical stability experiment indicated that the SLN were stable for 2 months under room temperature. Moreover, the cellular cytotoxicity of VB against MCF-7 cells could be improved by the entrapment of SLN.\textsuperscript{[103]}

- Guihua Huang et al. (2008) formulated temozolomide loaded solid lipid nanoparticles (TMZ-SLN), to evaluate its physiochemical characteristics, and to investigate the specific drug targeting of intravenous (i.v.) injected solid lipid nanoparticles of temozolomide. TMZ-SLN were prepared by an emulsification and low-temperature solidification method. The AUC ratio of TMZ-SLN to TMZ-Sol in the brain was the highest among the organs. These results indicated that the SLN is a promising sustained-release and drug-targeting system for antitumor drugs. It may also allow a reduction in dosage and a decrease in systemic toxicity.\textsuperscript{[104]}

- Jie Liu et al. (2008) studied novel nebulizer-compatible solid lipid nanoparticles (SLNs) for pulmonary drug delivery of insulin were developed by reverse micelle-double emulsion method. The influences of the amount of sodium cholate (SC) and soybean phosphatidylcholine (SPC) on the deposition properties of the nanoparticles were investigated. A pharmacological bioavailability of 24.33% and a relative bioavailability of 22.33% were obtained using subcutaneous injection as a reference. Incorporating fluorescent-labelled insulin into SLNs, we found that the SLNs were effectively and homogeneously distributed in the lung alveoli. These findings suggested that SLNs could
be used as a potential carrier for pulmonary delivery of insulin by improving both in vitro and in vivo stability as well as prolonging hypoglycemic effect, which inevitably resulted in enhanced bioavailability.[35]

➢ **Sagar Mandawgade et al. (2008)** developed solid lipid nanoparticles (SLNs) from indigenous, natural solid lipids by using a simple microemulsion technique. Furthermore, the aim was to characterize these SLNs and evaluate its potential in the topical delivery of a lipophilic drug, tretinoin (TRN). TRN-loaded SLN-based topical gels were formulated and the gels were evaluated comparatively with the commercial product with respect to primary skin irritation, in vitro occlusivity and skin permeation. The results of the study showed mean particle size <100nm of the SLN dispersions with the novel lipids. The research work could be concluded as successful production of SLNs using highly purified stearine fraction of natural solid lipids. The results of the characterization and evaluation established the safety for use, suitability and compatibility of indigenous natural lipids as a novel excipient.[105]

➢ **Qingzhi LV et al. (2009)** formulated penciclovir SLN for topical drug delivery. The technique used in the formulation of the SLN was double (W/O/W) emulsion technique. The SLNs presented spherical with the mean diameter of 254.9 nm. The entrapment efficiency, drug loading, and zeta potential were 92.40%, 4.62%, and −25.0 mV, respectively. The cumulative amount of penciclovir penetrated through excised rat skin from SLNs was more than 2-fold that of the commercial cream as a control at 12 h after administration. It was concluded from study that SLNs may be a promising carrier for topical delivery of Penciclovir.[106]

➢ **Maryam Ghadiri et al. (2012)** studied Solid Lipid Nanoparticles (SLN) which was a very well tolerated carrier system for dermal application due to the employment of physiological and/or biodegradable lipids. The effects of five factors, two categorical and three quantitative factors, were studied on the mean diameter and entrapment efficiency of the produced SLNs using Response Surface Method (RSM), D-optimal design. Two methods of microemulsion and solvent diffusion and two types of lipid, cetyl palmitate and stearic acid, were examined comparatively. The quantitative variables were studied in three levels; amount of original Paromomycin (60, 90 and 120 mg), fraction of surfactant (0.5, 0.75 and 1 w/v %) and drug to lipid ratio (2, 4 and 6). Mean particle size
and entrapment efficiency of the loaded Paromomycin were modeled statistically and the optimal condition was determined to approach to the maximum entrapment efficiency. The drug release profile of the optimal formulated material was examined in aqueous media and 64% of the Paromomycin loaded in SLN was gradually released during 24 h, which reveals efficient prolonged release of the drug.⁹⁷

Shailesh Chalikwar et al. (2012) developed Nimodipine loaded Solid Lipid Nanoparticles to increase oral bioavailability and to target intestinal lymphatic transport system. NMD-SLN were prepared with Palmitic Acid (PA), Poloxamer 188 and soya lecithin as a lipid, surfactant and co-surfactant respectively using high pressure homogenizer. A 2³ factorial design was employed; three factors such as lipid, surfactant and co-surfactant concentration were included. The pharmacokinetic study of optimized SLNs conducted in male Albino Wister rats showed 2.08-fold increase in relative bioavailability than that of NMD solution, when administered orally. Differential scanning calorimetry study revealed absence of any chemical interaction between NMD and PA while SEM study confirmed the non spherical shape of optimized SLNs. Accelerated stability studies showed that there was no significant change in the mean particle size and PDI after storage at 25 ± 2°C/60 ± 5% RH for the period of three months. Due to enhanced bioavailability, these NMD-SLN are considered to be promising vehicles for oral delivery.⁹⁸

Song-hong Zhang et al. (2008) developed a new method for producing Solid Lipid Nanoparticles (SLN) with small sizes (mean diameter less than 250 nm) and relatively narrow size distribution (polydispersity less than 0.26). The preparation process was conducted in a co-flowing micro channel assembled with inner and outer capillaries. A lipid-solvent phase was injected into the inner capillary, while an aqueous phase with surfactant was injected into the outer capillary. Softisan 100 (triglyceride mixture of fatty acids with chain lengths of C10 to C18) was used as the test lipid and SLNs were prepared in the present micro channel system under various operation conditions. The results showed that the diameter of the SLN decreased with the increases of the aqueous phase velocity and the lipid concentration, while increased slightly with the increases of the surfactant concentration and the lipid-solvent velocity under the test conditions.⁹⁹
Rajesh Pandey et al. (2005) studied the chemotherapeutic potential of oral solid lipid nanoparticles (SLN) incorporating rifampicin, isoniazid and pyrazinamide against experimental tuberculosis. The SLN were prepared by the “emulsion solvent diffusion” technique with high encapsulation efficiencies. Following a single oral administration to mice, therapeutic drug concentrations were maintained in the plasma for 8 days and in the organs (lungs, liver, and spleen) for 10 days whereas free drugs were cleared by 1–2 days. In M. tuberculosis, H37Rv infected mice, no tubercle bacilli could be detected in the lungs/spleen after 5 oral doses of drug loaded SLNs administered at every 10th day whereas 46 daily doses of oral free drugs were required to obtain an equivalent therapeutic benefit. Thus, SLN based ant tubercular drug therapy forms a sound basis for reducing dosing frequency and improving patient compliance for better management of tuberculosis.\textsuperscript{[110]}

P. Ekambaram et al. (2012) presented a comprehensive review on SLN for drug delivery. This review discussed a broad treatment of solid lipid nanoparticles discussing their aims, production procedures, advantages, limitations, and their possible remedies. Appropriate analytical techniques for the characterization of SLN like photon correlation spectroscopy, scanning electron microscopy, differential scanning calorimetry were highlighted. Aspects of SLN route of administration and the in vivo fate of the carriers were also discussed.\textsuperscript{[111]}

Rohit Bhandari et al. (2013) formulated Isoniazid-solid lipid nanoparticles (SLN) to achieve improved bioavailability and prolonged effect, thus minimizing pulsatile plasma concentrations (and associated side effects at peak plasma concentrations). Developed SLN showed high entrapment efficiency (69\%) and small size such that they are expected to bypass Reticulo-Endothelial System (RES) pickup resulting in prolonged circulation times and since liver is the major site of metabolism of isoniazid, RES avoidance will reduce its elimination from the body. Single dose (25 mg/kg BW) oral pharmacokinetic studies were performed in plasma and various tissues of rats. A significant improvement in relative bioavailability in plasma (6 times) and brain (4 times) was observed after administration of isoniazid-SLN with respect to the free drug solution at the same dose.\textsuperscript{[112]}
Waree Tiyaboonchai et al. (2007) formulated curcuminoids loaded solid lipid nanoparticles (SLN) using a microemulsion technique at 75°C. It was found that variation in the amount of ingredients had profound effects on the curcuminoids loading capacity, the mean particle size, and size distribution. At optimized process conditions, lyophilized curcuminoids loaded SLN showed spherical particles with a mean particle size of 450 nm and a polydispersity index of 0.4. Up to 70% (w/w), curcuminoids incorporation efficacy was achieved. In vitro release studies showed a prolonged release of the curcuminoids from the solid lipid nanoparticles up to 12 h following the Higuchi’s square root model.\cite{113}

Hashem Heiati et al. (1998) formulated solid lipid nanoparticles (SLN) were prepared using trilaurin as the SLN solid core and a mixture of neutral and negatively charged phospholipid. To produce SLN with a polyethylene glycol (PEG) coating PEG was incorporated in SLN using dipalmitoylphosphatidyl-ethanolamine-N-[poly(ethylene glycol)2000] (PE-PEG). 3-azido-3-deoxythymydine palmitate (AZT-P) with [3H]-AZT-P as tracer were synthesized and incorporated in SLN. Their subsequent retention in SLN with and without PEG was determined after incubation in 50% bovine plasma. Biodistribution studies were performed in mice using free AZT-P, AZT-P incorporated in SLN or AZT-P incorporated in PE-PEG coated SLN (SLN-PE-PEG). The presence of PE-PEG significantly reduced the SLN zeta potential from -22 to -5 mV. The results obtained in this study indicate that using SLNs as a drug carrier increases the bioavailability of incorporated AZT-P, and that the pharmacokinetic behavior of the incorporated drug can be modified by changing the surface characteristics of SLN by using the amphiphilic solvation enhancer PE-PEG. \cite{114}

Melike Uner et al. (2007) was investigated a solid lipid nanoparticles (SLN) that have been reported to be an alternative system to emulsions, liposome, microparticles and their polymeric counterparts for various application routes since the early 1990s due to their advantages. Various research groups have also increasingly focused on improving their stability in body fluids after administration by coating of particles with hydrophilic molecules such as polyethylene glycol (PEG) derivatives. Altering surface characteristics by coating SLN with hydrophilic molecules improves plasma stability and biodistribution, and subsequent bioavailability of drugs entrapped. Their storage stability is also increased. This paper reviews types of SLN, principles of drug loading and
models of drug incorporation. The influence of PEG coating on particle size and surface characteristics discussed followed by alteration in pharmacokinetics and bioavailability of drugs in order to target the site of action via SLN.[115]

**Qingzhi Lv et al. (2009)** developed solid lipid nanoparticles (SLN) of penciclovir and evaluate the potential of SLN as the carrier of penciclovir for topical delivery. Penciclovir-loaded SLN prepared by a double (W/O/W) emulsion technique. The SLN presented spherical with the mean diameter of 254.9 nm. The entrapment efficiency, drug loading, and zeta potential were 92.40%, 4.62%, and −25.0 mV, respectively. The cumulative amount of penciclovir penetrated through excised rat skin from SLNs was more than 2-fold that of the commercial cream as a control at 12 h after administration. It was be concluded from the study that SLN provide a good skin targeting effect and may be a promising carrier for topical delivery of penciclovir. [116]

**Zhenghong Xu et al. (2009)** developed new docetaxel-loaded hepatoma-targeted solid lipid nanoparticle (tSLN) designed and prepared with galactosylated dioleoylphosphatidyl ethanolamine. The cellular cytotoxicity, cellular uptake, sub cellular localization, in vivo toxicity, therapeutic effect, bio-distribution, and histology of tSLNs were investigated. The tSLN showed the particle size about 120 nm with encapsulation efficiency >90%, a low burst effect within the first day and a sustained release for the next 29 days in vitro. Cytotoxicity of tSLN against hepatocellular carcinoma cell line BEL7402 was superior to Taxotere and non-targeted SLN (nSLN). The tSLN also showed better tolerant and antitumor efficacy in murine model bearing hepatoma compared with Taxotere or nSLN. The studies on cellular uptake and biodistribution indicated that the better antitumor efficacy of tSLN was attributed to both the increased accumulation of drug in tumor and more cellular uptake by hepatoma cells. The histology demonstrated that tSLN had no detrimental effect on both healthy liver and liver with fibrosis. These results implied that this targeted nanocarrier of docetaxel could enhance its antitumor effect in vivo with low systemic toxicity for the treatment of locally advanced and metastatic HCC.[117]

**S. Tamizhrasi et al (2009)** prepared and evaluated polymethacrylic acid nanoparticles containing lamivudine in different drug to polymer ratio by nanoprecipitation method.SEM indicated that nanoparticles had a discrete spherical structure without
aggregation. The average particle size was found to be $121 \pm 8 \text{ - } 403 \pm 4 \text{ nm}$. The particle size of the nanoparticles was gradually increased with increase in the proportion of polymethacrylic acid polymer. It was found that drug content of the nanoparticles was increasing on increasing polymer concentration up to a particular concentration. FT-IR studies indicated that there was no chemical interaction between drug and polymer and stability of drug. The in-vitro release behaviour from all the drug loaded batches was found to be zero order and provided sustained release over a period of 24 h. The developed formulation overcame and alleviates the drawbacks and limitations of lamivudine sustained release formulations and could possibility be advantageous in terms of increased bioavailability of lamivudine.$^{[118]}$

- **Rajat Sharma et al (2011)** formulated and evaluated PSA-PEG nanoparticles containing paclitaxel as a model drug by nanoprecipitation method. The influence of different experimental parameters on the particles size, entrapment efficiency, percent drug released etc was evaluated. SEM indicated that nanoparticles have discrete spherical structure without aggregation. The average particle size was found to be $123 \text{ - } 405 \text{ nm}$. The particle size of nanoparticles increases gradually with PSA-PEG polymer concentration. The drug content of nanoparticles also increases with increasing polymer concentration up to particular value. The in-vitro drug release behavior from all drug loaded batches was found to be zero order and provided sustained release over a period of 24 hours.$^{[119]}$

- **S. Debnath et al (2010)** formulated and studied Cytarabine loaded nanoparticles which were prepared by ionotropic gelation. This was done to protect cytarabine from fast degradation and elimination. These were characterized by SEM and the particle size was found to in the range of $200 \text{ nm}$. The mechanism by which drug is being released was found to be non-Fickian (anomalous) solute diffusion mechanism. The in vivo biodistribution study results showed that the nanoparticles were having better distribution of drug compared to free drug in different organs like spleen, lungs, kidney etc.$^{[120]}$

- **M. Sivabalan et al (2011)** formulated and evaluated chitosan and Eudragit nanoparticles of 5- Fluorouracil for cancer therapy. Nanoparticles of 5- Fluorouracil were prepared
using chitosan, Eudragit S 100, liquid paraffin and Tween -20 using Emulsion droplet coalescence method. The nanoparticles prepared were evaluated for morphology, loading efficiency, invitro release and invitro anticancer activities. The particle shape and morphology of the prepared 5-Fluorouracil nanoparticles were determined by SEM analysis. The amount of 5-Fluorouracil entrapment in the nanoparticles was calculated by the difference between the total amount of drug added to the nanoparticle and the amount of non entrapped drug remaining in the aqueous supernatant. A franz diffusion cell was used to monitor 5-Fluorouracil release from the nanoparticles. In-vitro anticancer study revealed that the formulated nanoparticles were found to have good cidal activity on cancer cells in sustained manner.[121]

Partha Saha et al (2010) prepared ampicillin trihydrate loaded chitosan nanoparticles by ionic gelation method with the aid of sonication. Parameters such as the zeta potential, polydispersity, particle size, entrapment efficiency and in vitro drug release of the nanoparticles were assessed for optimization. The antibacterial properties of the nanoparticle formulation were evaluated and compared with that of a commercial formulation. Scanning Electron Microscopy revealed that the nanoparticles were in the nanosize range but irregular in shape. Concentrations of 0.35 %w/v of chitosan and 0.40 %w/v sodium tripolyphosphate (TPP) and a sonication time of 20 min constituted the optimum conditions for the preparation of the nanoparticles. In vitro release data showed an initial burst followed by slow sustained drug release. The nanoparticles demonstrated superior antimicrobial activity to plain nanoparticles and the reference, due probably to the synergistic effect of chitosan and ampicillin trihydrate. Thus it was concluded that modified ionic gelation method can be utilized for the development of chitosan nanoparticles of ampicillin trihydrate. Polymer and crosslinking agent concentrations and sonication time were identified as rate-limiting factors for the development of the optimized formulation.[122]

J. Adlin Jino Nesalina et al (2012) formulated zidovudine loaded nanoparticles by ionic gelation of chitosan with tripolyphosphate anions (TPP). Nanoparticles of different core: coat ratio were formulated and evaluated for process yield, loading efficiency, particle size, zeta potential, in vitro drug release, kinetic studies and stability studies. The chitosan nanoparticles had a particle diameter ranging approximately 342–468 nm and a zeta potential 20.4 to 37.08 mV. There was a steady increase in the entrapment
efficiency on increasing the polymer concentration in the formulations. The in vitro release behaviour from all the drug loaded batches were found to follow first order and provided sustained release over a period of 24 h.\textsuperscript{123}

- **Fabienne Danhier et al (2009)** developed Cremophor EL free nanoparticles loaded with Paclitaxel (PTX), intended to be intravenously administered. The main rationale behind this formulation was to improve the therapeutic index of the drug and devoid of the adverse effects of Cremophor EL. PTX-loaded PEGylated PLGA-based nanoparticles was prepared by simple emulsion and nanoprecipitation. The incorporation efficiency of PTX was higher with the nanoprecipitation technique. The release behavior of PTX exhibited a biphasic pattern characterized by an initial burst release followed by a slower and continuous release. From the work it was concluded that PTX-loaded nanoparticles are an effective anticancer drug delivery system for cancer chemotherapy.\textsuperscript{124}

- **Abhishek Garg et al (2011)** have presented a review about nanoparticles in which they have discussed about various methods of preparation, their characterization techniques, such as drug loading, release and the applications of Nanoparticles along with some marketed products.\textsuperscript{29}

- **Mahesh D. Chavanpatil et al (2007)** developed a novel polymer-surfactant nanoparticle formulation, using the anionic surfactant Aerosol OTTM (AOT) and polysaccharide polymer alginate, for sustained release of water-soluble drugs. Particle size of nanoparticles, as determined by atomic force microscopy and transmission electron microscopy, was in the range of 40–70 nm. Weakly basic molecules like methylene blue, doxorubicin, rhodamine, verapamil, and clonidine could be encapsulated efficiently in AOT-alginate nanoparticles. In vitro release studies with basic drug molecules indicated that nanoparticles released 60–70% of the encapsulated drug over 4 weeks, with near zero-order release during the first 15 days. Studies with anionic drug molecules demonstrated poorer drug encapsulation efficiency and more rapid drug release than those observed with basic drugs.\textsuperscript{125}

- **Rubiana Mara Mainardesa et al (2010)** described the preparation and evaluation of biodegradable poly(l-lactide) (PLA) and poly(IIactide– poly(ethylene glycol) (PLA–PEG) blend nanoparticles in their research work. Zidovudine was selected as the model
drug. The prepared nanoparticles were characterized in terms of size, zeta potential, morphology and drug entrapment efficiency. The pharmacokinetics of Zidovudine following intranasal administration in mice was assessed. The results showed that although PLA and blend nanoparticles had the same morphology, the particle size and zeta potential were changed by the PEG. The drug entrapment efficiency was increased by PEG presence. The pharmacokinetic study showed that all the nanoparticles were able to sustain zidovudine delivery over time, but greater efficiency was obtained with PLA–PEG blend nanoparticles, whose $T_{\text{max}}$ was twice that of PLA nanoparticles.$^{[126]}$

- **Bhaskar Chauhan SS et al (2004)** formulated floating risedronate sodium Gelucire 39/01 matrices were formulated based on the rationale that incorporation of bisphosphonates in the lipid reduces gastric irritation. Only gastric retention with sustained release allows the drug to reach the duodenum and jejunum and improves the availability of bisphosphonates. The sustained release floating matrices were evaluated for in vitro and in vivo floating ability and in vitro drug release which showed a marked increase in the bioavailability.$^{[127]}$

- **Lakshmi Sirisha Kotikalapudi LA et al (2012)** formulated Domperidone loaded SLN (DOM-SLN) were prepared by hot homogenization followed by ultrasonication technique. DOM- SLN were characterized for particle size, polydispersity index (PDI), zeta potential and entrapment efficiency and invitro drug release behaviour was investigated. P-XRD and DSC analysis was performed to characterize the state of drug and lipid modification. Shape and surface morphology were determined by transmission electron microscopy (TEM). SLN formulations were subjected to stability study over a period of 30 days. P-XRD and DSC studies revealed that DOM was in an amorphous state. Shape and surface morphology was determined by TEM revealed fairly spherical shape of nanoparticles. In vitro release studies demonstrated that the SLN formulation possessed a controlled release over a period of 48 hrs. SLN formulations were subjected to stability over a period of 30 days. Thus it was concluded that fairly spherical shaped, stable and controlled release DOM-SLN could be prepared by hot homogenization followed by ultrasonication technique.$^{[128]}$

- **Rubiana M. Mainardes et al (2005)** designed Spherical nanoparticulate drug carriers made of poly(d,l-lactide-co-glycolide) acid with controlled size. Praziquantel, a
hydrophobic molecule, was selected as the model drug. This was entrapped into the nanoparticles with theoretical loading varying from 10 to 30% (w/w). The study investigated the effects of some process variables on the size distribution of nanoparticles prepared by emulsion–solvent evaporation method. The results showed that sonication time, PLGA and drug amounts, PVA concentration, ratio between aqueous and organic phases, and the method of solvent evaporation have a significant influence on size distribution of the nanoparticles.[129]

- **Umland E et al (2001)** published a review review on biphosphonates which reported these classes of drugs to be effective in the treatment of osteoporosis and Paget's disease of bone. Risedronate is approved by the US Food and Drug Administration for the prevention and treatment of postmenopausal osteoporosis and glucocorticoid-induced osteoporosis.[130]

- **Dissette V et al (2010)** formulated adducts based on a bisphosphonate drug and titanium dioxide (TiO$_2$) in order to improve the bioavailability of the particular class of drug. The work further demonstrated the effectiveness and enhancement of bioavailability of biphosphonates in male wistar rats.[131]

- **Perkins A.C et al (1999)** formulated a novel cellulose film-coated tablet of biphosphonate and the esophageal transit of this bisphosphonate was optimized. The esophageal transit of the film-coated tablet formulation of biphosphonate was compared with its original gelatin capsule dose form. The mean transit times of the capsules and tablets were 23.8 and 3.3 s, respectively. Esophageal transit of film-coated tablets was faster than gelatin capsules, suggesting that film-coated tablets would be the appropriate formulation for all pivotal trials and for subsequent commercialization.[132]

- **Ohtori S AT et al (2010)** performed clinical study on risedronate, an oral biphosphonate which demonstrated decreased bone resorption and improvement in low back pain in postmenopausal osteoporosis patients without vertebral fractures. This study assessed patients by dual-energy X-ray absorptiometry before and after administration of biphosphonates. This study showed the effectiveness of biphosphonates in treatment of osteoporosis.[133]
> **Francis RM (2010)** published a review of bisphosphonates which highlights the use of bisphosphonates in the treatment of osteoporosis. Additionally, this study highlights the advantages of bisphosphonates over hormone replacement therapy. Thus in brief, this paper reviews the evidence that bisphosphonates increase bone mass with no deleterious effects on the biomechanical properties of the bone, thus decreasing the rate of vertebral fracture in patients with osteoporosis.\(^{[134]}\)

> **Borah B DT et al (2004)** demonstrated the effectiveness of Risedronate, an oral bisphosphonate in the preservation of bone architecture in women with post-menopausal osteoporosis as measured by three-dimensional microcomputed tomography. The effect of the reduction of turnover with risedronate on trabecular architecture in postmenopausal women with osteoporosis was investigated. The results demonstrated that trabecular architecture deteriorated significantly in the placebo-treated women who had higher bone turnover at baseline, and this deterioration was prevented by 3 years of risedronate treatment, presumably because of the reduction in bone turnover.\(^{[135]}\)

> **BJ. Abel et al (1993)** reviewed novel formulation strategies for improving the bioavailability of drugs with poor membrane permeation or presystematic metabolism. Formulation strategies reviewed included the use of metabolism inhibitors, membrane permeation enhancers, ion pairing and complexation, and particulate carriers. Also reviewed are lipid and surfactant formulations, which have been shown to increase bioavailability by various mechanisms.\(^{[136]}\)

> **Samdancioglu S et al (2006)** formulated bisphosphonate loaded microspheres were for implantation in osteolysis. Solvent evaporation method was used to prepare AS loaded PLGA microspheres and emulsion polymerization method was used to prepare Alendronate loaded chitosan microspheres. Particle size, loading efficacy, surface characteristics, and in vitro release characteristics were examined on prepared formulations. It was found that chitosan microspheres gave first-order release while PLGA microspheres gave zero-order release.\(^{[137]}\)

> **Nafea EH et al (2007)** formulated Alendronate PLGA microspheres which demonstrated high drug loading efficiency. Biocompatible, biodegradable PLGA
microspheres incorporating alendronate sodium with high loading efficiency obtained in this study offered promise as a delivery system.[138]  

- **Lasota A et al (2004)** demonstrated different methods of overactomy in rats which is a method of inducing osteoporosis. In the first group, ovariectomy was preceded by a midline dorsal skin incision, 3 cm long. After removing the ovary, the previous incision of the muscle required suturing. In the second group, ovariectomy was performed by two dorso-lateral incisions, approximately 1 cm long above the ovaries. With the use of a sharp dissecting scissors, the skin was cut almost together with the dorsal muscles and the peritoneal cavity was accessed. There was no need of muscle suturing. The Conclusion drawn from this experiment was that the operation, performed in the second group, was technically easier, less time consuming and less harmful for the used female white rats.[139]  

- **DN Khalafallah et al (1991)** studied an animal model in which similar characteristics were observed between ovariectomy induced bone loss in the rat and postmenopausal bone loss in women. These included: increased rate of bone turnover with resorption exceeding formation; and initial rapid phase of bone loss followed by a much slower phase; greater loss of cancellous than cortical bone; decreased intestinal absorption of calcium; some protection against bone loss by obesity; and similar skeletal response to therapy with estrogen, tamoxifen, bisphosphonates, parathyroid hormone, calcitonin and exercise. These wide-ranging similarities are strong evidence that the ovariectomized rat bone loss model is suitable for studying problems that are relevant to postmenopausal bone loss.[140]  

- **V. Ashajyothi et al (2010)** published a comprehensive review of osteoporosis in which it is highlighted that osteoporosis is fragility of the bone due to low bone mineral density (BMD) which alters the quality of life (QOL) in patients. Osteoporosis is a major and growing public health problem for older women and men in western society. Bone is the major reservoir for the calcium and phosphate and is in constant state of remodeling during stress, many factor effects the bone resorption. Understanding the physiology, pathophysiology and treatment of Osteoporosis will direct the patients about precautions to be taken, to select the correct treatment regimen and to improve the quality of life of
the patients. The beneficial effects of treatments can be assessed by the outcome study using quality of life assessment tools.\cite{141}