Chapter 2

Literature Review
Heba M Aboud et al., (2016) developed carvedilol-loaded transfersomes containing different edge activators (EAs) evaluated the *in vivo* behavior of the optimized formula in rabbits. The vesicles were prepared by incorporating different EAs including Span 20, Span 60, Tween 20, Tween 80, and sodium deoxycholate in the lipid bilayer and each EA was used in three different ratios with respect to phosphatidylcholine (PC) including 95:5%, 85:15%, and 75:25% w/w (PC:EA). Evaluation of transfersomes were carried out in terms of shape, size, entrapment efficiency, *in vitro* release, *ex vivo* permeation, confocal laser scanning microscopy, and stability studies. The pharmacokinetic study of the optimized formula was conducted in rabbits. The mean diameter of the vesicles was in the range of 295–443 nm. Transfersomes prepared with 95:5% (w/w) (PC: EA) ratio showed highest EE% where Span 60 gave the highest values. Whereas those prepared using 85:15% w/w ratio showed highest percentages of drug release where SDC was superior to other EAs. The developed transfersomes exhibited significantly higher amounts of carvedilol permeated through nasal mucosa. CLSM of formula T14 containing SDC with 85:15% (w/w) (PC: EA) ratio revealed high permeation across the nasal mucosa. The nanotransfersomal vesicles were significantly more efficient in nasal delivery of carvedilol with absolute bioavailability of 63.4%.

Bo Wang et al., (2015) investigations focused on modifying the drug structure from crystalline insoluble form to amorphous soluble form, reducing drug particle size to provide high surface area subjected to solvent, enhancing porosity degree, and improving wettability. A wide variety of polymers was used in order to achieve these goals. Carvedilol inclusion complex with Cyclodextrin (CD) and derivatives, solid dispersion with water-soluble carriers such as Polyvinylpyrrolidone K-30 (PVP K-30), Gelucire 50/13, porous silica (Sylysia 350), and Soluprurs® (polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer) were previously investigated using different preparation methods such as solvent evaporation method, fusion method, kneading method, and spray drying method.
Analytical tests were conducted to characterize these preparations. FTIR, SEM, DSC, XRD were among the most commonly used. The paper summarized different drug-carrier combinations used for solubility, dissolution rate and/or bioavailability enhancement of Carvedilol, with emphases on the preparation methods of Carvedilol inclusion complex and solid dispersions, and different tests used for their characterization.

Pankaj Kumar et al., (2015) developed controlled release tablets of salbutamol sulphate using graft copolymers of methyl methacrylate on starch and acetylated starch. Formulations were evaluated for physical characteristics like hardness, friability, drug release, drug content and weight variations, which fulfilled all the official requirements of tablet dosage form. The release rates from formulated matrix tablets were studied at pH 1.2 followed by pH 6.8. The in-vitro release study showed that the graft copolymer based matrix formulations (F3 & F4) exhibited highest correlation value ($r^2$) for higuchi kinetic model and Korsmeyer's model with $n$ values between 0.61 and 0.67 proved that release mechanisms were governed by both diffusion and erosion mechanism. The potential of graft copolymers to sustain the drug release is well supported by in-vivo pharmacokinetic studies and their adequate physicochemical properties make them promising excipients for controlled drug delivery system.

Gelareh Arzani et al., (2015) to overcome the low, variable oral bioavailability of carvedilol, niosomal formulations were prepared and characterized: plain niosomes, bile salt-enriched niosomes and charged niosomes. All formulations were characterized in terms of encapsulation efficiency, size, zeta potential, release profile, stability, and morphology. Various formulations were administered orally to ten groups of Wistar rats (n=6 per group). The plasma levels of carvedilol were measured by a validated high-performance liquid chromatography (HPLC) method and pharmacokinetic properties of different formulations were characterized. Contribution of lymphatic transport to the oral bioavailability of niosomes was also investigated using a chylomicron flow-blocking approach. Of the bile salt-enriched vesicles examined, bilosomes containing 20% sodium cholate (F2) and 30% sodium taurocholate (F5) appeared to give the greatest enhancement of intestinal
absorption. The relative bioavailability of F2 and F5 formulations to the suspension was estimated to be 1.84 and 1.64, respectively. With regard to charged niosomes, the peak plasma concentrations ($C_{\text{max}}$) of carvedilol for positively (F7) and negatively charged formulations (F10) were approximately 2.3- and 1.7-fold higher than after a suspension. Bioavailability studies also revealed a significant increase in extent of drug absorption from charged vesicles. Tissue histology revealed no signs of inflammation or damage. The study proved that the type and concentration of bile salts as well as carrier surface charge had great influences on oral bioavailability of niosomes. Blocking the lymphatic absorption pathway significantly reduced oral bioavailability of carvedilol niosomes. Overall two fold enhancement in bioavailability in comparison with drug suspension confers the potential of niosomes as suitable carriers for improved oral delivery of carvedilol.

Sateesh K Vemula et al., (2015) made efforts to develop the flurbiprofen fast dissolving tablets using sublimating agents in the presence of crosspovidone as super disintegrant and studied the effect on dissolution rate when compared to conventional tablets. In the present study, sublimated fast dissolving tablets were prepared by direct compression method. The prepared tablets were characterized for physical parameters and drug release behaviour and the best formulation was subjected to pharmacokinetic studies. From in vitro drug release studies, the formulation F2 showed fast drug release of about 99.94±0.26% in 30 min, and disintegration time 34.42 ± 0.74 sec. The dissolution efficiency was found to be 53.44 and it is increased by 4.5 fold with F2 sublimated tablets. From the pharmacokinetic evaluation, the conventional tablets producing peak plasma concentration (Cmax) was 9023.68±561.83 ng/ml at 3 h Tmax and F2sublimated tablets showed Cmax 11126.71±123.56 ng/ml at 2 h Tmax.

Ahmed laith et al., (2014) the present investigation is concerned with the formulation and evaluation of Flurbiprofen solid dispersion and microsphere for prolonging the duration of action of the drug. The dose is prepared as a capsule containing two types of units, one is the fast release unit (solid dispersion) and the other is controlled release unit (microspheres). Microspheres were prepared by solvent evaporation method using ethyl cellulose and different types of eduragit
polymers. Microsphere Formula R14 was selected as the best selected formula due to its high entrapment efficiency, high drug loading concentration and its good release profile. A hard gelatin capsule containing Flurbiprofen equivalents to 100mg of fast release dose and 100 mg of controlled release unit were prepared.

Sanjit Singh Lamba et al., (2013) conducted studies on the enhancement of solubility and dissolution rate of efavirenz by cyclodextrin complexation. The objective of the study is to enhance the solubility and dissolution rate of efavirenz by cyclodextrin complexation along with Poloxamer 407 and PVP K30 and to evaluate the individual main effects and combined effects of β cyclodextrin (β-CD), surfactant (Poloxamer 407) and PVP K30 on the solubility and dissolution rate of efavirenz in a series of 2^3 factorial experiments. Solid inclusion complexes were prepared by kneading method. It was found out that a combination of β-CD with Poloxamer 407 and / or PVP K30 or Poloxamer 407 and PVP K30 alone is recommended to enhance the solubility and dissolution rate.

Thomas Taupitz et al., (2013) conducted studies to improve the solubility and dissolution behaviour of a poorly soluble, weakly basic drug, using itraconazole. Binary inclusion complexes of itraconazole with two commonly used cyclodextrin derivatives and a recently introduced cyclodextrin derivative were prepared & their solubility and dissolution behaviour was compared with that of the pure drug and the marketed formulation sporanox. Ternary complexes were prepared by addition of soluplus, a new highly water soluble polymer, during the formation of the itraconazole/cyclodextrin complex. It was found out that the bioavailability of itraconazole is likely to be increased after oral administration of ternary complex formulations, especially when itraconazole is formulated as a ternary complex comprising hydroxyl propyl β-CD.

Preeti Mehta et al., (2013) studied the effect of hydrophilic polymers PVP (0.25%w/v) and HPMC (0.1%w/v) on Cefixime complexation with β-cyclodextrin. The rationale of the present study was to investigate the effect of hydrophilic polymers PVP and HPMC on cefixime complexation with β-cyclodextrin and thus to study combined effect of hydrophilic polymers and cyclodextrin on the solubility and dissolution rate of Cefixime. Binary and ternary mixtures were
prepared by physical mixing and Lyophilisation method. It was found out that the combined use of cyclodextrin and hydrophilic polymers greatly improved drug solubility and dissolution rate because of enhanced complexation efficiency of cyclodextrin.

Sasidhar et al., (2013) made an attempt to mask the metallic taste and enhance the solubility and dissolution rate of poorly soluble Olmesartan by formulating it as inclusion complexes with β-cyclodextrins as complexing agent in 1:1 molar ratio. The drug - CDs complexes were prepared by physical mixing and co-evaporation methods. From the prepared inclusion complexes, or dispersible tablets were formulated by using Super disintegrants like sodium starch glycolate and crosspovidone in various concentrations (5-15%). It was concluded that combination of inclusion complexation and using of superdisintegrants were a promising approach in the preparation of taste masked tablets of Olmesartan.

Y Sirisha et al., (2013) formulated and evaluated solubility enhanced fast disintegrating tablets of telmisartan using natural super disintegrants. Inclusion complexes were prepared using β-CD by physical mixing and kneading methods. Complex prepared by kneading method in 1:3 ratio was incorporated into tablets and were formulated using gum karaya and soy polysaccharides in three concentrations. It was concluded that the tablets formulated using gum karaya shows highest dissolution.

Jain Aarti M et al., (2013) prepared, formulated and characterized inclusion complexes of Clopidogrel bisulphate with PVP K-30, PEG 4000 and HP-β-CD. The inclusion complexes were prepared by kneading method. This study showed that there was significant improvement in solubility & dissolution rate of Clopidogrel bisulfate by its inclusion complexes with PVP K-30 (1:0.5) ratio prepared by kneading method. It showed highest solubility and fast dissolution rate.

Shaundarya kumar et al., (2013) formulated and studied on of solubility enhancement of Dicyclomine using solid dispersion technique containing different drug to polymer ratio by kneading method and modified solvent fusion method, using PEG 6000 and β– cyclodextrin as carrier. The solid dispersion were
characterized for drug content *in-vitro* release studies, FTIR and XRD. The cyclodextrin complexes formulated by employing 1:1 (drug: complexing agent) with kneading technique showed higher drug release.

**Mahmoud E I Badry et al., (2013)** performed various methods to enhance the dissolution rate of insoluble drug Nimesulide. It was dispersed in a water-soluble carrier poloxamer 407. Different methods were employed to prepare such dispersion, namely: Solvent method, Melting method and Kneading method in different drug:carrier ratios. Nimesulide solid dispersions were characterized for their physicochemical properties using SEM, DSC and the powder X-ray diffractometry. In addition to dissolution studies, the results revealed that Nimesulide was converted to its amorphous state.

**Pankajkumar S yadav et al., (2013)** aimed of the study was to improve the solubility and dissolution rate of poorly water soluble drug Ketoprofen by solid dispersion approach using by PVP K30 and D-mannitol in different drugs to carrier ratios using kneading and solvent evaporation method, various formulations were prepared. These formulations were characterized by DSC, FTIR spectroscopy, X-ray diffraction and SEM. Solid dispersions prepared with PVP K30 showed the highest improvement in dissolution rate of Ketoprofen.

**Smita D More et al., (2013)** aimed to enhance the solubility and dissolution rate of a poorly soluble drug, Gliclazide by solid dispersion method using soluplus and kollidon VA64 as a carrier and PEG 4000, sorbitol, cremopher EL as a plasticizer. The solid dispersions were characterised by DSC, FTIR, X-ray diffraction and *in vitro* dissolution studies were performed. The solid dispersion of KollidonVA64 and PEG 4000(1:1) showed the best cumulative drug release. The solid dispersions were then formulated as tablets and subjected to various preformulation and post formulations studies. The evaluation of tablet batches i.e. hardness, friability, drug content, *in-vitro* release, and stability parameters have been studied.

**U D Shivhare et al., (2013)** aimed to prepare a time dependent pulsed release system for the programmed release of losartan potassium for the treatment of hypertension. The core tablets of losartan potassium were prepared using wet
granulation containing a super disintegrant. The design was based on $3^2$ full factorial design containing 2 factors evaluated at 3 levels and the experimental trials were performed on coating of the core tablets. Factors influenced the lag time and \textit{in vitro} drug release of formulations, called dependent factors. Dissolution studies of coated tablets in media with 1.2 and 6.8 showed that drug release could be modulated by optimizing the concentration of Eudragit L100 and Eudragit S 100. Polynomial mathematical model generated for various response variable using multiple linear regression analysis, were found to be statistically significant. Contour plots and response surface plots were drawn and optimum formulation were selected by feasibility and desirability function. The experimental values obtained from the optimized formulation highly agreed with the predicted values. Stability study of the optimized formulation indicates no significant difference in release profile after a period of one month.

\textbf{Vinay Pandit et al., (2012)} investigated on \textit{in-vitro} or \textit{in-vivo} behaviour of fast dissolving tablets containing solid dispersions of pioglitazone hydrochloride. The effect of various hydrophilic polymers on the aqueous solubility of pioglitazone was studied by kneading method using PVPK 30 as carrier. Evaluation of solid dispersion for percentage yield, drug content, solubility, and Fourier Transform Infrared-indicated kneading method were found to be most appropriate.

\textbf{B P Patel et al., (2012)} reviewed on importance and application of various bioavailability enhancing methods by increasing the solubility of drug. Solid oral dosage forms cover highest market due to their easy administration and greater stability. About 40\% of identified new drugs faces problem of poor water solubility. The bioavailability of poor water soluble drugs can be increased by enhancing the water solubility of these drugs. There are many methods available for solving this problem. This article emphasis on solid dispersion, particle size reduction, salt forms of drug and complexation. It also covers the work done by other scientist on these techniques.

\textbf{Ajaykumar Sav et al., (2012)} aimed to enhance the solubility and dissolution rate of Curcumin by solid dispersion method using Fenugreek gum (FG) and HPMC 5cP as hydrophilic carrier. Solid dispersions were prepared by various techniques
like kneading, freeze drying and emulsion solvent diffusion methods and were compared for their solubility and dissolution rate. The solid dispersions were characterized for physical parameters like flow behavior, density, compressibility, wetting property, FTIR, SEM, PXRD and DSC. The present study indicates that solid dispersed product can improve solubility and dissolution rate.

Rajender Guleria et al., (2012) designed PEG based solid dispersions of domperidone to enhance its solubility. PEG 8000 based solid dispersions containing the drug in different mass ratio i.e. 1:1, 1:3, 1:5 and 1:7 were prepared using fusion method. The prepared solid dispersions were characterized for their drug content, phase solubility studies, FT-IR spectroscopy, DSC, XRD and in-vitro dissolution studies.

Annamma devi et al., (2012) studied the effect of PVP on Cyclodextrin complexation of Efavirenz. The objective of the present investigation is to study the complexation of efavirenz with two cyclodextrins, β- cyclodextrin and hydroxypropyl β-cyclodextrin alone and in the presence of polyvinyl pyrrolidone. Solid inclusion complexes in 1:1 and 1:2 ratios were prepared with and without PVP K30 by physical mixing, kneading and co-precipitation and were evaluated. It was found out that the solid inclusion complexes of β-CD and HPβ-CD with PVP gave higher rates of dissolution than those of efavirenz and its complexes with CDs alone.

Lade Swati N et al., (2012) designed a study to study solubility properties of inclusion complexes of atorvastatin, with β-cyclodextrin and hydroxypropyl-β-cyclodextrin and to analyze the effect of hydrophilic polymer on complexation, aqueous solubility and dissolution of drug. The highest improvement in solubility, drug content were observed in inclusion complex prepared with HPβCD and polymer. The findings confirms the addition of small amounts of hydrophilic polymers improves solubilising and complexing ability of cyclodextrin which further related to increased release of drug in dissolution medium. This study signified the use of hydrophilic polymers in combination with HPβCD for the formation of inclusion complex of atorvastatin.
Sonam Jain et al., (2012) reviewed that Solvent deposition technique can overcome the problems faced by solid dispersion up to a great extent. Even though solid dispersion is the mostly using technique in solubility enhancement; delivery of solid dispersion into tablet and capsule dosage form is a challenging task due to physiochemical, stability and manufacturing problems. Excipients used for preparing tablet with high surface area can be a good candidate for use as carrier in solvent deposition system. Solvent deposition technique when applied with super disintegrants provided fastest release of drug. Thus, a combination of drug adsorption in minuscule form on carrier and disintegrant action gives good results.

Sanjay J Kshirsagar et al., (2011) investigated on the functionality of the sodium alginate to predict lag time and drug release and it was statistically analyzed using the response surface methodology (RSM). RSM was employed for designing of the experiment, generation of mathematical models and optimization study. The chosen independent variables, i.e. sodium alginate and potassium bicarbonate were optimized with a $3^2$ full factorial design. Floating time and cumulative percentage drug release in 6 h were selected as responses. Results revealed that both the independent variables are significant factors affecting drug release profile. A second-order polynomial equation fitted to the data was used to predict the responses in the optimal region. The optimized formulation prepared according to computer-determined levels provided a release profile, which was close to the predicted values. The floating beads obtained were porous (21-28% porosity), hollow with bulk density <1 and had $F_{70}$ of 2–11 h. The floating beads provided expected two-phase release pattern with initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer. The proposed mathematical model is found to be robust and accurate for optimization of time-lagged formulations for programmable pulsatile release of valsartan.

Derle Dilip V et al., (2010) Solvent deposition system has been developed for solubility enhancement by adsorbing poorly water soluble drug over lactose particles exposing fine particles of drug in dissolution media. This solvent deposition system was formulated as orodispersible tablet through wet granulation, using camphor as subliming agent and sodium starch glycolate as super
disintegrant. The formulations were evaluated for weight variation, hardness, friability, drug content, wetting time, in vitro dispersion time and in vitro dissolution. All the formulations showed low weight variation with in vitro dispersion time less than 40 seconds and rapid in vitro dissolution. Fine particles of drug adsorbed over lactose and porous nature of tablet gave higher drug dissolution and hence rapid drug release. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Siavoush Dastmalchi et al., (2005) prepared Glibenclamide solid dispersion by solvent deposition technique using microcrystalline cellulose as the carrier in different ratios and their dissolution rates were compared to those of pure drug and its physical mixture with carrier. The solid dispersion with the drug to carrier ratio of 1:19 showed the highest dissolution rate with the dissolution efficiency (DE) of 44.42 in comparison to pure drug (DE = 3.82). The study results concluded that solid dispersion technique enhances the dissolution rate and the bioavailability of Glibenclamide.

K V Ramana Murthy et al., (2000) Prepared solvent deposition systems of felodipine with biologically inactive carriers like MCC, lactose, potato starch and aerosil in different ratios. These systems were evaluated for drug content uniformity, drug carrier interactions, and drug release profiles. Drug-carrier interactions were evaluated by using differential scanning calorimetry, IR and TLC. The results of drug - carrier interaction studies indicated that there was no interaction between the drug and the carrier. Release of drug from solvent deposition system was markedly increased than that of the corresponding physical mixture. The increase in the order of dissolution rate of felodipine from solvent deposition system was found to be: MCC > aerosil > potato starch > lactose.