# Chapter - 2

## Chapter - 2. LITERATURE SURVEY

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2. LITERATURE SURVEY

2.1 PAST STUDIES ON SOLID DISPERSIONS

Ahmed et.al., formulated simvastatin orodispersible tablets by using solid dispersions of simvastatin using pluronic F68 as carrier. Crosscarmellose sodium was used as superdisintegrant and the tablet formula containing 12% superdisintegrant, showed the highest dissolution rate with an acceptable disintegration time (43 sec)\textsuperscript{121}.

Ashish kumar et.al., prepared Solid dispersions of Lovastatin β-cyclodextrin and polyvinylpyrrolidone K90 (PVP K90) as carriers in different drug-to-carrier ratios by solvent evaporation technique and characterized. Solid dispersions showed efficient wetability and dispersability along with decreased crystallinity of the drug\textsuperscript{122}.

Bhumika et.al., prepared Telmisartan solid dispersions by Surface solid dispersion method using polymers like poloxamer 407, PEG-6000 by Solvent evaporation method. The solid dispersions prepared by using poloxamer 407 exhibited higher dissolution when compared to the pure drug\textsuperscript{123}.

Ahmed et.al., formulated Solid dispersions of Simvastatin with mannitol, pluronic F-68, PEG-4000 and PVP K-30 and evaluated. They studied the effects of several variables related to both solid dispersion preparation and tablet coating on drug dissolution. 1:5 Simvastatin/ Pluronic® solid dispersions showed the greatest improvement in dissolution efficiency at the lowest carrier ratio\textsuperscript{124}. 
Balaji et al., prepared Simvastatin solid dispersions in 1:1, 1:2, 1:3, 1:4 and 1:5 ratios of drug to carrier by solvent evaporation and kneading methods. The prepared solid dispersions were evaluated. Faster dissolution was exhibited by solid dispersion prepared by solvent evaporation containing 1:4 ratio of Simvastatin: Urea. They proved that kneading method was more effective than solvent evaporation\textsuperscript{125}.

Vidyadhara et al., prepared Lovastatin solid dispersions with PEG-6000 by physical mixing, fusion and co-grinding methods. They found that solid dispersions of Lovastatin with PEG-6000 (fusion method) were found to release drug faster than the pure drug. The dispersions prepared by fusion method were further compressed as tablets with various super disintegrants and observed the faster disintegration\textsuperscript{126}.

Kohli et al., improved the solubility and dissolution of Lovastatin was improved by solid dispersion technique using hot melt, solvent evaporation and kneading method with Poloxamer F-68. They concluded that dissolution rate of Lovastatin was directly proportional to increment in proportion of the carrier and Solid dispersion prepared by solvent evaporation method using Poloxamer F-68 showed faster in vitro drug release in comparision to pure drug \textsuperscript{127}.

Khayyam et al., formulated Solid dispersions of Lovastatin to improve its solubility and dissolution characteristics, reduce dosing frequency and to improve its stability by solvent evaporation method
and characterized. Dissolution data of all solid dispersions indicated increase in dissolution as compared to pure drug and increase was due to wetting phenomenon of superdisintegrants used for preparation of solid dispersions. The bioavailability increased was due to increased wettability of the solid\textsuperscript{128}.

Milani et.al., prepared Solid dispersion of prednisolone with PEG-6000 or different carbohydrates such as lactose and dextrin with various ratios of drug to carrier i.e., 1:10, 1:20 and 1:40 by co-evaporation method and were evaluated. The results indicated that lactose was suitable carrier to enhance the in vitro dissolution rate of prednisolone\textsuperscript{129}.

Patil et.al., prepared Solid dispersions of gliclazide with polyethylene glycol by fusion method. In vitro dissolution study of gliclazide, its physical mixture and solid dispersion was carried out to demonstrate the effect of PEG-6000. They showed that solid dispersion and physical mixture showed greater improvement in dissolution when compared to that of the pure drug\textsuperscript{130}.

Monica et.al., prepared surface solid dispersions of Simvastatin with two different super disintegrants in three different drug-carrier ratios by co evaporation method. Prepared surface solid dispersions exhibited rapid solubility and dissolution rate when compared to pure drug\textsuperscript{131}. 
Dipika et al., prepared solid dispersions of Simvastatin with PEG-4000 and PEG-6000 by fusion method in various ratios of 1:1, 1:3, and 1:5 and inclusion complexes with HP-β-CD obtained by kneading method in a ratio of 1:1. Inclusion complex prepared with HP-β-CD by kneading method showed highest dissolution rate than pure Simvastatin this was due to highest improvement in wettability and amorphous nature of the drug in solid dispersions\textsuperscript{132}.

Punitha et al., prepared solid dispersions of Simvastatin using different ratios of β-CD by Physical mixture, Solvent evaporation, Kneading and Fusion Method and evaluated. The solubility profile indicated that there is increase in solubility of Simvastatin when β-CD concentration is increased. The solid dispersion complex of drug gave better dissolution profile as compared to pure drug and other solid dispersions\textsuperscript{133}.

Taizia et al., prepared Simvastatin solid dispersions with PEG-6000 or PVP-K15 in 1:1, 1:2, 1:3, 1:4, and 1:5 ratios by melting method, solvent evaporation method and melting solvent method. Drug release from all solid dispersions was significantly improved when compared to their corresponding physical mixture or drug alone. They concluded that the preparation of Simvastatin SD with PEG or PVP is a promising strategy to improve the bioavailability of the drug\textsuperscript{134}.

Nivaldo et al., prepared Solid dispersions of Simvastatin (SIM) with inert carriers PEG-6000 or PVP K15 in 1:1, 1:2, 1:3, 1:4, and 1:5
ratios. Drug release from all solid dispersions was significantly improved when compared to their corresponding physical mixture or pure drug alone. They showed that Simvastatin solid dispersion with PEG is more advantageous than PVP\textsuperscript{135}.

Bindumadhavi et.al., prepared solid dispersions of Simvastatin with super disintegrants like crospovidone, croscarmellose sodium and Sodium starch glycolate by solvent evaporation method. The solubility of solid dispersions with crospovidone was improved about eightfold compared to plain simvastatin\textsuperscript{136}.

Shavi et.al., prepared solid dispersions of Gliclazide using PEG-4000, PEG-6000, PVP-K 30 by fusion method and solvent evaporation method. They observed that dissolution rate was enhanced compared to pure drug. The study clearly showed addition of PVP-K 30 improved dissolution rate significantly due to solubilization and improved wetting of drug in PVP-K 30\textsuperscript{137}.

Ganesh et.al., prepared solid dispersions of Furosemide and the study showed that the dissolution rate of Furosemide was enhanced considerably by formulating it as a solid dispersion using Sodiumstarch glycolate by kneading method. Incorporation of superdisintegrants in the solid dispersions played a critical role in dissolution enhancement\textsuperscript{138}.

Moreshwar et.al., studied the effect of polyethylene glycol-4000 (PEG-4000) on \textit{invitro} dissolution of Gliclazide from solid dispersions prepared by the melting or fusion method. They concluded that
dissolution of Gliclazide can be enhanced by the use of hydrophilic carrier\textsuperscript{139}.

Rakesh et.al., prepared solid dispersions of Simvastatin with polyethylene glycol 4000 by fusion cooling and solvent evaporation techniques. Solid dispersion prepared with PVP showed highest improvement in wettability and dissolution rate of Simvastatin\textsuperscript{140}.

Patel et.al., enhanced solubility of Lovastatin by using modified locust bean gum (LBG) as carrier using solid dispersion technique. They observed the increase in solubility of Lovastatin with increase in concentration of MLBG (modified LBG) In vivo studies carried showed significant reduction in HMG Co-A reductase activity in case of solid dispersion than pure drug\textsuperscript{141}.

Patel et.al., prepared solid dispersions of Lovastatin with PEG-4000 by fusion-cooling and solvent evaporation, whereas dispersions containing PVP K30 were prepared by solvent evaporation technique and characterized. Solid dispersion prepared with PVP showed the highest improvement in wettability and dissolution rate compared to pure Lovastatin. Tablets containing solid dispersion prepared with PEG and PVP showed significant improvement in the release profile of Lovastatin compared with tablets without PEG or PVP\textsuperscript{142}.

Dixit et.al., prepared solid dispersions of Celecoxib containing drug and hydrophilic carriers in ratios of 9:1, 4:1, 2:1, 1:1, 1:4 and 1:9 of drug:carrier by Physical mixing, co-evaporation and co-
grinding. They observed the increase in the dissolution rate and consequent enhancement of anti inflammatory effect in rats of Celecoxib this was due to reduced particle size of Celecoxib deposited on the surface of carrier and enhanced wettability of the drug particles brought about by the carrier\textsuperscript{143}.

Sheetal et.al., prepared fast dissolving tablets of Oxcarbazepine by wet granulation method using Avicel pH 102 as diluent, Ac-Di-Sol as superdisintegrant and starch as binder. An effective, stable and pleasant tasting formulation containing 12\% Ac-Di-Sol, was found to have a disintegration time of 28±5 sec and drug release of not less than 90\% within 30 min\textsuperscript{144}.

Bhanubhai et.al., solid dispersions of Etoricoxib with polyethylene glycol 4000 (PEG) and PVP K30 by physical mixing, solvent evaporation method and the influence of polyethylene glycol-4000 (PEG) and PVP-K30 on \textit{in vitro} dissolution of Etoricoxib from solid dispersions was studied. Solid dispersions were prepared using the solvent evaporation method containing PEG was found to be more effective in increasing the drug dissolution compared to PVP\textsuperscript{145}.

Vijayakumar et.al., prepared Meloxicam solid dispersions at various drug concentrations (5-40\%) with polyethylene glycol-6000 by different techniques (physical mixing, solvent evaporation) and were characterized. The solid dispersions of the drug demonstrated higher drug dissolution rates than physical mixtures and pure meloxicam, as
a result of increased wettability and dispersibility of drug in a solid dispersion system\textsuperscript{146}.

 Patel et.al., prepared solid dispersions of Valdecoxib with mannitol, polyethylene glycol-4000 and PVP-K-12 by various methods and were evaluated for drug release. Valdecoxib solid dispersion with PVP-K-12 showed maximum drug release\textsuperscript{147}.

 Anshuman et.al., prepared amorphous solid dispersions of Simvastatin with relatively lower glass transition temperature by spray drying technique and characterized. Dichloromethane suspensions of Simvastatin either alone or in combination with PVP (1:1 or 1:2 parts by weight) were spray dried with proposed quantity of Aerosil 200 (1:1, 1:1:1, 1:2:2 parts by weight of SIM, Aerosil 200 and PVP, respectively). They showed a dramatical improvement in rate and extent of in vitro drug release of solid dispersion 1:2:2\textsuperscript{148}.

 Soniwala et.al., conducted a study to improve the solubility and dissolution of drug by formulating the solid dispersions of Rofecoxib with various hydrophilic carriers (Polyethylene glycol-6000, Polyvinyl pyrrollidone K-30, Eudragit E-100) and inclusion complex with β-cyclodextrin. The dissolution was obtained as high as 75% in Rofecoxib: β-cyclodextrin in molar ratio of 1:5 prepared by kneading method\textsuperscript{149}.

 Urbanetz et.al., prepared solid dispersion of Nimodipine in water using PEG-2000 by melt embedding method to investigate cooling rate during preparation and storage conditions like
temperature and relative humidity. They concluded that determination of crystallinity and dispersivity of drug in solid dispersion can be successful by combining different methods like DSC, hot stage microscopy, x-ray diffraction\textsuperscript{150}.

Hadi et.al., formulated solid dispersions of Indomethacin with polyethylene glycol-6000 (PEG-6000), Myrj 52, Eudragit E100, and different carbohydrates such as lactose, mannitol, sorbitol, and dextrin by three different methods depending on the type of carrier. They concluded that lactose, mannitol, sorbitol, and especially Myrj 52 are suitable carriers to enhance the in vitro dissolution rate of Indomethacin at pH 7.2. Eudragit E100, Myrj 52, and mannitol increase the dissolution properties at pH 1.2\textsuperscript{151}.

Criag,D.Q.M.; prepared solid dispersions of 10%w/w Griseofulvin in different polyethylene glycols (PEGs) with or without incorporation of alkali dodecyl sulphates by the melting method. The investigations showed that it is possible to increase the solubility and dissolution rate by using polyethyleneglycols\textsuperscript{152}.

Zerrouk et.al., prepared solid dispersions of Carbamazepine using PEG-6000. The study showed that a linear increase in carbamazepine solubility with increase in PEG-6000 concentration. The dissolution profile indicated that percentage drug dissolved was dependent on proportion of PEG-6000\textsuperscript{153}. 
Ritthidej et.al., prepared solid dispersions of Nifedipine with polyethylene glycols (PEG-4000 and PEG-6000), HPβCD, and poloxamer 407 (PXM 407) in four mixing ratios by melting, solvent, and kneading methods. Highest dissolution rate and the $T_{80\%}$ as short as 15 min were obtained from PXM 407 solid dispersion prepared by melting method at the mixing ratio of 1:10\(^{154}\).

Shah et.al., prepared Solid dispersions of Etoposide by coprecipitating the drug with polyethylene glycols (PEG) of different molecular weights in various ratios. It was found that the coprecipitate of Etoposide with PEG 8000 increased its solubility 2-fold and dissolution rate 42-fold\(^{155}\).

Kedzierewicz et.al., prepared solid dispersions of Tolbutamide by Solvent method and co-precipitate method. The study concluded that it is possible to prepare stable solid dispersions by solvent and co-precipitate\(^{156}\).

### 2.2 PAST STUDIES ON ATORVASTATIN CALCIUM SOLID DISPERSIONS

Bhumika et.al., enhanced the solubility and dissolution rate of hydrophobic drug Atorvastatin Calcium by preparing solid dispersions using various carriers like PEG-4000, PEG-6000, PVP-K30 and Poloxamer 407 in different ratios by fusion and solvent evaporation methods. The solid dispersion prepared with poloxamer 407 in the ratio of 1:2 showed the enhanced dissolution when compared to others\(^{157}\).
Anamika et al., showed that it is possible to increase the dissolution rate of poorly soluble drugs like Aceclofenac, Atorvastatin Calcium, Irbesartan by preparing solid dispersions using tamrind seed polysaccharide a water soluble polymer as solubilizer. 

Khairulalam et al., prepared Solid dispersions of some poorly soluble drugs were prepared by solvent method using carriers like PEG-6000 and HPMC6cps. The results of the dissolution studies performed on the solid dispersions showed that PEG-6000 is a good carrier to enhance the solubility and dissolution rate of poorly water soluble drugs.

Bobe et al., prepared solid dispersions of Atorvastatin with PEG-4000, mannitol and PVP-K30 to increase the solubility of poorly soluble soluble drug. The solid dispersions prepared with PEG-4000 has shown the improved dissolution rate than the pure drug.

Lakshminarasaiah et al., prepared Atotvastatin calcium physical mixtures and solid dispersions with PEG-4000 in the ratios of 1:1, 1:2 and 1:3. The Phase and saturation solubility study, in vitro dissolution studies of physical mixtures and solid dispersions prepared by dropping method showed effective increase in the solubility and dissolution rate of Atorvastatin calcium than pure drug.

Lakshminarasaiah et al., improved the physicochemical properties of Atotvastatin calcium like solubility, dissolution properties and stability of poorly soluble drug was improved by forming
solid dispersion with PEG-6000 as water soluble carrier. The solid
dispersion with PEG-6000 (1:3) prepared by dropping method showed
faster dissolution rate when compared to other solid dispersions\textsuperscript{162}.

Sanjeevraghavendra et.al., improved the dissolution rate of
poorly soluble, highly permeable drugs such as Atorvastatin Calcium
by preparing liquisolid compacts. The release rates of liquisolid
compacts were markedly higher compared with directly compressed
tablets, due to increasing wetting properties and surface area of the
drug\textsuperscript{163}.

\textbf{2.3 PAST STUDIES ON ROSUVASTATIN CALCIUM SOLID
DISPERSIONS}

Swyamprakash et.al., improved the solubility and dissolution
rate of poorly soluble drug Rosuvastatin Calcium by developing self
(Micro) emulsifying drug delivery system. Capmul-PG8, Acconon-MC8,
Tween-80 and propylene glycol for development with high efficiency.
The study concluded that it is possible to increase the solubility and
dissolution rate by self micro emulsifying drug delivery system\textsuperscript{164}.

Akbari et.al., prepared Rosuvastatin Orodispersible tablets by
exploiting the solubilizing effect of HP-β-CD. Drug–CD complex
systems, prepared by different techniques. The inclusion complex
containing RST: HP-β-CD (1:1) was formulated into tablets using
super disintegrants like sodium starch glycolate, Crosspovidone and
Crosscarmellose by direct compression and evaluated. A significant
improvement of the drug dissolution profile was achieved from tablets containing drug–CD systems\textsuperscript{165}.

Pankaj et.al., prepared solid dispersions of Rosuvastatin Calcium by solvent evaporation method using PEG-4000, mannitol and urea as carriers. Hydrotrophic studies were carried out using different hydrotrophic agents and micellar solubilization was carried out using different surfactant solutions. The solubility enhancement of Rosuvasatain calcium by different solubilization techniques was Hydrotrophy > Solid dispersion > Micellar Solubilization\textsuperscript{166}.

Akbari et.al., improved the solubility and dissolution profile of poorly soluble drug Rosuvastatin Calcium was improved through inclusion complexation with β-cyclodextrin and hydroxy propyl β-cyclodextrin. Incusion complexes were prepared by employing physical mixing, coevaporation and kneading methods. Kneaded products containing hydroxy propyl β-cyclodextrin showed highest dissolution profile than β-cyclodextrin inclusion complex, physical mixture and pure drug\textsuperscript{167}. 