Chapter 2

Literature Survey on work done
# Chapter 2

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2.1 DISSOLUTION ENHANCEMENT OF ROFECOXIB

Singh et al [1] investigated the influence of water-soluble polymers namely sodium carboxymethyl cellulose (Na CMC), polyvinylpyrrolidone (PVP) and polyethylene glycol(PEG)-6000 on hydroxypropyl β-cyclodextrin (HP β-CD) complexation of Rofecoxib (RXB). The complexes were prepared by kneading, autoclaving and precipitation techniques in 1:1 and 1:2 molar ratios. The aqueous solubility enhancement of RXB by these polymers was found to be of the following order: Na CMC > PVP > PEG-6000.

Ahuja et al [2] studied dissolution enhancement and mathematical modeling of a poorly water-soluble drug, RXB using water-soluble carriers such as polyethylene glycols (PEG 4000 and 6000), polyglycolized fatty acid ester (Gelucire 44/14), polyvinylpyrrolidone K25 (PVP), poloxamers (Lutrol F127 and F68), polyols (mannitol, sorbitol), organic acid (citric acid) and hydrodrotropes (urea, nicotinamide). Phase-solubility studies revealed A type of curves for each carrier. All the solid dispersions (SDs) showed dissolution improvement. However, citric acid, PVP and poloxamers were found to be most promising carriers. Mathematical modeling of in vitro dissolution data indicated the best fitting with Korsemeyer-Peppas model and the drug release kinetics primarily as Fickian diffusion. Solid state characterization of the drug-poloxamer binary system using X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC) and scanning electron microscopy (SEM) techniques revealed distinct loss of drug crystallinity in the formulation, ostensibly accounting for enhancement in dissolution rate.

Liu and Desai [3] prepared and evaluated RXB-PEG 4000 SDs and tablets based on RXB SDs. The dissolution rate of RXB from its solid dispersions increased with an increasing amount of PEG. FTIR spectroscopic studies showed the stability of RXB and absence of well-defined RXB -PEG interaction. The DSC and XRD studies indicated the
amorphous state of RXB in SDs of RXB with PEG. SEM pictures showed the formation of effective SDs of RXB with PEG. Solid dispersion-based RXB tablets (solid dispersion with highest drug dissolution rate (RXB: PEG 1:10 ratio) was obtained by direct compression, with a hardness of 8.1 Kp exhibited rapid drug dissolution and produced quick anti-inflammatory activity when compared to conventional tablets containing pure RXB at the same drug dosage.

Seedhar & Bhatia [4] examined the solubility enhancement of 4 cox-2 inhibitors, celecoxib, RXB, meloxicam, and nimesulide, using a series of pure solvents and solvent mixtures like water, alcohols, glycols, glycerol, and PEG 400, water-ethanol, glycerol-ethanol, and polyethylene glycol-ethanol. A pH-solubility profile of drugs was obtained in the pH range 7.0 to 10.9 using 0.05M glycine-sodium hydroxide buffer solutions. Lower alcohols, higher glycols, PEG 400 and PEG 400-ethanol system were found to be good solvents for these drugs. It was observed that the aqueous solubility of celecoxib, RXB and nimesulide could be enhanced significantly by using ethanol as the second solvent. In the case of meloxicam and nimesulide, solubility increased significantly with increase in pH value.

Rawat S and Jain SK [5] improved the solubility and dissolution rate of RXB via complexation with CD. Phase solubility studies indicated the formation of a 1:1 complex in solution and the value of apparent stability constant was 769 M⁻¹. Solid inclusion complexes of RXB and CD were prepared by the kneading method in different molar ratios. DSC studies indicated the formation of solid inclusion complexes of RXB and CD at different molar ratios and the solid complexes exhibited a higher rate of dissolution than the physical mixture and the pure drug.

Sammour and coworkers [6] formulated RXB mouth dissolve tablets from its solid dispersion. Solid dispersion was prepared using solvent evaporation method and PVP K30 as a carrier. For the preparation of RXB mouth dissolve tablets, its 1:9 SD with PVP-K30 was used with various disintegrants and sublimable materials. 3² randomized full and reduced factorial design was used to optimize the influence of the amounts of superdisintegrant and subliming agent. The obtained results indicated that dispersion of the drug in the polymer considerably enhanced the dissolution rate. FTIR spectra revealed no chemical incompatibility between the drug and PVP K30. XRD and DSC data indicated amorphous form of RXB. The multiple regression analysis revealed that an
optimum concentration of camphor and a higher percentage of crospovidone are required for obtaining rapidly disintegrating tablets of rofecoxib.

Baboota et al [7] prepared inclusion complexes of RXB with HP-β-CD to improve the aqueous solubility of the drug, thus enhancing its dissolution rate and thereby leading to a faster onset of action and less GI mucosal toxicity. The complex was prepared by spray drying method. The phase solubility study confirmed the 1:1 complex. FTIR spectra of complex showed some change than pure drug spectra and HP-β-CD. DSC studies indicated disappearance of endothermic peaks thus suggesting maximum/complete complex formation. XRD showed peaks of diminished intensity thus, suggests complete amorphization of the drug. SEM suggested the existence of an amorphous product with the presence of a single component in the complex. In vitro dissolution studies of 1:1 and 1:2 complexes gave a 90.3% drug release at 2hrs and complete drug release after 45 min. respectively. The complex also showed faster onset of anti-inflammatory activity as compared to pure RXB.

Baboota et al [8] improved the solubility of RXB by formulating an inclusion complex using dimethyl-beta-cyclodextrin (DIMEB). The prepared complex was evaluated in-vivo in laboratory animals. The complexes were prepared by kneading and by the spray drying method. The prepared complexes showed better anti-inflammatory activity and decreased ulcerogenic potential than the pure drug in laboratory animals.

Mashru et al [9] prepared solid dispersion of RXB to enhance its dissolution. DSC and X-ray diffraction XRD were used for the characterization of SDs of PVP:talc:drug (3:1:1) and hydroxypropyl methylcellulose (HPMC):talc:drug (4:1:1). The DSC study indicated that PVP solid dispersion showed formation of fusion solution while HPMC solid dispersion showed no intermolecular fusion during the preparation of SDs by spray drying process. The study showed better dissolution rate for PVP than HPMC solid dispersion. The XRD study confirmed the result of DSC i.e. the conversion of crystalline to amorphous form in PVP solid dispersion.

Chengsheng and coworkers [10] enhanced dissolution of RXB using urea as solid dispersion carrier. The solubility study of RXB in the presence of PEG 4000, (PVP) K30, mannitol and urea in water indicated increase in the solubility of RXB with increasing concentrations of these carriers in water except mannitol. Urea exhibited higher
solubilizing power than the other carriers. Hence, SDs of RXB with urea were prepared at 1:1, 1:2, 1:5, and 1:10 (RXB: urea) ratios by the fusion method. Evaluation of the properties of the SDs was performed using dissolution studies, FTIR spectroscopy, DSC, XRD and SEM. The mean dissolution time (MDT) of RXB decreased after preparation of SDs and physical mixtures with urea. FTIR spectroscopic studies showed the stability of RXB and the absence of a well-defined RXB-urea interaction. DSC and XRD studies confirmed the amorphous state of RXB in SDs of RXB with urea. SEM pictures showed the formation of effective SDs of RXB with urea since well-defined changes in the surface nature of RXB, SDs, and physical mixture were observed.

*Soniwala and others* [11] used various approaches for dissolution enhancement of RXB. SDs with various hydrophilic carriers (PEG-6000, PVP K-30, Eudragit E-100) and inclusion complex with (β-CD) were prepared. PVP was found to be more effective in increasing the drug dissolution, when compared with PEG and Eudragit. The dissolution was obtained as high as 75 percent in RXB: β-CD molar ratio of 1:5 prepared by kneading method. For further dissolution enhancement the combination of two dissolution enhancing agent, i.e. PVP K-30 and β-CD were used. Factorial design approach was used to optimize the amount of both the agent.

*Chavanpatil et al* [12] investigated the effect of complexation of RXB with β-CD on its dissolution characteristics and bioavailability. Inclusion complexes were made by freeze-drying technique. Phase solubility studies confirmed the formation of a 1:1 complex. The samples were characterized by performing dissolution studies, XRD and DSC. Freeze drying technique showed enhanced dissolution rate in comparison with all the marketed formulations. This is attributed to the increased solubility and wettability along with decreased crystallinity caused by complex formation, which is confirmed, by XRD and DSC studies. The bioequivalence studies performed showed statistically significant enhancement in bioavailability as compared to the marketed formulation. Apparently, tablets containing complexes of RXB with CD shows faster onset of action due to improved solubility, enhanced dissolution and faster absorption of the molecule.

*Gopal Rao et al* [13] improved the solubility and dissolution rate of RXB using solid dispersion approach. Polyethylene Glycols (PEG-4000, PEG-6000 & PEG-8000) were used for the preparation of SDs by solvent evaporation method using chloroform as the
solvent. Thin Layer Chromatography and Infra Red spectral analysis confirms the absence of interaction between the drug and the carriers. A marked improvement in the dissolution rate was observed in all the SDs compared with the pure drug. Among the carriers used in SDs the PEG8000 in the ratio of 1:9 (drug and carrier ratio) gave higher rate of dissolution.

Kale, Tayade and Saraf [14] performed comparative study on co-ground products of RXB with β-CD and its sulfobutyl ether-7 derivative in solution and in the solid state. Drug-CD solid systems were prepared by cogrinding in a ball mill. A phase solubility method was used to evaluate the stoichiometries and stability constants of RXB-β-CD (1: 1 and 62 M\(^{-1}\)) and RXB-SBE7β-CD (1: 1 and 132 M\(^{-1}\)) complexes. The formation of inclusion complexes in the solid state were confirmed by FTIR, DSC, XRD, SEM and in the liquid state by phase solubility analysis, nuclear magnetic resonance spectroscopy and circular dichroism studies. Solubility enhancement and stability constant were much greater for the RXB-SBE7β-CD complex compared to RXB-β-CD complex. Dissolution profiles obtained suggest that SBE7CD is more effective than CD in improving the pharmaceutical properties of RXB.

Bakhle and coworkers [15] studied effect of various carriers on the solubility of RXB. The carriers used were mannitol, lactose, PVP K-30, PEG 6000-Tween 80(60:40 and 80:20). Phase solubility of pure drug and above carriers was carried out. The solubility data obtained showed that the carriers PVP K-30, PEG 6000-Tween 80(60:40) showed a remarkable increase in the solubility of RXB as compared to other carriers.
2.2 DISSOLUTION ENHANCEMENT OF CARVEDILOL

Miro A et al [16] enhanced dissolution of Carvedilol (CAR) by preparing inclusion complex of CAR with hydroxypropyl-β-cyclodextrin (HPβCD) to modulate drug release from gastroretentive tablets of it. Complex was prepared by physical mixing, kneading, co-melting and freeze drying. Poly (ethylene oxide) (PEO) was incorporated in CAR/(HPβCD) binary systems to control drug release property from tablets. The amount of CAR dissolved from all HPβCD containing systems was higher than pure CAR. The incorporation of binary system in PEO tablets resulted in CAR release rate much higher than tablets containing only CAR. They found that the time necessary to achieve complete drug release from the tablet was linearly related to dissolution parameters of carvedilol / HPβCD powders. The result demonstrated that the incorporation of drug/ cyclodextrin solid systems in erodable PEO matrices intended for the delivery of poorly water-soluble drugs is useful to modulate the release rate by controlling the dissolution properties of the drug inside the tablet.

Maria et al [17] formulated tablet for the buccal delivery of the poorly soluble drug carvedilol (CAR), based on poly (ethylene oxide) (PEO) as bioadhesive sustained-release platform and HPβCD as modulator of drug release. When the drug was incorporated as CAR/HPβCD freeze-dried product, all CAR content release from the tablet in about 10 h, displaying a constant release regimen after a transient. In the second part of the study, the potential of HP-β-CD containing PEO tablets as buccal delivery system for CAR was investigated. The amount of CAR permeated from PEO tablet was higher in case of HPβCD-containing tablets. Their result demonstrated that, when the tablet is employed as transmucosal system, the role of drug dissolution enhancement in the hydrated tablet is much more relevant than in solution for increasing the delivery rate.

Xianhong et al [18] prepared an inclusion complex of β-CD with CAR by using a convenient new method of microwave irradiation. Phase-solubility studies demonstrated the ability of β-cyclodextrins to complex with CAR and increase drug solubility. The structure of inclusion complex was determined by fluorescence spectroscopy and 1H NMR, 13C NMR measurements in solution. The solid inclusion was characterized by FTIR, DSC and element analysis. These experimental results confirmed the existence of 1:2 inclusion complex of CAR with β-CD, the formation constant of complex was
determined by the fluorescence method. Molecular modeling predicted the energy-
minimized structure of the complex.

**Weisan et al [19]** developed a new self-emulsifying drug delivery system (SEDDS) and
self-microemulsifying drug delivery system (SMEDDS) to increase the solubility,
dissolution rate, and ultimately the oral bioavailability of a poorly water soluble drug,
CAR. Ternary phase diagrams were used to evaluate the self-emulsification and to select
microemulsification domains. The minimum self-emulsification time was found at a
Tween80 content of 40%. The particle size distribution and zeta potential were
determined. The in vitro dissolution rate of CAR from SEDDS and SMEDDS was more
than two-fold faster compared with that from tablets. The developed SEDDS formulations
significantly improved the oral bioavailability of CAR, and the relative oral
bioavailability of SEDDS compared with commercially available tablets was 41.3%.

**Yang J [20]** studied effect of carvedilol SDs on in vitro dissolution rate. PEG and PVP
were used as a carrier. The in vitro study showed faster drug dissolution with increasing
concentration of carriers. Solid dispersion with PVP was faster than PEG.

**Sharma S and coworkers [21]** developed fast dissolving tablets of carvedilol allowing
fast, reproducible, and complete drug dissolution, by using drug solid dispersion in
polyethylene glycol. Solubility studies were performed to investigate the drug-carrier
interactions in solution. The tablets were prepared by direct compression technique. The
prepared tablets were evaluated for thickness, uniformity of weight, content uniformity,
hardness, friability, wetting time, in vitro disintegration time and in vitro drug release.
The tablet was found better than those from various conventional tablets at the same drug
dosage.
2.3 DISSOLUTION ENHANCEMENT BY TERNARY DISPERSIONS/ COPRECIPITATES

Cirri and coworkers [22] characterized ibuprofen binary and ternary dispersions with hydrophilic carriers such as PVP, PEG, or urea, alone or in combination. Phase-solubility studies showed that the carrier solubilizing power was in the order PEG>PVP>urea and evidenced a synergistic effect in drug solubility improvement when using carrier combinations. Binary and ternary systems were characterized by DSC, HSM, and SEM analysis. The results of dissolution tests (USP paddle method), in terms of Dissolution efficiency, indicated that ternary systems were up to 35% more effective than the corresponding binary preparations and coevaporated products were up to 45% more efficacious than the corresponding co-ground ones.

Gohel et al [23] studied the influence of various dissolution enhancers such as PEG 400, propylene glycol, PVP K30, sodium lauryl sulfate, and Tween 80 on in vitro dissolution of a model active pharmaceutical material—nimesulide. Preliminary studies were conducted using a physical blend of nimesulide, and the adjuvants and SDs were prepared using solvent evaporation and cocrushing methods. A 3^3 factorial design was adopted in a cocrushing method using the concentration of PEG 400, propylene glycol, PVP K30 as independent variables. Tween 80 and sodium lauryl sulfate were added in all the batches. PVP was found to be more effective in increasing the drug dissolution, compared with PEG and propylene glycol. Improved drug dissolution was attributed to improved wetting and the solubilizing effect of adjuvants from the pseudosolid dispersions of nimesulide. Significant improvement in drug dissolution was observed (Q₁₂₀ = 70%), compared with pure drug powder (Q₁₂₀ = 15%).

Cirri, Maestrelli et al [24] prepared fast dissolving tablets of glyburide based ternary solid dispersions with PEG and surfactants to get complete drug dissolution. Tablets were prepared by direct compression or wet granulation containing the drug with each surfactant or drug: PEG: surfactant ternary dispersions at different PEG: surfactant w/w ratios. The presence of surfactants significantly increased (p<0.01) the drug dissolution rate, but complete drug dissolution was never achieved. On the contrary, in all cases tablets containing ternary solid dispersions achieved 100% dissolved drug within 60 min. The best product was the 10:80:10 w/w ternary dispersion with PEG 6000 and sodium
lauryl sulphate, showing a dissolution efficiency 5.5-fold greater than the reference tablet formulation and 100% drug dissolution after only 20 min.

**Basavaraj et al [25]** enhanced the bioavailability of DRF-4367, a poorly water-soluble and weakly acidic anti-inflammatory molecule via HP-β-CD and polyhydroxy base, N-acetyl glucamine (also know as Meglumine), as a ternary component. The solid complexes of DRF-4367 and HP-β-CD with or without meglumine (binary and ternary systems, respectively) were prepared as coevaporated product in different stoichiometric ratios and compared against physical mixture. The formation of inclusion complexes was confirmed by using classical instrumental techniques. Phase solubility studies suggested that meglumine was responsible for solubility improvement via multiple factors rather than just providing a favorable pH. Inclusion ternary complex showed significant improvement in dissolution compared with uncomplexed drug and binary system.

**Gupta and Bansal [26]** prepared ternary amorphous system of celecoxib, PVP and meglumine. Coprocessing of celecoxib (CEL), poly (vinyl pyrrolidone), and meglumine by spray drying resulted in an amorphous drug product that provided enhanced solubility and stability to an otherwise poorly soluble crystalline form of CEL. The spray-drying process parameters were optimized to provide an amorphous product with required characteristics. The product was stable for 3 months under the accelerated stability storage conditions. This technique can serve as a suitable means for generating a ready-to-formulate amorphous drug-additive(s) composite that can be directly filled into hard gelatin capsules.

**Itoh K and coworkers [27]** prepared nanoparticles for poorly water-soluble drugs N-5159, griseofulvin (GFV), glibenclamide (GBM) and nifedipine (NFP) by mixing with PVP and sodium dodecyl sulfate (SDS) and then adding it to distilled water. Nanoparticles which were 200 nm or less in size were formed and had excellent stability. Zeta potential measurement suggested that the nanoparticles had a structure where SDS was adsorbed onto the particles that were formed by the adsorption of PVP on the surface of drug crystals. Stable existence of crystalline nanoparticles was attributable to the inhibition of aggregation caused by the adsorption of PVP and SDS on the surface of drug crystals. Furthermore, the electrostatic repulsion due to the negative charge of SDS on a shell of nanoparticles could be assumed to contribute to the stable dispersion.
**Gong et al** [28] prepared and characterized porous indomethacin (IM)-PVP coprecipitates using solvent-free supercritical fluid technology to improve the dissolution rate of IM. The coprecipitates were prepared at various proportions. The dissolution rate of IM was increased by incorporation of PVP. IM and PVP at various weight fractions exhibited comparatively higher dissolution rates than that of crystalline IM alone. The sc-CO$_2$ based process produced a solvent free, completely amorphous porous IM solid dispersion with a rapid dissolution rate.

**Eel-GazayerlyON** [29] characterized tenoxicam coprecipitates prepared using the solvent evaporation method, and the ratio used was 1:3 drug to additive. Dissolution profiles of most of the prepared coprecipitates demonstrated higher dissolution than pure tenoxicam. Characterization of the coprecipitates by IR and DSC techniques revealed structural changes in the prepared coprecipitates from the plain drug, which may account for increased dissolution rates.

**Rodriguez-Espinosa and coworkers** [30] studied dissolution kinetics for coprecipitates of diflunisal with PVP K30 solid dispersions of diflunisal and PVP prepared by the solvent method, using percentage proportional compositions ranging from 20:80 to 50:50. X-ray diffraction analysis suggested crystalline or amorphous state in solid dispersion depending on the PVP content. The thermal behavior of diflunisal observed in the DSC curves of solid dispersion systems, was attributed to a solid-state interaction. The increased release of the PVP-drug dispersion as compared to the PVP-drug physical mixture was attributed to the formation of a complex resulting from the interaction of the drug and the polymer.

**Adel MS and coworkers** [31] prepared and evaluated coprecipitates of different ratios of flutamide with polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG) 4000 and 6000. Drug solubility in carrier solutions, thin layer chromatography (TLC), DSC, IR, uniformity of drug content, drug dissolution from its respective systems and effect of aging on the physico-chemical parameters of stored flutamide-polymer system were studied. PEG 6000 was found to be the most efficient polymer in increasing both the solubility and the release rate of flutamide. Interaction was found to be complete in certain ratios of drug/polymer systems. The dissolution pattern of flutamide from all the
prepared systems appeared to fit a first order mechanism. Physico-chemical parameters of flutamide/carrier systems were not influenced by storage.

Karavas et al [32] investigated the release mechanism, physical state of the drug and drug-polymer interactions of a sparingly soluble drug felodipine from its solid dispersion prepared FT-IR data indicated that a N-H...O hydrogen bond is formed between FELO and polymers. Both the experimental and theoretical data indicated that a stronger interaction of FELO with PVP than with PEG was developed. In the FELO/PVP dispersions, the drug is found as amorphous nanoparticles whereas in FELO/PEG dispersions the drug is dispersed as crystalline microparticles. In situ DLS measurements indicate that the large initial particles of FELO/PVP and FELO/PEG solid dispersions with low drug content (10-20 wt%) are very rapidly decreased to smaller particles (including nanoparticles) during dissolution, leading to the observed impressive enhancement of FELO release rate from these dispersions.

Narang AS and Srivastava Ak [33] prepared and evaluated SDs of clofazimine (CLF). SDs of CLF was formulated PEG and PVP) to increase the aqueous solubility and dissolution rate of the drug. Different molecular weights of PEG (1500, 4000, 6000, and 9000 Da) and PVP (14,000 and 44,000 Da) were used in different drug: carrier weight ratios (1:1, 1:5, and 1:9) and their effect on the dissolution was ascertained. The dissolution rate improved with the decreasing weight fraction of the drug in the formulation. PVP SDs gave a better drug release profile as compared to the corresponding PEG SDs. The effect of molecular weight of the PEG polymers did not follow a definite trend, while PVP 14,000 gave a better dissolution profile as compared to PVP 44,000. Further, IR spectroscopy indicated drug: carrier interactions in solid state in one case and XRD indicated reduction in the crystallinity of CLF in another.
2.4 DISSOLUTION ENHANCEMENT USING POLOXAMER

Wong SM, Kellaway IW and Murdan S. [34] improved the bioavailability of poorly soluble drug griseofulvin by preparing microparticles of it by spray drying the drug in the absence/presence of a hydrophilic surfactant. Poloxamer 407. In vitro dissolution studies showed that the dissolution rate and absolute oral bioavailability of the spray dried griseofulvin/Poloxamer 407 particles were significantly increased compared to the control. Although spray drying griseofulvin alone increased the drug's in vitro dissolution rate, no significant improvement was seen in the absolute oral bioavailability when compared to the control. Therefore, it is believed that the better wetting characteristics conferred by the hydrophilic surfactant was responsible for the enhanced dissolution rate and absolute oral bioavailability of the model drug.

Chutimaworapan S et al [35] studied effect of different water soluble carriers on nifedipine(NP) SDs. SDs of NP with polyethylene glycols (PEG4000 and PEG6000), hydroxypropyl-beta-cyclodextrin (HP beta CD), and poloxamer 407 (PXM 407) in four mixing ratios were prepared by melting, solvent, and kneading methods in order to improve the dissolution of NP. The enhancement of the dissolution rate and the time for 80% NP dissolution T80% depended on the mixing ratio and the preparation method. The highest dissolution rate and the T80% as short as 15 min were obtained from PXM 407 solid dispersion prepared by the melting method at the mixing ratio of 1:10. The X-ray diffraction (XRD) patterns of solid dispersions at higher proportions of carriers demonstrated consistent with the results from differential scanning calorimetric (DSC) thermograms that NP existed in the amorphous state. The wettability and solubility were markedly improved in the PXM 407 system. The presence of intermolecular hydrogen bonding between NP and PEGs and between HP- β-CD and PXM 407 was shown by infrared (IR) spectroscopy.

Reddy RK, Khalil SA, Gouda MW [36] studied dissolution characteristics of digitoxin and digoxin. A marked increase in the dissolution rates of both drug was attained by dispersing the drugs in two inert solid carriers, poloxamer 188 and deoxycholic acid. The 1 and 10% (w/w) drug-carrier solid dispersions were prepared by the solvent method. The former dissolved significantly faster than the latter. X-ray diffraction patterns indicated
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that both digitoxin and deoxycholic acid undergo crystalline modifications due to treatment by the solvent, but the exact nature of the drug-carrier solid dispersions was not revealed.

**Chen Y et al** [37] enhanced bioavailability of ABT-963 using SD containing Pluronic F-68 as a carrier. The SDs was prepared either by evaporation of the ethanol solutions containing ABT-963 and Pluronic, or by cooling the hot melt of the drug in the carrier. The dispersions were characterized using DSC, XRD, SEM, elemental mapping, and by constructing the melting point phase diagram. In vitro dissolution and in vivo oral bioavailability in fasted dogs were compared for the solid dispersion and a conventional IR capsule formulation. Results showed that, at a composition of approximately 7.5%, ABT-963 formed a eutectic mixture with Pluronic F-68. The SD substantially increased the in vitro dissolution rate of ABT-963. Dosing of the dispersion to fasted dogs resulted in a significant increase of oral bioavailability compared with the conventional IR capsule formulation.

**Chul Soon Yong and coworkers** [38] studied the rectal bioavailability of ibuprofen gels form the rat rectum. Gel was prepared using poloxamer and menthol. Solubility of ibuprofen increased until the ratio of menthol to ibuprofen increased from 0:10 to 4:6 followed by an abrupt decrease in solubility above the ratio of 4:6, indicating that four parts menthol formed eutectic mixture with six parts ibuprofen. The poloxamer gel with menthol/ibuprofen ratio of 1:9 and higher than 15% poloxamer 188 showed the maximum solubility of ibuprofen, 1.2 mg/ml. Menthol improved the dissolution rates of ibuprofen from poloxamer gels.

**Passerini et al** [39] enhanced the solubility of a poorly soluble drug using ibuprofen. The granules were prepared using lactose as a diluent and poloxamer 188 (Lutrol F68), as a new meltable hydrophilic binder. The in vitro dissolution tests showed an increase in the dissolution rate of granules compared to pure drug and physical mixture. The characterization of the samples, performed by DSC and XRD, suggests that the improvement of dissolution rate could be correlated to the formation of a eutectic mixture between the drug and the binder. Stability studies indicated that the granule properties do not change, at least after 1 year of storage at 25°C.
Vippagunta et al [40] prepared and characterized nifedipine solid dispersion (33.3% w/w) in a polymer matrix consisting of Pluronic F68 (33.3% w/w) and Gelucire 50/13 (33.3% w/w). The rate and extent of water uptake of the solid dispersion were determined by weight gain. Quantitative XRD showed that the saturation solubility of nifedipine in the polymer matrix is 2.1-3.0% w/w and indicated an excess of crystalline nifedipine in the solid dispersion. The maximum water uptake by the solid dispersion exposed to 75% RH at 45°C was 3.3 times higher than for the dispersion exposed to 65% RH at 25 °C for 8 days.

Shin SC and Cho CW [41] developed and characterized piroxicam-poloxamer gels. The gelling property of poloxamer and the solubility of piroxicam in the poloxamer were investigated. The interaction between piroxicam and poloxamer was studied by XRD, IR and differential thermal analysis (DTA) with a solid dispersion, coprecipitate, or physical mixture. Poloxamer 407 solutions showed the property of a gel when the concentration was higher than 15% (w/w) and poloxamer 407 increased the aqueous solubility of piroxicam by about 11-fold at the concentration of 22.5% (w/w). The results of XRD did not show the crystalline form of piroxicam in the solid dispersion and results of IR spectroscopic analysis showed an association between functional groups of piroxicam and poloxamer.

Rouchotas et al [42] compared surface modification and solid dispersion technique for drug dissolution of phenylbutazone (PB). PB was treated with a poloxamer, Synperonic ((R)) F127 by an adsorption method. Solid dispersions (10 and 20% w/w) were prepared with untreated PB or PB previously modified with Synperonic (R)) F127 (PBT) in molten F127. Dissolution tests of capsule formulations of PB, PBT and SD formulations, in pH 6.4 buffer at 37+/-.0.5 degrees C demonstrated that after 140 min, release of PB was 16.7%, but 71.4% from the solid dispersion, whereas from the PBT formulation 85.6% was released. However there was a significantly higher release rate for PBT. It is concluded that combination of techniques changes the rate but not the extent of release in comparison with the surface modification technique alone.
2.5 DISSOLUTION ENHANCEMENT BY SURFACE SOLID DISPERSION / USING GELUCIRE

Gupta and coworkers [43] enhanced drug dissolution poorly soluble drug BAY 12-9566 by combination of solid dispersion and surface adsorption techniques. Gelucire 50/13 (polyglycolized glycerides) was used as the solid dispersion carrier. Hot-melt granulation was performed to adsorb the melt of the drug and Gelucire 50/13 onto the surface of Neusilin US2 (magnesium alumino silicate), the surface adsorbent. Dispersion granules using various ratios of drug-Gelucire 50/13-Neusilin US2 were thus prepared. Dissolution of BAY 12-9566 from the dispersion granules was enhanced compared to the physical mixture. The dissolution of BAY 12-9566 increased as a function of increased Gelucire 50/13 and Neusilin US2 loading and decreased with increased drug loading. In contrast to the usually observed decrease in dissolution on storage, an enhancement in dissolution was observed for the dispersion granules stored at 40 °C/75% RH for 2 and 4 weeks. Additionally, the flow and compressibility properties of dispersion granules were improved significantly when compared to the drug alone or the corresponding physical mixture. The ternary dispersion granules were compressed easily into tablets with up to 30% w/w drug loading.

Deepti et al [44] utilized amalgamation of solid dispersion and melt adsorption technologies for enhancing the dissolution rate of poorly soluble drugs. Glibenclamide was employed as a model drug. PEG6000 and Gelucire 44/14 were used as hydrophilic carriers for the preparation of solid dispersions, and lactose was utilized as an adsorbent for the preparation of solid dispersion adsorbates. A high dissolution rate of solid dispersion adsorbates was observed when compared to solid dispersions alone and one of the marketed products.

Gupta et al [45] investigated the mechanism for further enhancement of two proton-donating drugs, BAY 12-9566, naproxen, and a nonproton-donating drug, progesterone dissolution from SDs granules upon storage. Gelucire 50/13 and polyethylene glycol 8000 were evaluated as SD carriers with low melting point. Neusilin US2 (magnesium aluminosilicate), a proton acceptor, was used as the surface adsorbent. The proposed mechanism for further increase in drug dissolution (BAY 12-9566 and naproxen) on storage at 40° C/75% RH (relative humidity) is based on hydrogen bonding between the
proton-donating drugs and the surface adsorbent, Neusilin US2 (proton acceptor). FTIR studies are indicative of an increase in the amount of drugs (BAY 12-9566 and naproxen) hydrogen bonded to Neusilin on storage. A corresponding decrease in the crystallinity of these drugs was measured using XRD. Granules containing progesterone (a nonproton-donating drug) do not show an increase in the amount of drug hydrogen-bonded to Neusilin upon storage. In contrast to the proton-donating drugs, decreased drug dissolution was found on storage of progesterone-containing granules.

**Johansen H and Moller N [46]** studied effect of drug to excipient ratio on dissolution of phenybutazone. Solvent deposition method was used. Dissolution rates and particle sizes of phenybutazone solvent deposited on lactose, starch, and silicon dioxide, separately, and of norethindrone and digoxin deposited on lactose were investigated. Microparticulate dispersed drugs on the surface of excipients result when drug-to-excipient ratios are low. Fast dissolution rates are observed for such systems. This effect can be extended to higher ratios when silicon dioxide is used as the excipient. Because of adsorption, however, the release from silicon dioxide is more or less limited.

**Smirnova I [47]** enhanced dissolution of poorly soluble drugs ketoprofen and griseofulvin by adsorption on hydrophilic silica aerogels. It is demonstrated that up to 30 wt% of ketoprofen and 5.4 wt% of griseofulvin can be deposited on hydrophilic aerogels through physical adsorption. The obtained drug-aerogel formulations were characterized by IR- and UV-spectroscopy, XRD and SEM. The release rate of ketoprofen from the drug-aerogel formulation is much faster than that of the corresponding crystalline drugs. The release rate of ketoprofen increases in 500% and that of griseofulvin in 450%, respectively. The reasons for the release enhancement are the enlarged specific surface area of drugs by adsorption on aerogels compared to their crystalline form and the immediate collapse of aerogel network in aqueous media.

**Fukusima et al [48]** enhanced oral bioavailability of Atazanavir (ATZ) by solid dispersion approach. ATV solid dispersions in SLS were prepared by a conventional solvent method and, at ratios of ATV to SLS of 1:2 and 1:3, were demonstrated to form an amorphous state in PXRD analysis and exhibited 2.26- and 2.36-fold improvement in a dissolution test in comparison to bulk ATV, respectively. After oral administration to rats, ATV solid dispersion in SLS at a ratio of 1:2 showed a 3.5-fold increase in BA compared
with bulk ATV. Moreover, the addition of Gelucire 50/13 to ATV solid dispersion, at a total ratio of Gelucire 50/13, ATV and SLS 1:1:2 gave 7.0- and 4.7- fold increase in Cmax and BA compared with bulk ATV, respectively, when the relative BA to RTV-boosted ATV reached 93%.

Yang et al [49] studied effect of melt granulation technique on the dissolution characteristics of griseofulvin. This technique uses meltable binder. Thus, do not require water or organic solvent. Granules were prepared in a lab scale high shear mixer, using a jacket temperature of 60°C and an impeller speed of approximately 20,000 rpm. The effect of drug loading (2.5/5%), binder (PEG 3350/Gelucire 44/14), filler (starch/lactose), and HPMC on the dissolution of griseofulvin was investigated using a half two level-four factor factorial design. The granules were characterized using powder XRD, DSC and SEM techniques. A significant enhancement in the in vitro dissolution profiles of the granules was observed compared to the pure drug and drug excipient physical mixtures. The factorial design results indicated that higher drug loading and the presence of HPMC reduced the extent of dissolution of the drug, whereas, the presence of starch enhanced the dissolution rate. XRD data confirmed crystalline drug in formulation matrices. DSC results indicated monotectic mixtures of griseofulvin with PEG in the granulated formulations.

Deferme et al [50] determined the intestinal absorption of antiviral agent UC-781 and to optimize the experimental conditions of the in vitro system for low solubility compounds. The low solubility of UC-781 was increased by use of solubility/dissolution rate enhancing agents (e.g. VitE-TPGS, Gelucire 44/14). Gelucire 44/14 as a solubilizing agent resulted in a batch-dependent degradation of UC-781. The inclusion of the solubility/dissolution rate-enhancing agent VitE-TPGS did not result in absorption enhancement in the intestinal perfusion technique.

Chauhan B, Shimpi S and Paradkar A. [51] formulated SDs of glibenclamide (GBM). Solid dispersions (SDs) was prepared using polyglycolized glycerides (Gelucire with the aid of silicon dioxide (Aerosil 200); as an adsorbent, were prepared by spray drying technique. SDs and spray dried GBM in comparison with pure GBM and corresponding physical mixtures (PMs) were initially characterized and then subjected to ageing study up to 3 months. Initial characterization of SDs and spray dried GBM by DSC and XRPD
Chapter 2 showed that GBM was present in its amorphous form (AGBM). Improvement in the solubility and dissolution rate was observed for all samples. DRIFT spectroscopy revealed presence of hydrogen bonding in SDs. During ageing study, almost no decrease of in vitro drug dissolution was observed, over the period of 3 months as compared with freshly prepared.

Dixit and Nagarsenker [52] developed surface solid dispersion of celecoxib with superdisintegrants using various techniques like grinding, physical mixing and coevaporation. Coevaporation showed highest drug release. Surface solid dispersion exhibited superior dissolution profiles and improved anti-inflammatory activity in rat paw oedema model. This can be attributed to reduced particle size of celecoxib deposited on the surface of the carrier and enhanced wettability of the drug particles brought about by the carrier.
2.6 INCLUSION COMPLEX USING β-CD BY KNEADING/MICROWAVE DRYING

Yang et al [53] studied structure, thermal stability and water solubility of (Tanshinone II-A)/β-CD. The inclusion complex was prepared by microwave irradiation. The association constant of the complex in water is 210 M⁻¹ as determined from the double reciprocal curve by spectroscopy. The enhanced water solubility of the complex was found. Thermal stability proved the increased thermal stability of the inclusion complex.

Shen et al [54] studied on structure and characterization of inclusion complex of gossypol/β-CD. The inclusion complex was synthesized by microwave irradiation. The structure was determined by means of DTA and TGA. The association constant between gossypol and β-CD measured via UV spectroscopy was 4462 M⁻¹ at room temperature, following stoichiometry 1:2.

Reddy et al [55] prepared and evaluated celecoxib-β-CD complexes. The molecular modeling suggested better correlation in terms of orientation of celecoxib inside the cyclodextrin cavity. Phase solubility profile indicated that the solubility of celecoxib was significantly increased in presence of 3-CD and was classified as Aₘ type indicating 1:1 stoichiometric inclusion complexes. Complexes was prepared by freeze drying, kneading and evaporation. The increase in solubility was observed by complexation. Freeze drying method showed higher dissolution rate than the other complexes.

Francisco et al [56] prepared and characterize the inclusion complex of tolbutamide (TBM) with β-CD. The inclusion complexes in molar ratio of 1:2 were prepared by kneading, coprecipitation, freeze drying and spray drying methods. Characterization was made using DSC, XRD and Raman spectroscopy. In vitro dissolution study showed improvement in the dissolution over physical mixture and free TBM. It was observed that dissolution rate is dependent on method of preparation.

Ozdemir N, Ordu S [57] increases the solubility of furosemide (FR) with inclusion compound of β-CD). The interaction between FR and beta-CD in solution was studied by the solubility method. The phase solubility studies reveal a Bs-type diagram with an
inclusion complex of 1:1 molar ratio and a stability constant of 823.5 M$^{-1}$. The solid complexes of FR with beta-CD were prepared by using freeze-drying, kneading, and co-precipitation methods. Inclusion complexation was confirmed by the results from the studies of XRD, DSC and IR. The dissolution rate of FR was significantly enhanced by inclusion of the beta-CD in the formulations. The rate of release of the active material was found to be dependent on the preparation method of the complexes, and the drug prepared by the kneading method was shown to have the fastest dissolution profile compared to the other methods used in this study.

Chowdry et al [58] prepared and characterized inclusion complex of Nimesulide with $\beta$-CD. Phase solubility study indicated formation of 1:1 complex in solution. Solid inclusion complexes were prepared by kneading and coevaporation. DSC study indicated the formation of inclusion complex at 1:2 ratio. Higher dissolution rates were observed with kneaded complexes.

Ammar et al [59] developed inclusion complexes of glimepiride with $\beta$-CD, Hydroxy propyl - $\beta$-CD and sulfobutylether- $\beta$-CD with or without hydrophilic polymers (PEG 4000) by kneading method. Phase solubility study indicated A$_t$ type of curve in all the systems. It was observed that association of water soluble polymers helps in improving therapeutic efficacy of the product.

Aggarwal et al [60] increased the bioavailability of gliclazide (Gz) by complexation with $\beta$-CD in presence of hydroxyl methyl cellulose (HPMC). Gz-CD complexes were prepared in 1:1 and 1:2 Drug:CD molar ratio by autoclaving, neutralization and kneading methods. The same were prepared also in presence of 0.05 $^\wedge$ w/w HPMC. It was observed that complex enhanced significantly the dissolution rate and addition of HPMC increase its enhancement of dissolution.
2.7 REFERENCES


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