## Chapter 2

### Review of Literature

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2.1 Review of Literature on Ritonavir

Lledo Garcia and his co-workers has proposed pharmacokinetic model to describe the *in vivo* behavior of ritonavir (RTV). Pure RTV at 3 mg dose was administered intravenously and Norvir was given orally at 4.6±2.5 mg dose to male Wistar rats. At the end of 24 hr period blood samples were analyzed of the rats by HPLC technique. A two-compartment model with zero order kinetics was found to be better to the oral and intravenous data. About 76.4% oral bioavailability was obtained by this compartmental approach. Thus, the results suggest saturation of possible specialized transport mechanisms involved in the incorporation of RTV in the body. Thus, low dose of RTV is required for improving the bioavailability when used with other protease inhibitors (Lledó-García et al. 633).

Law, Krill and co-workers prepared amorphous RTV SD with polyethylene glycol 8000 (PEG). The SD prepared showed considerable improvement in the dissolution rate of RTV. PEG was found to have very minimum plasticizing effect on amorphous RTV, which is responsible for its improved stability. Thus, the performance of SD has been attributed to the physicochemical properties of amorphous RTV (Law, Krill, et al. 1015).

Law, Schmitt, et al. formulated amorphous RTV SD with polyethylene glycol 8000 as a carrier with different drug loadings. The *in vitro* and *in vivo* performances were evaluated of the dispersions. Oral bioavailability was determined relative to crystalline drug in beagle dogs by applying a crossover design. The *in vitro* results revealed about 10-fold improvement in the intrinsic dissolution rate compared to crystalline counterpart. Solid dispersions containing 10-30% drug exhibited significant increase in AUC and $C_{\text{max}}$ compared to crystalline part confirmed by *in vivo* study. Increased drug loading thus decreased the dissolution and bioavailability leading to a multiple Level C IVIVC (Law, Schmitt, et al. 563).

Sinha and his co-workers developed SD of RTV by solvent evaporation and melt method for enhancement of dissolution and bioavailability. Gelucire was used as a carrier in ratio of 1:4 of drug to carrier. Solid dispersions prepared were then characterized for DSC, XRD, SEM and FTIR. Biorelevant media was used for dissolution testing to study the effect of food. Bioavailability study was done in Albino Wistar rats of SD prepared by solvent evaporation and melts method and compared with untreated Active Pharmaceutical Ingredient (API). The SD showed significant improvement in the dissolution rate compared to pure drug. The SD
prepared by solvent evaporation method showed slight higher rate of absorption compared to SD prepared by melt method. This was due to formation of eutectic kind of SD. Thus, it can be concluded that SD approach is favorable for enhancement in the dissolution and bioavailability of RTV (Sinha et al. 518).

Harsoliya developed controlled release floating microspheres of RTV by dripping method. The main aim was to increase the gastric residence time. Polymers like sodium alginate and HPMC were used while sodium bicarbonate was used as gas forming agent. The developed microspheres were evaluated for particle size distribution, floating behavior, drug content, entrapment efficiency, morphology and in vitro release study. The developed formulation showed enhanced buoyancy and controlled release of drug (Harsoliya n.pag).

2.2 Review of Literature on Lamotrigine

Amrutkar and his co-workers made an attempt to prepare chewable dispersible tablet of lamotrigine (LTG) and mask its taste by complexation with Precirol ATO-05. The drug to Precirol ATO-05 ratio was varied from 1:0.5 to 1:2 and tablets prepared were evaluated for appearance, content uniformity, hardness, friability, taste evaluation, mouth feel, in vitro disintegration time, and in vitro dissolution studies. Around 90% drug was released in 1 hr from the formulation. The prepared formulation was found to be stable based on the results of stability studies (Amrutkar et al. n.pag).

Patil and Das evaluated the effect of various super-disintegrants on the disintegration time and release profile of LTG. Direct compression method was used to prepare orally disintegrating tablets (ODT) of LTG as it forms porous tablets compared to wet granulation technique. Three super-disintegrants were used i.e. sodium starch glycolate, croscarmellose sodium and crosspovidone XL -10 in combination to get optimum release profile. The tablets were evaluated for weight variation, hardness, friability, in-vitro disintegration time and drug release characteristics. The results revealed good mechanical strength of 3 kg/cm² and dispersion in mouth within 8 seconds. The dissolution profile was found to be similar to the marketed product. Thus, addition of super-disintegrants is beneficial in preparing ODT of LTG (Patil and Das 76).
Goudanavar and Hiremath prepared ODT of LTG by inclusion complexation with hydroxypropyl β-cyclodextrin (HPβCD) by kneading method. The prepared complex was then compressed to tablets using different superdisintegrants such as Kyron T-314, Sodium stach glycolate, Indion 414, Croscarmellose sodium and Crospovidone in different concentration. The prepared tablets were evaluated for weight variation, thickness, hardness, and friability, in vitro dispersion time, wetting time, in vitro disintegration time, drug content and in vitro drug release. Also, they were characterized by FTIR, DSC, and PXRD. The bitter taste was masked successfully by HPβCD. The optimized formulation showed disintegration time of 22.71 seconds and maximum drug release (~99%) within 12 minutes (Goudanavar, Shah, and Hiremath 208).

Rani and Wessam formulated suspension of LTG using locust bean gum as suspending agent, sodium alginate as viscosity enhancer and sodium citrate as anti-flocculant agent. Full factorial design was applied with amount of each ingredient as independent variables and viscosity and sedimentation volume as dependent variables. The results obtained were analyzed for ANOVA and models were generated using multiple linear regression analysis. Contour plots were generated and based on desirability value a checkpoint batch was prepared. The model was found to be validated, as predicted and experimental values were similar. Thus, the prepared suspension showed high sedimentation volume, high redispersibility and optimum viscosity following non-Newtonian type behavior (Rani and Wessam 751).

Gupta and co-workers prepared fast disintegrating tablet of LTG as it is used in epilepsy and convulsion treatment. The main rationale was to provide rapid onset of action and avoidance of abundant amount of water in oral route, which is highly desirable. Full factorial design was applied for optimization. Direct compression method was used for preparing tablets. Here, Kyron T-314 and sodium starch glycolate were used as super-disintegrant, MCC and lactose monohydrate were used as diluents and aspartame as sweetner. The formulations were evaluated for pre- and post- compression characteristics. All the physical characteristics of blend and tablet were found in the acceptable range. The best batch showed around 98.70% drug release in 25 min with disintegration time of 17 seconds and friability value of 0.91% (Gupta et al. 68).
Reddy aimed at improving the solubility of LTG by SD technique and formulate it as ODT. This averted the problem of swallowing and provided rapid onset of action. Tween 80 and Gelucire 44/14 were used as solubility enhancers. Orally disintegrating tablets were prepared by direct compression technique using Kyron T-314, Kyron T-154, and Kyron T-104 as crosslinked polymers at different concentrations. The optimized batch showed 100% drug release in 6 min and disintegration time of 9 sec. The developed formulation was compared with the marketed product and was found to be superior. The stability studies showed that the developed formulation was stable upon storage for three months (Reddy and Reddy 1).

2.3 Review of Literature on Febuxostat

Ahuja and co-workers adopted wet milling technology to prepare febuxostat (FEB) nanosuspension. Nanocrystals were formed using combination of HPMC E3 and Vitamin E-TPGS. Central composite design was adopted for optimization. Bead volume, milling time, polymer and surfactant concentrations were selected as independent variables whereas particle size, polydispersity index and zeta potential were selected as dependent variables. Formulation was characterized by DSC, PXRD, SEM and TEM. In vitro dissolution study was done in media’s of all pH conditions. The results revealed that crystallinity was retained in the structure. A significant increase was observed in the saturation solubility and dissolution rate. Oral bioavailability studies showed significant enhancement in $C_{\text{max}}$ and AUC with about 221.6% increase in relative bioavailability (Ahuja et al. 540).

Asif and his co-workers developed FEB film coated tablet by direct compression method. Optimization was done employing the central composite design. Amount of Avicel PH-102, Magnesium stearate and Croscarmellose sodium were chosen as independent variables. Tablets were evaluated for different parameters pre- and post-coating process. In vitro dissolution study was done in three different dissolution media i.e. 0.1 N HCl, phosphate buffer pH 4.5 and 6.8. The release profile of optimized product was compared with the innovator product. For comparison model-independent and model-dependent methods were used. The optimized batch showed around 81%, 75% and 67% similarity with the innovator in three selected dissolution media respectively. The release kinetics followed the Weibull model. The developed formulation was found to be stable based on the results obtained from accelerated stability studies (Asif et al. n.pag).
Das, Jaiswal and Gupta formulated FEB β-Cyclodextrin complex by kneading method. The complex formed was incorporated into tablets by direct compression method using excipients like crospovidone, croscarmellose, locust bean gum, lactose and microcrystalline cellulose. Tablets prepared with locust bean gum as superdisintegrant was considered as superior. At 10% concentration the tablets showed minimum disintegration time and wetting time. The inclusion complex showed increased solubility around 378.77%. Thus solubility and dissolution rate was enhanced of FEB significantly by this approach (Dass, Jaiswal, and Gupta n.pag).

Kumar and his co-workers aimed at solubility and dissolution enhancement of FEB by preparing its spherical agglomerates. Quasi-emulsion solvent diffusion method was used to prepare it. N, N-dimethyl formamide, chloroform and water were selected as good solvent, bridging liquid and poor solvents respectively. Polyethylene glycol, Poloxomer-F68 and Polyvinyl alcohol were used as a carrier. Spherical agglomerates prepared with Poloxomer-F68 in ratio of 1:1 with FEB showed highest drug release in 60 min. The developed agglomerates were incorporated in to ODT. Different superdisintegrants were tried but the tablets prepared with crospovidone showed rapid drug release (Kumar et al. 191).

Kuchekar et al. prepared FEB complexes with β-cyclodextrin and HPβCD in order to improve its solubility and dissolution. The inclusion complexes with βCD were prepared by spray drying method and showed solubility of about 305.09%. The inclusion complexes with HPβCD were prepared by co-evaporation method that showed highest solubility of about 330.24%. They were further incorporated in to rapid disintegrating tablets utilizing different super-disintegrants by direct compression method. Tablets showed improved dissolution rate as compared to untreated FEB (Kuchekar et al. 168).

2.4 Review of Literature on Candesartan cilexetil

Shukla and Patel together formulated self microemulsifying drug delivery system (SMEDDS) of candesartan cilexetil (CC) for its dissolution enhancement. Various pseudoternary phase diagrams were plotted in order to obtain suitable microemulsion region. SMEDDS developed were evaluated for its microemulsifying properties, other evaluation parameters and in vitro dissolution test. The optimized formulation was composed of Transcutol P as oil phase, Capryol 90 as surfactant and Plurol Oleique as co-surfactant. The SMEDDS formulation
showed complete drug release in 60 min. Thus, it can be used as possible alternative to existing conventional formulations of CC and improvement in bioavailability can be obtained (Shukla and Patel 143).

Detroja, Chavhan and Sawant tried to enhance the oral bioavailability of CC by preparing nanosuspension. It was prepared by media milling method using zirconium oxide beads. Spray drying was used to convert it to solid state. Spray dried suspension was evaluated for particle size, zeta potential, saturation solubility, crystallinity, surface morphology and dissolution behavior. The saturation solubility was increased up to 20 times of spray dried suspension compared to pure drug. In vitro dissolution study showed complete release in 15 min. Antihypertensive activity was studied in rats using DOCA model. About 26.75% decrease in systolic blood pressure was seen with the nanosuspension while with plain drug it showed around 16% reduction. Thus, significant enhancement in antihypertensive activity was seen of nanosuspension of candesartan due to increase in the dissolution rate (Detroja, Chavhan, and Sawant 635).

Nekkanti and his co-workers developed and characterized SMEDDS of CC and filled it in to hard gelatin capsules. Self-microemulsification region was identified from pseudoternary phase diagrams. The optimized liquid formulation was converted in to free flowing powder by adsorption on to a solid carrier and filled in capsules. The liquid formulation, solid SMEDDS and commercial formulations were compared by in vitro dissolution study. Both the solid SMEDDS and liquid formulation showed significant improvement in the rate and extent of drug dissolution compared to commercial tablet formulation. Thus, this approach can be considered as favorable for improving the solubility, dissolution and bioavailability of CC(Nekkanti et al. 9).

Chandan and Maheshwari explored the concept of mixed solvency approach to improve the dissolution rate of CC. This approach helped to reduce the total amount of surfactant employed in designing of SEDDS. Thus, the author proposed here alternate system of solubilizer in place of novel surfactant/cosurfactant system to aid the traditionally involved components in formulation of SEDDS (Chandan and Maheshwari 83).

Sathali, Abdul and Varun designed a unique drug delivery system, which is targeted at small intestine. They prepared mucoadhesive microbeads of CC, which will retain in small intestine
and get absorbed through the mucus layer. This will increase its residence time in intestine, which will increase its bioavailability, reduce the frequency of dosing and prolong the drug release. Ionotropic gelation method is used to prepare the microbeads. The optimized batch comprised of sodium alginate as polymer, calcium chloride as cross linking agent and 1% chitosan as a mucoadhesive agent. Microbeads were evaluated for various test parameters. The mean particle size was found to be increased with increase in the polymer concentration. The entrapment efficiency was in the range of 70-90% for all formulations. The swelling index was reduced with increase in sodium alginate and divalent ions concentration. \textit{In-vitro} drug release followed zero order kinetics, Korse Meyer & Peppas model. The diffusional exponent, n, (0.43 and 0.85) specified anomalous transport or non fickian type and controlled by diffusion through swollen matrix (Sathali, Abdul, and Varun 109).

Sayyad, Tulsankar and Kolap attempted to improve the dissolution of CC by formulating it as liquisolid compact. Tween 80 was used as liquid vehicle, microcrystalline cellulose as carrier, silica as coating material and sodium starch glycolate as superdisintegrant. $^3$ full factorial design was employed for optimization. All the formulations showed higher drug release compared to conventional tablet. Here the drug loses its crystalline structure due to solubilization by the substrate. Thus, the drug gets molecularly dispersed and leads to improvement in dissolution (Sayyad, Tulsankar, and Kolap 381).

Kamalakkannan and his co-workers prepared controlled release polar lipid microparticles using erodible lipophilic excipients like hydrogenated castor oil, stearic acid, cetostearyl alcohol and carnauba wax by fusion method. The particle sizes of the microparticles were found to be not more than 50 microns and the drug content ranged between 98.96 ± 2.1 and 101.9 ± 1.6% in all the formulations. The \textit{in vitro} release profile of all the formulations was followed Higuchi model. Accelerated stability studies revealed the formulated product to be stable. The X-ray diffraction peak of solid dispersion showed disappearance of crystalline peaks and no appearance of new peaks, suggesting the absence of interaction between drug and excipients (Kamalakkannan, Puratchikody, and Ramanathan 125).


2.5 Review of Literature on Lutrol F127

Ahuja, Katare and Singh studied the role of various water-soluble carriers for dissolution enhancement of poorly soluble drug. They prepared solid dispersion of rofecoxib with carriers such as PEG 4000 and 6000, Gelucire 44/14, PVP K25, Lutrol F127 and F68, various polyols, organic acids and hydrotropes. Linear relationship was found between each carrier and the drug solubility from the phase solubility study. Amongst all the carriers poloxamers were found to be most promising for dissolution enhancement. Korsemeyer-Peppas model fitted the *in vitro* dissolution data indicating Fickian diffusion type drug release. Solid state characterization of drug-poloxamer binary system revealed distinct loss of drug crystallinity which can be reason of dissolution enhancement (Ahuja, Katare, and Singh 26).

Kim and his co-workers prepared felodipine SD by solvent wetting method in presence of various carriers. The dissolution rates of SD were much faster than their corresponding mixtures. The dissolution rate was found to be dependent on the type of carrier used. With HPMC as a carrier the dissolution rate of felodipine increased slowly while rapid initial dissolution rate was found with PVP and poloxamer. Also the ratio of drug to carrier affects the dissolution rate. From the X-ray diffraction study it was found that the drug converts to amorphous state due to carriers like PVP, HPMC and poloxamer which can be the reason for the dissolution enhancement (Kim et al. 200).

Ali, William and Rawlinson studied the molecular interactions between model drugs ibuprofen and ketoprofen and poloxamers 407 and 88. Solid dispersions were prepared at different mole ratios. The 2:1 drug:carrier mole ratio SD of ibuprofen showed shifting of carbonyl stretching peak to a higher wave number in the infrared spectra, indicating hydrogen bond formation between the drug and carrier. X-ray diffraction studies revealed no evidence of crystalline form of drug in the said mole ratio systems whereas higher drug loadings retained crystalline ibuprofen. Similar results were obtained with ketoprofen-poloxamer SD. Dissolution rates from solid solutions were 12-fold greater followed by the eutectic system which gave a 6-fold improvement over the powder. Thus, the nature of drug:carrier interactions are governed by the stochiometry of the composition, and thus is an important parameter for consideration of formulating solid dispersions to improve the delivery of poorly-water soluble drugs (Ali, Williams, and Rawlinson 162).
Chutimaworapan and his co-workers prepared SD of nifedipine with PEG 4000 and 6000, HPβCD, and poloxamer 407 in four mixing ratios by melting, solvent, and kneading methods in order to improve the dissolution. The dissolution rate enhancement was found to be dependent on the mixing ratio and the preparation method. The highest dissolution rate was obtained with poloxamer 407 SD prepared by the melting method in the ratio of 1:10 of drug to carrier. Around 80% of drug release was obtained in 15 min. Conversion from crystalline form to amorphous form was confirmed from the XRD and DSC study. Thus dissolution rate enhancement can be the result of hydrogen bonding between the drug and poloxamer which is confirmed by IR spectroscopy (Chutimaworapan et al. 1141).

Shazly and co-workers formulated flufenamic acid SD using Pluronic F-127 and Gelucire 50/13 as carriers. The main objective of this study was to enhance the dissolution rate of the drug. Solvent evaporation technique was used to prepare SD at different drug:polymer ratios. The dissolution study showed enhancement of drug dissolution in ratio of 1:1 of drug:polymer. The in vitro skin permeation from Carbopol 940 gel base through abdominal rat skin membranes showed that highest drug permeation was found from flufenamic acid-Pluronic combination followed by flufenamic acid-Gelucire SD while untreated drug showed slower permeation. Furthermore, about 96% and 84% of local anti-inflammatory activity was seen in 4 hr in the formalin induced paw edema by flufenamic acid SD with Pluronic and Gelucire respectively (Shazly et al. 299).

AlMuhaissen and co-workers identified the role of two surface-active carriers, Gelucire® 44/14 and Lutrol® F127, for improvement of solubility and dissolution of the high-dose, poorly water-soluble drug, albendazole, using SD approach. The solubility of albendazole showed improvement with the studied carriers. Higher percentages of Lutrol® F127 were found to be best solvents. Melting method was used to prepare the SD, which was further compressed into tablets. In vitro dissolution of the tablets showed enhanced dissolution. Thus, increase in the wettability of albendazole by the carriers and formation of partial solid solutions of it in the carrier system can be considered to be the mechanisms of the improvement in its dissolution (AlMuhaissen et al. n.pag).
2.6 Review of Literature on Labrasol

Yuksel et al. investigated the *in vitro* and *in vivo* performance of the semi-solid dispersion of piroxicam prepared with Gelucire 44/14 and Labrasol into hard gelatin capsules for enhancing the dissolution rate of the drug. The prepared dosage form was then compared with pure API and commercial available tablets of piroxicam. The dissolution studies were carried out in different media. The SD dosage form showed about 85% drug release within 30 min in each of the media. Oral bioavailability study was also done and results were compared after administration of a single dose of 20 mg piroxicam to eight healthy volunteers. Highest apparent rate of absorption was seen of piroxicam from the SD followed by commercial product and the pure drug. The relative bioavailability of SD with respect to pure drug and commercial product was found to be 221 and 98.6% respectively. Thus, it can be concluded that the formulated SD of piroxicam shows rapid onset of action, and hence can be useful especially in various painful condition (Yüksel et al. 453).

Hu et al. aimed at finding the effect of a novel emulsifier, Labrasol, on the absorption of gentamicin from the GI tract of rats. Labrasol microemulsions of gentamicin were prepared and administered to rat intestine and colon. Plasma levels following intestinal application were compared with intravenous (i.v.) administration route. A 5 mg/kg dose of gentamicin preparation containing Labrasol, 1 ml/kg, administrated into colon resulted in the mean AUC of 21.179±1.374 µg.h/ml, compared to 7.813±0.105 µg.h/ml obtained with i.v. administration of gentamicin, 1 mg/kg. The absolute bioavailability of the Labrasol preparation was found to be 54.2 %. Thus, Labrasol is responsible for enhanced drug absorption from GI lumen into the systemic circulation and inhibition of efflux of gentamicin from the enterocytes to the GI lumen (Hu et al. 2899).

Soliman and Khan studied the increase in the dissolution characteristics of flurbiprofen by preparing a semi-solid dispersion with Gelucire 44/14 and Labrasol in hard gelatin capsules. The results were evaluated by comparing several *in vitro* parameters with powdered drug filled into hard gelatin capsules. The *in vitro* dissolution testing of the dosage forms was performed in different media. Characterization of semi-solid dispersions and physical mixtures was performed using FTIR, DSC, and particle size analysis and turbidity measurement. The results suggest that all semi-solid dispersions of flurbiprofen showed a remarkable improvement in the rate and extent of drug dissolution. The dissolution of
flurbiprofen within 30 min in pH 1.2 was 55%, in pH 4.5 was 67%, pH 6.8 was 96%, pH was 7.2 98% and in water was 88%. FTIR indicated no strong drug: excipient interactions and DSC studies indicated a loss of crystalline nature of the drug. The particle size analysis revealed an average size diameter from 194 to 278 nm. Therefore, a semi-solid dispersion of flurbiprofen with Gelucire and Labrasol may have the potential of improved bioavailability because of the enhanced in vitro properties (Soliman and Khan 288).

Li, Yi and Lam investigated the effects of spray drying and the use of different solid carriers on concentrations of Labrasol® and Transcutol® in solid SMEDDS of scutellarin. Here, lactose, HPMC and MCC were used as solid carriers. Lactose and HPMC were found to better than MCC in preserving the Labrasol and Transcutol content as well as in maintaining the desired droplet size. Thus, it can be concluded that spray-drying could increase the droplet size of solid SMEDDS and decreased the concentration of Labrasol and Transcutol therein, but use of water-soluble solid carriers could overcome the problem better than insoluble carriers used in the solid SMEDDS (Li, Yi, and Lam 545).

Sheen et al. tried to improve the bioavailability of a poorly water-soluble drug, RP 69698 (RP) by formulating it as SD. Melt method with water-soluble carriers was used for its preparation. The aqueous solution of drug showed bioavailability of about 6%. The formulation consisting of PEG 3350, Transcutol and Labrasol showed bioavailability of 11.8%. Addition of a surfactant, polysorbate 80, at strength of 10% to the dispersion with PEG 3350 and Labrasol as carriers increased the bioavailability from 11.8 to 27.6%. DSC and powder XRD data revealed that the major fraction of drug was dissolved in the carrier. Thus, increase in the wettability and spreadability of the drug in a solubilized state once released in the gastrointestinal medium due to the surfactant property is considered to be responsible for this improvement (Sheen et al. 221).

Shafiq and Shakeel evaluated the capacity of a combination of Labrasol and Plurol oleique as surfactant and cosurfactant on self-nanoemulsification efficiency of ramipril nanoemulsion. Sefsol-218, Labrasol, Plurol oleique, and standard buffer solution (pH 5.0) were selected as oil phase, surfactant, cosurfactant, and aqueous phase, respectively. Spontaneous emulsification method was chosen to develop the nanoemulsion formulations of ramipril. Selected formulations were evaluated for thermodynamic stability tests using centrifugation, heating–cooling cycles, and freeze–thaw stress test. Thermodynamically stable formulations
were taken for self-nanoemulsification efficiency test. All the selected formulations passed self-nanoemulsification test in grade E. As none of the formulations passed the self-nanoemulsification efficiency test in grades A and B, it was concluded that a combination of Labrasol and Plurol is not suitable as surfactant and cosurfactant, respectively, for oral or self-nanoemulsifying drug delivery system of ramipril (Shafiq and Shakeel 7).

2.7 Review of Literature on Transcutol

Panchagnula and Ritschel developed a topical delivery system using 50% Transcutol to decrease the body burden of topically administered dexamethasone and hydrocortisone. The *in-vitro* dissolution studies showed 29.6% dexamethasone and 45.5% hydrocortisone release in 10 hr, while control formulation showed 23.0 and 39.9 %, respectively. *Ex-vivo* evaluation study using rat whole skin in a diffusion cell showed a 2-fold increase in the retention of dexamethasone and a 3-fold increase in the retention of hydrocortisone in the skin at the end of the permeation experiments compared with control formulations. *In-vivo* studies were made using a formulation containing [3H] hydrocortisone applied to rat skin, followed by measurement of total radioactivity in the blood. For the Transcutol formulation the area under the blood concentration-time curve (0–96 h) was 6.06± 1.27 compared with 2.52 ± 0.43 × 10^6 d min^{-1} mL^{-1} h for the control formulation, indicating a 58% reduction in body burden (Panchagnula and Ritschel 609).

Xi et al. formulated a self-nanoemulsified drug delivery system (SNEDDS) of a poorly water-soluble herbal active component oleanolic acid for oral delivery. Four formulations were prepared utilizing Sefsol 218 as oil phase, Cremophor EL and Labrasol as primary surfactants, and Transcutol P as cosurfactant. The oleanolic acid concentration was fixed at 20 mg/g. The *in-vitro* dissolution studies showed a remarkable increase in dissolution for the SNEDDS in comparison to the commercial tablet. The oral absorption of oleanolic acid from SNEDDS showed a 2.4-fold increase in relative bioavailability compared with that of the tablet, and an increased mean retention time of oleanolic acid in rat plasma was also observed compared with that of the tablet. These results suggest the potential use of SNEDDS to improve dissolution and oral bioavailability for poorly water-soluble triterpenoids such as oleanolic acid(Xi et al. 172).
Hong et al. developed self-emulsifying drug delivery system (SEDDS) of itraconazole to enhance its dissolution and oral absorption. Among the surfactants and oils studied, Transcutol®, Pluronic® L64 and tocopherol acetate were chosen as they showed the maximal solubility of itraconazole. Itraconazole in the SEDDS rapidly dissolved in both the dissolution medium (simulated gastric fluid without pepsin (pH 1.2) and simulated intestinal fluid (pH 6.8)) whereas the Sporanox® showed different dissolution patterns. In vivo bioavailability study was done in rats. AUC$_{(0-24)}$ and C$_{max}$ of SEDDS were comparable to Sporanox in fasted state conditions. However, in fed lipidic diet group, AUC and C$_{max}$ after oral administration of SEDDS in rats were 3.7- and 2.8-fold higher, respectively, compared with those of Sporanox. Thus, the results demonstrate that the SEDDS of itraconazole composed of Transcutol®, Pluronic® L64 and tocopherol acetate greatly enhanced the bioavailability of itraconazole. Thus, this system may provide a useful dosage form for oral water-insoluble drug (Hong et al. 332).

Mustafa et al. aimed at targeting ropinirole, an anti-Parkinson drug to brain via intranasal route. They formulated a thermodynamically stable and infinite dilutable nanoemulsion (o/w). The optimized formulation contained 2 mg of ropinirole along with Sefsol 218 (10% v/v), tween 80 (18% v/v), Transcutol (18% v/v) and water (54% v/v) as matrix, surfactant, cosurfactant and aqueous phase respectively. The optimized formulation showed adequate drug release (72.23±9.56%), globule size (58.61±5.18), polydispersity (0.201), viscosity (31.42±6.97 mPas), and infinite dispersion capability. The ex vivo study showed significant high (p<0.005) drug translocation in different parts of Wister rat brain. From in vitro, ex vivo and in vivo results it can be concluded that the intranasal ropinirole nanoemulsion is a promising approach for better management of Parkinson’s disease (Mustafa et al. 348).

Singh et al. worked on formulation development of liquid SNEDDS to enhance the bioavailability of carvedilol. Capmul PG8, Cremophor EL and Transcutol HP were selected as oil phase, surfactant and co-surfactant respectively for formulation of SNEDDS. The central composite design was used for optimization of SNEDDS. Optimized batch was evaluated for various parameters like drug release, emulsification time, emulsion droplet size, and mean dissolution time. In vitro drug release studies depicted a non-Fickian kinetic behavior from SNEDDS. Accelerated studies of 6 months of the optimized formulation indicated high stability of the formulation. The in situ perfusion studies carried out in wistar rats showed several fold augmentation in the permeability and absorption rate of the
optimized formulation compared to marketed formulation. Thus, the present studies justified the potential of SNEDDS in improving the oral bioavailability of BCS class II drugs (Singh et al. 599).

2.8 Review of Literature on Neusilin

Gumaste et al. developed tablet formulations of probucol by adsorbing its liquid SEDDS onto Neusilin®US2, a porous silicate. Capmul MCM, Captex 355 and Cremophor EL were selected as oil and surfactant phase respectively. The solutions were directly adsorbed onto Neusilin®US2 at 1:1 w/w ratio. The powders were evaluated for content uniformity, bulk and tap density, compressibility index, Hausner ratio and angle of repose. The powders were then compressed into tablets. Tablets with good tensile strength were obtained. Complete drug release from tablets was observed if the SEDDS. Thus, liquid SEDDS were successfully developed into tablets by adsorbing them onto Neusilin US2 (Gumaste, Dalrymple, and Serajuddin 3186).

Krupa et al. evaluated the influence of Neusilin US2 on ibuprofen stability at higher temperatures. Seven binary mixtures of the drug and the silicate were prepared. They were examined by thermogravimetry, quadrupole mass spectrometry and differential scanning calorimetry. The results confirmed that in the presence of Neusilin US2 ibuprofen free acid reacted to form a higher melting, less volatile salt. The presence of the salt was additionally confirmed by FT-IR and H-NMR spectra. Thus, it can be concluded that Neusilin US2 had a beneficial effect on the drug stability. The drug to silicate ratio to protect the highest amount of the drug was found to be 40:60 and 50:50 weight percent (Krupa et al. 12).

Mallapa et al. formulated calcium alginate and Neusilin US2 nanocomposite microbeads containing preconcentrate of aceclofenac sodium liquid microemulsion for enhancement of oral bioavailability. The preconcentrate liquid microemulsion was prepared by using Labrafac PG, Labrasol, and Span 80 as oil, surfactant, and cosurfactant, respectively. The solid calcium alginatenanocomposite microbeads of liquid microemulsion were prepared by microemulsification internal gelation technique. Liquid microemulsion was found to have good thermodynamic stability with globule size of 32.4nm and polydispersity index of 0.219 and $-6.32\text{mV}$ zeta potential. All the formulations showed minimum drug release in simulated gastric fluid (SGF) pH 1.2 for initial 2hr, maximum drug release in pH 6.8 phosphate buffer
solution at 6hr, followed by sustained release in simulated intestinal fluid of pH 7.4 up to 12hr. This was due to the interaction of sodium alginate with Neusilin US2 which creates a thick gel like structure and act as a barrier to control the release of drug in the alkaline pH environment. Thus, liquid microemulsion solid nanocomposite microbeads prepared using Neusilin US2 enhanced the dissolution rate of poor water soluble drugs and sustained the drug release for prolonged period of time (Mallappa, Kes arla, and Banakar n.pag).

Park et al. prepared a liquid SMEDDS of simvastatin. The SMEDDS was prepared using Capryol 90 as the oil phase, Kolliphor® EL as a surfactant and Transcutol® P as a co-surfactant. Four types of adsorbents with high specific areas were used namely Aerosil® 200, Silysia® 350, Neusilin® US2, Neusilin® UFL2. SEM, DSC, and PXRD results revealed rough-surfaced particles that represent the amorphous state of s-SMEDDS. The optimized formulation with Neusilin® UFL2 markedly improved drug release. Thus, the present study concluded that s-SMEDDS was effectively formulated via adsorption with solid carriers (Park, Choi, and Kang 1).

Patel and Dave developed an eco-friendly technique using liquid salt, which can offer improvement in dissolution while maintaining long-term stability. The liquid salt formulations of poorly soluble model drugs ibuprofen, gemfibrozil and indomethacin were developed using 1-Ethyl-3- methylimidazolium ethyl sulfate (EMIM ES) as a non-toxic and environmentally friendly alternate to organic solvents. Liquid medications containing clear solutions of drug, EMIM ES and polysorbate 20, were adsorbed onto porous carrier Neusilin US2 to form free flowing powder. Liquid loading as high as 70% w/w was achieved while maintaining good flowability and compressibility. The liquid salt based formulations demonstrated greater rate and extent of dissolution compared to crystalline drugs. These samples exposed to 40°C/80% RH for 8 weeks, demonstrated excellent physical stability without any signs of precipitation or crystallization. Thus, the liquid salt formulation technique served as compelling alternate to the conventional techniques for the development of poorly soluble compounds (Patel and Dave 2316).

Vadher et al. enhanced the dissolution of poorly water-soluble drug aceclofenac by co-grinding with novel porous carrier Neusilin US2. Aceclofenac was co-grinded with Neusilin US2 in a ratio of 1:5 in ball milling for 20 hr. Samples of co-ground mixtures were withdrawn at every 5 hr. and characterized for FTIR, DSC and XRD. The analysis revealed the
conversion of crystalline aceclofenac to its amorphous form upon milling with Neusilin US2. The *in vitro* dissolution rate of aceclofenac from co-ground mixture was significantly higher compared to its untreated form. The accelerated stability study of was carried out for 4 weeks, and showed no reversion of amorphous to crystalline form. Thus, a porous carrier like Neusilin US2 is very helpful in improvement of dissolution of poorly soluble drugs (Vadher et al. 606).

### 2.9 Review of Literature on Vitamin E-TPGS

Dai et al. studied the potential of various surfactants and their combinations at low concentrations as potent inhibitor of drug precipitation in aqueous medium. A model compound used in this study showed a sharp pH-dependent solubility profile with more solubility in simulated gastric fluid (pH 1.2) than in simulated intestinal fluid (pH 7.4). The compound was first dissolved in simulated gastric fluid with each surfactant. The solutions were then dispensed into the wells of a 96-well microtiter plate by a TECAN robot and diluted 10-fold with simulated intestinal fluid. After a preset incubation time at room temperature, the solutions were filtrated. HPLC was used to measure the compound concentration in the filtrate. Pluronic F127 and Pluronic F108 inhibited the compound precipitation in simulated intestinal fluid below their critical micelle concentration. Combinations of Pluronic F127 or Pluronic F108 with Vitamin E TPGS showed significantly stronger inhibition than the individual surfactants, indicating synergistic effects on inhibition of drug precipitation (Dai et al. 31).

Zhao and Feng formulated paclitaxel loaded polymeric nanoparticles composed of PLGA with vitamin E TPGS as emulsifier for oral chemotherapy. Nanoparticles prepared by a modified solvent extraction/evaporation technique were observed in spherical shape of 200–300nm diameter with high drug encapsulation efficiency of 80.9%. The *in vitro* viability experiment showed that at 2.5µg/mL concentration of paclitaxel, the nanoparticulate formulation was found to be 1.28, 1.38, 1.12 times more effective than Taxol® after 24, 48, 72hr incubation with MCF-7 human breast cancer cell line. *In vivo* evaluation showed 10 times higher oral bioavailability of TPGS-emulsified PLGA NP formulation than Taxol. This resulted in 9.74-fold higher therapeutic effect and 12.56-fold longer sustainable therapeutic time. Thus, the formulation of vitamin E TPGS emulsified PLGA nanoparticles is a promising approach for paclitaxel oral administration (Zhao and Feng 3552).
Ghosh et al. developed a nanosuspension of a poorly soluble drug with Vitamin E TPGS by wet media milling technique to achieve superior *in vitro* dissolution and high *in vivo* exposure in pharmacokinetic studies. Due to the strong hydrophobic interaction between vitamin TPGS and the drug molecule the formulation showed significant improvement in the *in vitro* dissolution and *in vivo* plasma level. HPMC 3 cps was found to be the best stabilizer amongst others to prevent crystal growth that was observed during stability studies (Ghosh et al. 260).

Mu and Seow investigated the molecular interaction of TPGS at the air–water interface, its effect on a model bio-membrane composed of dipalmitoylphosphatidylcholine lipid monolayer, and the interaction between the TPGS coated nanoparticles with the lipid model membrane. Paclitaxel loaded polymeric nanoparticles were prepared with TPGS and characterized for drug encapsulation efficiency and release kinetics. The results demonstrate that surfactant stabilizer influences the drug incorporation capability and the release characteristics of drug-loaded nanoparticles. Also, TPGS exhibited noticeable effect on the surface properties of air–water interface as well as the lipid monolayer. The penetration of various nanoparticles into the model membrane revealed an optimal balance between hydrophilicity and hydrophobicity on nanoparticle surface. Thus, balance is essential for an effective cellular uptake of nanoparticles (Mu and Seow 90).

Pawar et al. developed lipid based oral formulations for ‘difficult to deliver’ molecules like curcumin. They prepared lipid based oral formulations for curcumin using Gelucire 44/14, Labrasol, Vitamin E-TPGS and PEG 400 with superior drug loading and enhanced oral bioavailability. The optimization of formulation for curcumin was carried out by Box–Behnken design. The loading and post dilution droplet size was evaluated. Oral bioavailability of optimized formulation was evaluated in male Sprague-Dawley rats at a dose of 250 mg/kg. Control curcumin showed $C_{\text{max}}$ and $AUC_{0-\infty}$ of 32.29 ng/ml and 38.07 ng h/ml, respectively. Lipid based oral formulations improved $C_{\text{max}}$ and $AUC_{0-\infty}$ by 11.6 and 35.8 folds respectively over control (Pawar et al. 617).

Mi, Zhao and Feng developed a Vitamin E-TPGS prodrug micelle system with cisplatin as a model hydrophilic drug. A high drug load of 4.95% (w/w) and a pH-responsive drug release kinetics and higher cellular uptake was observed in comparison with the original drug and the TPGS-cisplatin prodrug itself. They demonstrated that such a system can successfully deliver the drug with a low critical micelle concentration (CMC) of only 5.01 mg/L. The cell viability
experiment showed great enhancement of the cisplatin chemotherapy. The IC50 value was reduced from 3.95, 0.98, 0.19 for cisplatin to 1.36, 0.51, 0.08 µg/mL for the TPGS prodrug micelle formulation after 24, 48, 72 hr culture with the HepG2 hepatocarcinoma cells, respectively. Additionally, TPGS prodrug micellar formulation showed significant neuroprotective effects by greatly increasing IC50 value for the SH-SY5Y neuroblast-like cells. The TPGS prodrug micelles can also be generalized to become a new strategy for co-delivery of hydrophilic and hydrophobic drugs and/or imaging agents (Mi, Zhao, and Feng 98).

2.10 Review of Literature on Solid Dispersion Adsorbate

Charumanee and co-workers prepared surface solid dispersion of piroxicam to improve its dissolution behavior. The surface solid dispersion was prepared by coevaporation method using microcrystalline cellulose and potato starch. It was found from the dissolution study that the dissolution of the drug from the surface solid dispersion was higher than those of the untreated drug. The degree of the dissolution rate enhancement depended on the nature and the amount of the carrier. The dissolution rate of the drug in potato starch based surface solid dispersion was considerably higher than that in the microcrystalline cellulose based. Also higher the amount of the carrier used, higher the dissolution rate was obtained. Thus, surface solid dispersion is of piroxicam is useful in dissolution enhancement (Charumanee, Okonoki, and Sirithunyalug 77).

Makar et al. did a comparative study between carriers and techniques used to prepare solid mixtures with glimepiride. Mixtures were evaluated for drug content and dissolution. Physical and co-ground mixtures, SD and their adsorbates, triple solid dispersions and their adsorbates, microwave generated or treated SD was prepared. Results revealed that maximum enhancing effect was achieved with ternary solid dispersion adsorbate. Among the carriers used the highest dissolution rate was attained with pregelatinized starch. This was due to differences in chemical nature and relative water solubility of carriers. Thus, the combined effects of incorporating surfactants, polymers and adsorbents to glimepiride contributed together to improve wetting, reduce crystallinity and caused substantial increase in the surface area which made them the most promising approach for enhancing dissolution of glimepiride (Makar et al. 115).
Shah et al. made an attempt to enhance dissolution of nebivolol using SD and SDA techniques. Various hydrophilic excipients such as PEG 6000, gelucire 50/13, and Neusilin US2 at different ratios were used. The prepared SDA was characterized for % drug yield and other physical characteristics and *in vitro* drug dissolution studies in 0.1N HCl. The FTIR study indicated no interaction between the drug and polymer. DSC thermograms showed the significant change in melting peak of the drug when prepared as SDA suggesting the change in crystallinity. The data from the XRD showed that the drug was still detectable in its solid state in the SDA of PEG and disappeared in case of higher ratio of Gelucire. An increased dissolution rate of NB at pH 1.2 was observed when the drug was dispersed in these carriers in the form of physical mixtures, SDs by solvent evaporation methods, SDs by fusion method and SDAs by fusion method. Nebivolol released faster from the SDAs than from the pure crystalline drug, the physical mixtures, or the SDs. Thus, this study was proved as a promising approach for the improvement of dissolution rate and solubility of nebivolol (Shah et al. 49).

Zayed studied the effect of surface solid dispersion of ketoprofen with Aerosil 200 on the dissolution rate. Surface solid dispersion containing increased amount of the carrier (1:1 and 1:2) were prepared by surface deposition of ketoprofen from alcoholic solution on the surface of aerosil 200. The increase in the dissolution rate of the adsorbate compared with untreated drug is due to the conversion of the drug form the crystalline state to the highly energetic amorphous state as proved by DTA and XRD. The surface solid dispersion proved to be efficient method for improving the dissolution of low water soluble drug which results in dramatic increase in the dissolution rate, rapid absorption, enhanced biological activity and reduced side effects (Zayed 33).
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