Chapter 3
Review of Related Literature

REVIEW OF RELATED LITERATURE

Bhise *et. al.* developed Rifampicin (RIF) loaded porous microspheres employing Eudragit for sustained release action. They reported that microspheres were prepared by emulsion solvent diffusion method. The critical findings of the investigation suggest that ratio of drug to Eudragit was critical for entrapment efficiency. Scanning Electron Microscopy studies conducted by researchers confirmed the spherical and porous structure of microspheres. *In vitro* drug release studies reported that drug to polymer ratio of 2:1 demonstrated more than 85% drug release over the period of 3 hr [1].

Pillay *et. al.* developed dry reconstitutable multiparticulate of anti-TB drugs RIF and isoniazid (INH). In that ionotropically crosslinked polymeric enterospheres for delivery of INH to the small intestine were developed. Response surface methodology was employed for the design and optimization of the formulation and processing variables. They varied concentration of zinc sulfate salting out and crosslinking electrolyte, the crosslinking reaction time, the drying temperature and the concentration of triethyl citrate plasticizer for determination of their effect on the molar amount of zinc (nZn) incorporated in the crosslinked enterosphere, drug entrapment efficiency (DEE), and mean dissolution time (MDT) at t_{2hr} in acidic media (0.1 M HCl). The results reported that the salting out and crosslinking agent and the plasticizer significantly affected nZn and the DEE. The temperature at which the enterospheres were annealed also significantly affected the DEE. For RIF, they prepared reconstitutable granules for suspension [2].

Gohel *et. al.* developed dosage form of RIF and INH comprising two floating tablets of RIF 150 mg and enteric coated capsule containing INH 150 mg blend (immediate release) together in one size 00 hard gelatin capsules. They found that RIF was released over 4 hours following zero order kinetics and INH was released more than 90% in phosphate buffer pH 7.4. They reported noteworthy reduction of degradation of RIF from the dosage form containing enteric coated INH capsule and floating RIF tablet at the end of 75 minutes of dissolution [3].

Zhonggui *et. al.* developed enteric coated tablets of RIF and INH for improving bioavailability of theirs fixed dose combination (FDC). They studied RIF stability in presence and in absence of INH at various pH buffers from 1.0-7.4. The results

reported that RIF degraded in the presence of INH to a higher extent at pH 1.0-4.5 and degradation of RIF is suppressed by the existence of INH in pH 6.8. Hence, enteric coated tablet of combination was developed by them [4].

Avachat and Bhise developed FDCs of RIF and INH based on degradation studies of RIF in presence of INH in different ratios. They studied degradation in ratios RIF:INH (i) 1:0.1, (ii) 1:0.25, (iii) 1:0.5, and (iv) 1:0.75 in 250 ml solution having pH of 1.2, 2.0 and 3.0 medias in USP apparatus II at 25 rpm. Their studies revealed that degradation of RIF is reduced to less than 10% when the ratio of RIF: INH is below 1:0.25. Based on the above findings they prepared bilayered tablets with this concept and checked human bioavailability of formulation. Bioavailability studies revealed that both Cmax and AUC for RIF were increased. The finding also suggests the pH of microenvironment surrounding of RIF, specifically in the presence of INH affects its degradation significantly [5].

Samad *et. al.* developed reconstituted powder for suspension of RIF and INH, formulated as microspheres. The results stated that RIF slowly diffuses out through the hydrogel matrix formed due to swelling of gelatin in acidic environment thereby sustaining the drug release in an acidic environment, while release of INH from alginate microspheres was very low in simulated gastric fluid pH 1.2 but its release was sustained in simulated intestinal fluid pH 7.4 [6].

Hiremath and Saha developed and evaluated controlled release RIF formulation using HPMC as controlled release polymer. In one study they used HPMC 15 cps and found that release was controlled upto 16 hours using 40% w/w HPMC of the drug content. Further increase in concentration did not result in significant change in release rates. They also found variation in release rates and release character on varying in compression force. In another study they evaluated three different grades of HPMC low, medium and high viz. HPMC 100 cps, HPMC 4000 cps and HPMC 15000 cps respectively and studied the influence of drug: HPMC ratio, viscosity grade of HPMC, drug particle size and compression force on the formulation characters and drug release. Results reported that in general, decrease in the drug particle size decreased the drug release and lower viscosity HPMC polymer was found to be more sensitive to the effect of compression force than the higher viscosity. They developed

series of formulations varied extending release from 12 hours to 24 hours with various release mechanism [7, 8].

Pund *et. al.* reported delayed release INH formulation consisted of INH pellets for site specific release into intestine. The core pellets were prepared with high drug loading using extrusion and spheronization. The core pellets were enteric coated using aqueous coating of Sureteric®. The study demonstrated importance of various parameters like amount of binder, water and spheronization speed on several physicomechanical properties of INH core pellets [9].

Ahmed *et. al.* developed enterosoluble microparticles of acid labile protein lactase using solvent evaporation method employing various kind of Eudragit. They found percentage yield and entrapment efficiency was directly proportional to solid content. Moreover, the prominent factor that affected lactase stability was Eudragit type followed by processing conditions and solid content. Their results revealed dependable control of lactase release using pH dependant polymers but lactase activity was preserved only in acetone based formulations [10].

Majumdar *et. al.* developed submicron particle of enzyme papain for its enteric delivery employing w/o/w emulsion solvent evaporation technique and using various pH sensitive polymers like hydroxypropyl methylcellulose phthalate (HPMCP), Eudragit L100, and Eudragit S100, to avoid gastric inactivation of papain. The results disclosed that maximum entrapment efficiency, smallest particle size and minimal loss of enzyme activity were provided by smaller internal and external aqueous phase volumes. Eudragit L100 and HPMCP particles showed complete release of papain in the pH environment of small intestine within few hours in comparison to Eudragit S 100 which needed longer time for drug release. Stability studies results revealed that formulations with approximately 6% overages would provide two year shelf life at room temperature [11].

Singh *et. al.* developed delayed release micropellets of lansoprazole using fluid bed processor. The process included firstly drug layering onto sugar spheres, then barrier coating and finally enteric coating. Optimized formulation exhibited good gastric resistance in acidic media and showed comparative dissolution with marketed preparation in buffer media [12].

D'Souza *et. al.* carried out surface coating of bromophenol blue loaded albumin microspheres with Eudragit L-100-55 using spray dryer. The procedure employed involved suspending microspheres in polymeric solution and spray drying it. The efficiency of enteric coating was determined in simulated gastric fluid. The results revealed that drug release from coated microspheres was significantly lower than uncoated microspheres [13].

Saraf *et. al.* developed and optimized gentamycin loaded Eudragit RS100 microspheres for sustained release upto 24 hour using modified double emulsion method. They employed 3^2 full factorial design to study effect of amount of glycerol and sodium chloride on entrapment efficiency, size and % yield. The results divulge that effect of sodium chloride was more on entrapment efficiency and % yield while effect of glycerol was more on size [14].

Lauro *et. al.* developed gastroresistant microparticles of hseperidin for its oral delivery employing spray drying technique and using cellulose acetate phthalate as enteric polymer. They prepared microparticles in different polymer : drug ratio and a series of enhancers of the dissolution rates like Tween 80, carboxymethylcellulose crosslinked or sodium dodecylbenzene sulfonate. They found that microparticles showed good gastro resistance but incomplete drug dissolution in simulated intestinal fluid. The incorporation of release enhancers was able to augment the dissolution rate in simulated intestinal fluid without altering polymer ability to protect hespiridin in acidic media [15].

Saraf *et. al.* studied influence of various formulation parameters on in preparation of enzyme loaded Eudragit S 100 microspheres. A 3^2 full factorial experimental design was used to investigate effect of amount of solvent (dichloromethane) and stabilizer (Tween 20, 40 or 80) on drug content and particle size. The results unveil that effect of stabilizer was higher on both the responses i.e. drug content and particle size whereas solvent concentration comparatively produced significant effect on particle size. *In vitro* proteolytic activity was used to assess effect of formulation variable on integrity of enzyme. Moreover, results also demonstrated that approximately 6 to 7% release of enzyme in the acidic media [16].

Maghsoodi prepared naproxen microparticles comprising Eudragit L100 and Aerosil to avoid its local gastrointestinal irritation. The microparticles were prepared using

emulsion solvent diffusion method. The process engross ethanol as good solvent, dichloromethane as bridging liquid, water as poor solvent, Aerosil as antiadherent and sodium dodecyl sulphate as dispersing agent. The microparticles demonstrated incorporation efficiency > 79% and yield>71%. Moreover, enhanced incorporation efficiency was observed with increasing excipient to drug ratio and initial difference of temperature between solvent and non solvent. The microparticles also demonstrated good gastroresistance [17].

Radhika *et. al.* developed delayed release microspheres of aceclofenac using cellulose acetate phthalate. They further evaluated effect of other enteric polymers like hydroxyl propyl methyl cellulose phthalate (HPMCP), Eudragit L 100, and Eudragit S -100 on release of aceclofenac from CAP microspheres. The results disclosed that HPMCP exhibited positively whereas Eudragit L100 and Eudragit S 100 exhibited negative influence on drug release [18].

Shah *et. al.* studied impact of variables on aceclofenac microspheres prepared by spray drying. They studied impact of drug to polymer ratio and feed flow on percent yield, particle size and encapsulation efficiency using 3^2 full factorial design. The results revealed that impact of drug to polymer ratio was more on yield and encapsulation efficiency while that of feed flow was more on particle size [19].

Wu *et. al.* prepared solid dispersion of lansoprazole with povidone (PVP) for solubility enhancement using fluid bed coating technique. In brief procedure involved dissolving lansoprazole and PVP in organic mixture of acetone/ethanol and spraying onto fluidized non pareil cores. *In vitro* dissolution test in pH 7.4 revealed significant enhancement of dissolution at lansoprazole/PVP ratio of 1:1.75 or more. The differential scanning calorimetry and powder X-ray diffraction technique revealed amorphous nature of drug. The Fourier Transform-Infra Red spectrometry revealed hydrogen bonding between lansoprazole and PVP [20].

Wu *et. al.* prepared and evaluated lansoprazole/cyclodextrin complexation using fluid bed coating technique. They employed both β-cyclodextrin (β-CD) and 2-hydroxypropyl-β-cyclodextrin (HPβ-CD) for inclusion complex preparation and studied their effect on dissolution and stability of lansoprazole. The results revealed enhanced stability and dissolution rate of lansoprazole in case of cyclodextrin complexation. The differential scanning calorimetry and powder X-ray diffraction

technique revealed absence of crystallinity of drug. Moreover, the results also disclosed HPβ-CD was more effective in enhancing photostability than β-CD due to deeper inclusion of LSP into HPβ-CD cavity [21].

Chen *et. al.* found that incorporation of PVP K17 in supersaturable selfmicroemulsifying drug delivery system was able to delay precipitation of indirubin for ~2 h in the aqueous medium upon dilution. Moreover, in this case PVP K17 was found to be more effective precipitation inhibitor of indirubin in comparison to PEG 4000 and HPMC [22].

Yamashita *et. al.* studied effect of various polymers like polyethylene glycol 6000, PVP or HPMC on precipitation of tacrolimus by preparing their solid dispersions. Results unveil all the polymer generated high supersaturation as compare to plain drug but HPMC was able to maintain high concentration of tacrolimus over 24 hr in comparison to other two polymers. Thus HPMC was found to be more effective precipitation inhibitor of tacrolimus [23].

Omari *et. al.* studied the complexation parameters of dipyridamole with β-CD using several techniques. Complex formation of dipyridamole was driven by favorable entropy and enthalpy. Moreover, ^{1}H-NMR and molecular mechanical modeling studies signified the formation of different isomeric 1:1and 1:2 complexes. Additionally, molecular modeling studies also revealed prominent driving force for complexation was Van der Waals with lower contribution from electrostatic interactions [24].

Moes and Beten developed controlled release coevaporates of dipyridamole using combination of enteric and insoluble acrylic polymers. The coevaporates were prepared by solvent evaporation method. The paper depicts very low solubility of dipyridamole above pH 5 and a very low intrinsic dissolution rate 0.01 mg/cm^2 per min at pH 5. The results revealed amorphous nature of the solid dispersions. The results also revealed that solid dispersions with enteric polymers hindered the drug release in the acidic medium and simultaneously enhanced dissolution at high pH values. On the contrary, Eudragit RL and RS had no effect of whatever on the drug release. On the other hand combination of both of the above type of polymers can be optimized to modulate the drug release profile. Remarkably, particle size of coevaporates created much impact on dissolution profile [25].

Mehta *et. al.* explored acidic excipients as pH modifiers in developing sustained release formulations of weakly basic drug cinnarizine. They investigated combined effect of polymer; HPMCK100CR and ratio of acidic excipients (citric acid:fumaric acid) on percent drug release at 8 hr and 12 hr. The tablet surface pH measurements were conducted to determine presence of acidifiers. The research disclosed that citric acid could efficiently surmount pH dependant solubility as compared to fumaric acid but also speedily depleted from the matrix while fumaric acid could retain into the matrix for longer time but it displayed lower acidifying capacity. Thus judicious selction of acidifiers may give pH independent release profiles of weakly basic drugs like cinnarizine [26].

Lee *et. al.* investigated microenvironmental pH and crystallinity of Telmisartan for dissolution enhancement by employing nine alkalizers in PEG 6000 based solid dispersions. Out of nine alkalizers evaluated, magnesium oxide, sodium hydroxide, potassium hydroxide and sodium carbonate considerably increased dissolution in pH 6.8 and water. Change in microenvironmental pH as well change of crystalline nature to amorphous of drug were contributing factors in enhancement of dissolution. Thus incorporation of alkalizer worked synergistically with PEG 6000 in enhancement of dissolution of telmisartan [27].

Xu *et. al.* evaluated self-microemulsifying drug delivery system (SMEDDS) of dipyridamole to improve its dissolution and bioavailability due to pH dependant solubility. The results revealed that combination of oleic acid and Labrafac WL 1349 was more effective in increasing solubility than using just one oil. The *in vitro* dissolution in pH 6.8 buffer indicated that SMEDDS dissolved rapidly in comparison to commercial tablet which was less soluble [28].

Tang *et. al.* prepared none gastric resident dipyridamole sustained release pellets for enhancement in bioavailability. They prepared two diverse type of core pellets; one containing pH modifier citric acid and one without pH modifier. They further coated the core pellets with mixtures of enteric soluble and insoluble polymers or insoluble polymer alone. The results revealed combined effect of pH modifier in core pellets and mixture of enteric soluble and insoluble polymers as release modifiers can be used to obtain sustained release with no pH dependency in drug release [29].

Patel *et. al.* developed solid dispersion of furosemide for its solubility and dissolution improvement employing two polymers PVP K-30 and PEG 6000. The results disclosed that aqueous solubility of furosemide was improved by presence of both polymers. Solid state characterization revealed amorphous nature of the drug in polymeric matrix of solid dispersion. Solid dispersion prepared with PEG showed better improvement in dissolution and wettability. Additionally, tablets prepared with solid dispersions also showed significant enhancement of dissolution as compare with conventional tablets [30].

Potluri *et. al.* studied dissolution enhancement of poorly soluble carvedilol by preparation of solid dispersion with Gleucire 50/13. The increase in solubility showed linear relationship with increase concentrations of polymer. Solid state characterization revealed amorphous nature of drug in solid dispersion. On comparing various dissolution parameters like mean dissolution time, dissolution efficiency and drug release rate revealed enhanced solubility and dissolution rate of carvedilol from solid dispersion than its physical mixture and pure drug substance [31].

Lee *et. al.* investigated effect of various pH dependant and independent polymers on improvement of solubility and dissolution rate of itraconazole by solid dispersion technique. Results revealed pH dependant polymers resulted in highest augmentation in solubility than pH independent polymers. The dissolution rate of drug prepared from tablets was very fast with more than 90% drug released within 5 min. Moreover, as compared to marketed preparation manifold increase in dissolution was observed from tablets prepared from solid dispersions of pH dependant polymers [32].

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