3

LITERATURE REVIEW

3. Literature Review

3.1 Selection of Drugs

The inherent advantages of using mesoporous materials as drug carriers have led to many studies. Most of the reports indicate the successful loading of drugs of anticancer and NSAIDS for their better bioavailability. The studies of using MSNs for antiretroviral drugs are very few. Most of the antiretroviral drugs also suffer from low bioavailability issue. Ritonavir and Lopinavir are two widely used drugs and have been selected for this investigation.

3.2 Literature Review for Drugs

Ritonavir is widely used as the antiretroviral drug used for restricting the protease of the human immunodeficiency virus (HIV), and prevents its replication.[1] Ritonavir is presently used as a pharmacokinetic booster with other protease inhibitors, mainly due to ritonavir inhibit the cytochrome P450 3A4 enzyme (required for production of proteins needed for viral assembly). Therefore ritonavirs become a main integrant in combination therapy as highly active anti-retroviral therapy (HAART) [2-4]. Lopinavir is newer and most promising protease inhibitor use for the treatment of HIV infection. Lopinavir inhibits the HIV viral protease enzyme. Protease is one type of enzyme used to develop the new structural enzymes and proteins. The lopinavir obstructs the protease enzyme action, which forms defective viruses. These viruses do not infect the body's cells. Therefore growth and rate of harmful HIV viruses decreases in human body.[5-7]

Ritonavir and lopinavir are class-II drugs as per the biopharmaceutical classification system and strongly need efficient formulation strategies on solubility and bioavailability enhancement. Desai et al. enhanced the solubility of ritonavir by hot melt extrusion technique using soluplus.[8] Pranjali et al formulate nanoparticles by nanoprecipitation method for improvement in solubility of ritonavir.[9] Josephine et al. prepared ritonavir microsphere using ethyl cellulose for oral delivery.[10] Chowdary et al. prepared and characterized ritonavir tablets employing starch phosphate for improvement in dissolution rate of ritonavir.[11] Sinha S et al. prepared and evaluate solid dispersion for enhancement of solubility and bioavailability of ritonavir by solvent evaporation and melt method.[12] Law et al. developed and analyze ritonavir amorphous solid dispersions by using polyethylene glycol (PEG)-8000 for improving solubility and bioavailability enhancement.[13] Patil PS et al prepare and

evaluate nanoparticles of ritonavir for enhancement in rate of dissolution and oral bioavailability of ritonavir.[14] Deshmukh A et al formulate Solid Self-Microemulsifying Drug Delivery System (S-SMEDDS) by using Imwitor 988, capmul GMS K-50 , cremophor EL, cremophor RH 40, and porous material Neusilin US-2 as carrier for enhancing the solubility and bioavailability of ritonavir.[15] Guo S et al formulate self-assembly nanoparticles using oleic acid, TPGS and Aeroperl 300 using novel lipid-based nanotechnology by micro emulsion-precursor method.[16] Kataria VR formulated and evaluated solid dispersion for enhancing the solubility and rate of dissolution of RTV by using Kollidon VA 64.[17]

Punna RR et al prepared solid lipid nanoparticle (SLN) of lopinavir using stearic acid for oral bioavailability enhancement of lopinavir by hot melt emulsion method.[18] Patel G et al developed solid self-nanoemulsifying drug delivery system (S-SNEDDS) for improvement in dissolution rate and bioavailability of lopinavir by using surfactants propylene glycol, Capmul MCM C8 and Cremophor RH 40.[19] Aji Alexa MR et al successfully encapsulate poorly water soluble lopinavir in glyceryl behenate based SLN for targeted lopinavir in intestinal lymphatic vessels using combine chemotherapy.[20] Patel KP et al developed nanostructure lipid carriers for increasing the oral bioavailability of lopinavir. High Speed Homogenization method was used for the preparation of nanostructure lipid carriers for lopinavir by using the mixture of two lipid Glyceryl Behenate & Miglyol 812 was used for entrapment of lopinavir by using Poloxamer 188 as a surfactant.[21] Pekamwar SS et al developed a solid dispersion of lopinavir for improvement in solubility of lopinavir using soluplus as a polymer in solvent kneading method.[22] Rajam RP et al developed a solid dispersion for solubility enhances dissolution rate and stability of lopinavir. In this research various lipophilic materials were used as a carrier for the preparation of a solid dispersion of lopinavir such as PVP, SLS, mannitol and urea by using the solvent evaporation method.[23] Jain S et al prepare surface stabilize nanoparticles for enhancing the bioavailability of lopinavir. Surface-stabilized lopinavir nanoparticles were prepared by using anti-solvent precipitation method and PVA used as a suitable stabilizer.[24]

3.3 Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles have gained attention because of ability to increase the solubility as well as bioavailability of poorly water soluble drugs. Three different

mesoporous silica nanoparticles were synthesized in this study. Synthesized mesoporous silica materials have different pore size, structural properties and surface area and previously used in drug delivery. MCM-41, MCM-48 and SBA-15 MSNs have some attractive features like porous interior with different structure and large surface area with tunable pore size can entrap a drug molecule easily. Mesoporous silica materials have good biocompatibility and tailored size of pores makes them promising drug carrier for the dissolution as well as bioavailability enhancement of poorly water soluble drugs. [25-27]

Literature survey shows that a different categories number of poor soluble drugs such as Aceclofenac, carbazepamine, econazol, finofibrate, furosemide, atenolol, piroxicam, ibuprofen, methotrexate, paclitaxel, cilostazol and ampiciline could be successfully loaded into MCM-41, SBA-15 and MCM-48 mesoporous silica nanoparticles for various applications like solubility and bioavailability enhancement, controlled drug/gene release and targeted delivery carriers.[28-40] In this study we developed three different mesoporous silica carriers namely MCM-41, SBA-15 and MCM-48. These carriers have different pore size and surface area by using different surfactant and synthetic conditions. These synthesized carriers were used to load antiretroviral drugs in these nanoparticles to examine its effect on solubility and bioavailability of selected antiretroviral drugs.

The main characteristics of MCM-41, MCM-48 and SBA-15 are characterized below.

Table 3.1 Comparative characteristics of synthesized MSNs

MSNs / **Property**	**MCM-48**	**MCM-41**	**SBA-15**
Family	M41S	M41S	SBA
Mol. Formula	Sio_2	Sio_2	Sio_2
Mol. Weight	60.08	60.08	60.08
Structure	3D cubic sphere	2d Hexagonal	2d Hexagonal
Physical state	Solid	Solid	Solid
Pore size	2.3-3.7nm	2.9-4.5nm	5-14nm
Pore volume	0.70-98cm3/g	0.6-0.90cm3/g	0.4-0.9cm3/g
Surface area	>1000m2/g	>800m2/g	>800m2/g
Surfactant	CTAB	CTAB	P-123 Pluronic
pH	Alkaline	Alkaline	Neutral or Acidic
Silica Source	TEOS	Fumed silica	TEOS
Calcination	550-600^{0}C	550-600^{0}C	550-600^{0}C

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