Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6 suppl 2, 2014

Review Article

MICROPARTICULATE DRUG CARRIERS: A PROMISING APPROACH FOR THE DELIVERY OF ANTI HIV DRUGS

SELLAPPAN VELMURUGAN[a,b*], MOHAMED ASHRAF ALI[a, c], PRAVEEN KUMAR[b]

[a]Department of Pharmaceutics, Sunrise University, Alwar, Rajasthan, India. [b]Department of Pharmaceutics, KLR Pharmacy College, Paloncha, Andhra Pradesh, India. [c]Institute for Research in Molecular Medicine, Universiti Sains Malaysia, Penang, Malaysia.
Email: willard_cbe@rediffmail.com

Received: 11 Dec 2013 Revised and Accepted: 25 Jan 2014

ABSTRACT

Human immunodeficiency virus (HIV) is a retrovirus which causes acquired immuno deficiency syndrome (AIDS), a condition where immune system begins to fail in humans, leading to life-threatening infections. Recent advance in highly active antiretroviral (ARV) agents has led to tremendous reduction of viral load in plasma, progression of infection and mortality from AIDS. Various classes of antiretroviral agents are available nowaday but unfortunately most of these drugs have poor physiochemical properties which result in poor absorption, undesirable side effect and accumulation of the drug at inappropriate sites. To overcome these drawbacks, particulate systems like microparticles have been introduced to improve the pharmacokinetic and pharmacodynamic properties of various types of antiretroviral drugs and targeting them to particular sites. To formulate microcarrier based systems, different polymers are used in the antiretroviral micro particulate drug delivery research to increase therapeutic activity and minimize side effects. Among the recent approaches of novel drug delivery system ,microparticulate drug carriers is found to be the most important one. The aim of this review is to discuss the need for novel drug delivery, advantages, recent development in microparticulate drug delivery system for antiretroviral drugs and challenges standing ahead.

Keywords: HIV life cycle, Microcarriers, Antiretroviral therapy, Anti HIV agents

INTRODUCTION

The human immunodeficiency virus (HIV) is a retrovirus which infects the cells of immune system, destroying these cells and impairing the immune system's ability to fight with the invaders. Impaired cellular functions in the macrophage population leads to the development and clinical progression of acquired immune deficiency syndrome (AIDS). The main aim of antiretroviral therapy (ART) is to control the amount of HIV in the body at a low level. This therapy controls the weakening of immune system and facilitates to recover from any damage. The High Activity Antiretroviral Therapy (HAART) was introduced in 1996 and the formulation contains incorporation of at least three antiretroviral drugs. HAART is in use over a decade to extend the lifespan of HIV-infected patients [1]. Although several attempts have been made to eradicate HIV, it was found that globally a 40 million people are virus infected [2]. It is mandatory to continue HAART to control HIV infection [3]. Viral replication reverts back after several weeks upon withdrawal of therapy. The advances of highly active antiviral agents have led to reduction of viral load in plasma and mortality from AIDS.

However most of these drugs have poor physiochemical properties and metabolism that result in poor absorption and side effects [4]. This is often related to the accumulation of the drug at inappropriate sites [5]. In addition increased use of HAART does not offer complete elimination of HIV from the infected person. Intracellular and anatomical resting viral reservoirs contribute to the perpetuation of infection [6]. These resting reservoirs of HIV are inaccessible to current ARV agents. Blood-tissue barriers prevent drug penetration and dampened the eradication of viral pools by ARV agents. ATP-binding cassette (P-glycoprotein) involving Active transport mechanisms that are present in central nervous system (CNS) prevent the penetration of anti-HIV drugs into the brain [7]. Multiple daily dosing regimens and secondary side effects lead to the failure of long-term HIV-1 suppression in infected people [8-10]. The basic requirement for the use of any drug against retrovirus related diseases is its bioavailability. But many novel ARV agents are has poor bio distribution and insufficient cellular uptake [11]. Hence the aim of ARV therapy is now focused on reduction in the symptoms of disease progression to AIDS, elimination of HIV resting reservoirs, reducing the viral load to undetectable levels, minimizing the viral resistance, optimizing the drug therapy, reducing the adverse effects of the drugs and to improve the quality of life of the infected patients [12].

Life cycle of HIV

HIV infection is diagnosed by the presence of antibodies to HIV in the plasma. Various serological tests such as ELISA (Enzyme Linked Immune Sorbent Assay), Orasure western blot, SUDS (single used diagnostic system), Orasure HIV-118 are used for the diagnostic purpose. The U.S Center for Disease Control and Prevention (CDC) defines the signs or symptoms of AIDS. People are diagnosed with AIDS when they show certain systems defined.

The CDC's definition of AIDS includes:

- CD4+ T cell count less than 200 per cubic mm of blood compared with about 1,000 CD4+ T cells (healthy people).
- CD4+ T cells count lees than 14% of all lymphocytes.

Recommendations of CDC include of testing of CD4+T cell count for every three to six months in all HIV-infected persons, though the need may vary by patient to patient [13].

The steps of the HIV life cycle:

- HIV Binds to a specific type of CD4 receptor and to co-receptors present on the surface of a CD4+ T lymphocyte.
- Once binding over Virus can fuse with the host cell (CD4 cell) and release its genetic material into the host cell.
- The next step is reverse transcription of the genetic material of the virus by special enzyme reverse transcriptase and its integration into the host DNA by HIV enzyme integrase.
- Once integrated virus begins to produce new viral RNA and proteins, turning the cell into a HIV reservoir.
- This production leads to assembly, budding, and maturation, by which the new HIV particles are packaged and migrate out to infect new cells [14].

Each step in the life cycle of retroviral infection can be used as a potential target for antiviral therapy [15].

Therapeutics agents with different chemical structures and mechanisms of interference with the replication of viral cells have been described as antiviral agents [16, 17].

Hurdles in the conventional delivery of anti HIV drugs

Most of the available anti-HIV agents are formulated as solid dosage forms like tablets, capsules or liquid dosage forms such as solution,

suspension for oral and parenteral use. Though the marketed oral dosage forms offer many advantages, delivery of these drugs through oral route suffers from certain factors like first pass metabolism, variation of absorption and degradation in the GIT due to enzymes and extreme pH conditions. Many anti viral agents come under BCS Class IV category i.e., low aqueous solubility and permeability and have poor bioavailability.

First pass effect, systemic toxicity and limited stability are found to be main drawbacks of NRTIs

.

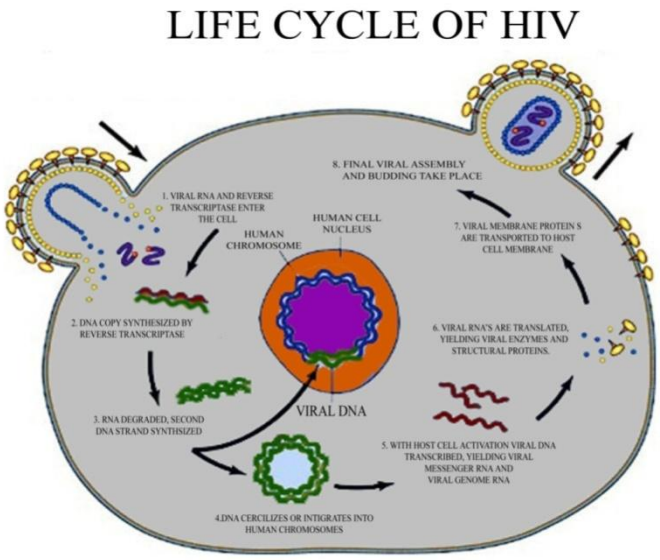

Fig. 1: Schematic representation of life cycle of HIV [15]

For example, Didanosine has poor stability under gastric conditions and 10% of drug degrades within 2 min at pH < 3 and undergoes hepatic first pass metabolism due to mesenteric circulation of the drug which results in low bioavailability. Tenofovir (nucleotide reverse transcriptase inhibitor) has bioavailability of 25-30% [18]. Efavirenz (recommended by the WHO) is used for the initial treatment of children above the age of three [19]. The very low solubility of Efavirenz (3-9 µg/ml) hinders absorption and biodistribution [20]. Its bioavailability is around 40-45% and produces a burning sensation upon swallowing which restricts the development of water-based liquid formulations [21]. Etravirine has very low absorption extent is due to low solubility (10µg/ml) and permeability [22].

Oral absorption is restricted for Protease inhibitor drugs as they are substrates for efflux pumps [23]. Due to their affinity for removal transporters, the pharmacokinetic profiles depend on pharmacogenetic patterns and require dose adjustment. This is a crucial factor in paediatric patients. In addition, the taste of some extemporaneous solutions of indinavir, tipranavir is often unpalatable for many children [24]. The extreme bitterness of ritonavir which is commercially available as paediatric aqueous solution hampers its compliance [25]. Bioavailability of saquinavir is extremely low (4-10%) due to low aqueous solubility which restricts absorption upon oral administration and due to its instability in the gastric environment. Enfuvirtide, upon injection local irritation and pain are observed and is administered subcutaneously twice a day [26]

Table 1: US FDA approved nucleotide reverse transcriptase inhibitors (NRTIs) [102,103]

Generic Name & US-FDA approved date	Brand name / manufacture	Oral adult dose/ Frequency	Half-life (Hours)	Bioavailability (%)	Solubility (mg/ml)	LogP
Abacavir (ABC) Dec.17,1998	Ziagen ViiV Healthcare	300 mg/Twice daily 600mg/once daily	1 - 1.5	83	77	1.1
Didanosine (ddI) Oct.09,1991	Videx EC Bristol-Myers Squibb	200 mg/Twice daily 400mg/once daily	1.3 - 1.5	21 - 43	27.3	-0.2
Emtricitabine (FTC) Jul.02,2003	Emtriva Gilead Sciences	200 mg /once daily	10	93	112	-1.4
Lamivudine (3TC) Nov.17,1995	Epivir ViiV Healthcare	150 mg/Twice daily 300mg/once daily	3-7	82 - 87	70	-1.4
Stavudine (d4T) Jun.24,1994	Zerit Bristol-Myers Squibb	30 – 40 mg /Twice daily	0.9 - 1.6	80 - 86	83	-0.8
Tenofovir disoproxil fumarate (TDF) Oct.26,2001	Viread Gilead Sciences	300 mg /Once daily	4-8	25 - 30	13.4	1.25
Zalcitabine (ddC) Mar.19,1992	Hivid Hoffmann-La Roche	0.75 mg /Every 8 hours	1-4	80 - 88	76.4	-1.3
Zidovudine (AZT) Mar.19,1987	Retrovir Glaxosmithkline	200 mg/ 3 times a day 300 mg /twice daily	0.5 - 3	64	20.1	-0.05

Table 2: US-FDA approved Non- nucleoside reverse transcriptase inhibitors (NNRTIs) [102,103]

Generic Name & US-FDA approved date	Brand name / manufacture	Oral adult dose/ Frequency	Half-life (Hours)	Bioavailability (%)	Solubility (mg/ml)	LogP
Delavirdine (DLV) Apr.04,1997	Rescriptor ViiV Healthcare	400 mg / 3 times a day	2-11	60 – 100*	0.2942	5.8
Efavirenz (EFV) Sep.17,1998	Sustiva Bristol-Myers Squibb	600 mg /Once daily	52 - 76	40-45	3-9µg/ml	1.75
Etravirine (TMC125) Jan.18,2008	Intelence Janssen Therapeutics	200 mg /Twice daily	41	Unknown	10µg/ml	5.2
Nevirapine (NVP) June.21,1996	Viramune Boehringer Ingelheim	200 mg/ Once daily – First 14 days; then Twice daily	45	90	0.007	1.75

(*Reported in animal studies)

The efflux transporters remove the absorbed drug in the basolateral apical direction and leads to the generation of one of the most challenging viral reservoirs. Accumulation in the CNS not only generates a virus pool that facilitates total elimination of the HIV from the host but also lead to neurodegeneration, neuroinflammation and dementia [28].

Thus, the technological approach should aim at improving effectiveness of the treatment by targeting different cellular and anatomical viral reservoirs. The use of polymeric microparticles has become the most attractive research for targeting these viral reservoirs. Micro carriers have number of advantages.

- Poorly aqueous soluble or unstable anti HIV drugs can be entrapped within the small spherical particles to attain enhanced solubility and stability under physiological condition.
- Easily taken up by phagocytic cells.
- To mask the unpleasant taste of anti- HIV drugs, the microparticles could be prepared using pH-dependent polymer that is insoluble under intake conditions but dissolves fast in the stomach in order to release the drug completely.
- Orally acceptable paediatric formulations of anti-HIV drugs could be developed easily.

Failure of HAART and potential targets in novel drug delivery of anti HIV drugs

Conventional antiretroviral therapy consists of combination of antiviral drugs interfering with various stages of the virus life cycle to decrease the mortality of HIV-1 infected patients [29]. Antiretroviral therapies (ART) are developed mainly to target and block key steps of the viral replication cycle like binding and fusing to host cell (CD4 cell), reverse transcription of the viral genetic material, and integration into host DNA.

Table 3: US-FDA approved Protease Inhibitors (PIs) [102,103]

Generic Name & US-FDA approved date	Brand name / manufacture	Oral adult dose/ Frequency	Half-life (Hours)	Bioavailability (%)	Solubility (mg/ml)	LogP
Amprenavir (APV) Apr.15,1999	Agenerase GlaxoSmithKline	1200 mg / Twice daily	7-10	25-19*	4.91e-02 g/l	1.85
Atazanavir (ATV) Jun.20,2003	Reyataz Bristol-Myers Squibb	Once daily	7	60-68	4-5	4.5
Darunavir June.23,2006	Prezista Janssen Therapeutics	600 mg / Twice daily 800 mg / once daily	15	37	0.15	1.8
Fosamprenavir (FOS-APV) Oct.20,2003	Lexiva ViiV Healthcare	1400 mg / Twice daily	7.7	Not established	0.04	0.84
Indinavir (IDV) Mar.13,1996	Crixivan Merck & Co.	800 mg / Every 8 hours	1.4-2.2	30	0.015	2.9
Lopinavir and Ritonavir (LPV/RTV) Sep.15,2000	Kaletra Laboratorios Abbott	400/100 mg / Twice daily 800/100 mg /once daily	4.4/6.1	No data available	No data available	No data available
Nelfinavir (NFV) Mar.14,1997	Viracept ViiV Healthcare	1250 mg / Twice daily 750 mg /3 times a day	3.5-5	20-80	1.91e-03 g/l	6
Ritonavir (RTV) Mar.01,1996	Norvir Laboratorios Abbott	600 mg /Twice daily	3-5	80*	1.26	3.9
Saquinavir (SQV) Dec.06,1995	Invirase La Roche	1200 mg /3 times a day	13	4-10	2.47e-03 g/l	3.8
Tipranavir (TPV) Jun.22,2005	Aptivus Boehringer-Ingelheim	500 mg / Twice daily	5.5-6	30*	2.07e-04 g/l	6.9

(*Reported in animal studies)

After CD4-virus binding conformational changes occurs in gp120 which initiate fusion of the two membranes by reorientation of the transmembrane protein gp41. This step can be used as target for preventive therapy. Several drugs and HIV entry inhibitors are under clinical trials. Among them Sifurvitide, Enfuvirtide blocks the surface envelope glycoprotein 41 of HIV-1, have been already approved [30]. Aplaviroc, Maraviroc and Vicriviroc are host co-receptor CCR5 antagonists [31], AMD11070 (CXCR4 antagonist is under phase II clinical trials) [32, 33] and other associated entry and fusion drugs are being developed and awaited for approval [34].

Reverse transcriptase enzyme of viral cells translates the single-stranded RNA into double-stranded DNA. Nucleosides (NRTI) and non-nucleosides (NNRTI) are two the fundamental groups of RT inhibitors. RT inhibitors being approved, effectively reduces the viral load, but the limiting factors include pharmacokinetics, drug clearance, and toxicity, dosing, cost and drug adherence. Multiple resistance also presents a main obstacle [35]. The clinical effect of RT inhibitors can by greatly improved by delivering them using non-toxic vehicles.

Once synthesized, viral proteins facilitate transportation and integration of the DNA chain into the host genome. In the late phase, mRNAs are produced and move out of nucleus to undergo translation and protein synthesis. After viral particle budding, viral DNA leaves the host cell by exocytosis process. The genome of HIV is encoded by single-stranded RNA [36]. HAART prevents HIV-1 infected patients from making a complete recovery [37] but this therapy is associated with undesired side-effects like mitochondrial toxicity and myopathy [38], lipodystrophy [39] which are associated with insulin resistance and lipid abnormalities [40], and induced liver injury [41].

These factors necessitated in finding the new approaches to treat HIV-positive individuals with anti HIV drugs using novel drug delivery systems that are selective and impact only on infected cells and do not have any effects on healthy cells. Drug delivery systems that facilitate the drugs to cross the blood-brain barrier would be advantageous, and gene therapy [42] or delivery using microstructures was found to be effective alternatives.

Table 3: US-FDA approved Protease Inhibitors (PIs) [102,103]

Generic Name & US-FDA approved date	Brand name / manufacture	Oral adult dose/ Frequency	Half-life (Hours)	Bioavailability (%)	Solubility (mg/ml)	Log P
Enfuvirtide March .13, 2003	Rescriptor ViiV Healthcare	One 90 mg subcutaneous injection every 12 hours	3.8	84.3	100µg/ml	0.05
Maraviroc Aug. 06, 2007	Selzentry ViiV Healthcare	One 150 mg tablet twice a day, or one 300 mg tablet twice a day, or two 300 mg tablets twice a day	14-18	23	1.06e-02 g/l	4.3
Raltegravir Oct. 12, 2007	Isentress Merck & CO. Inc	One 400 mg tablet twice a day	9	Not estabilished	<1 mg/mL	0.023

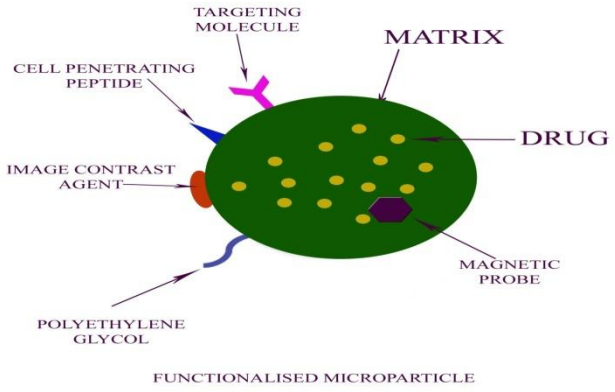

Fig. 2: Schematic representation of functionalised microparticle [103]

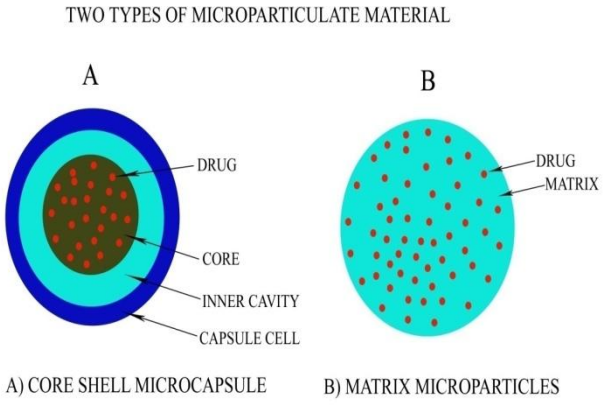

Fig. 3: Schematic morphologies of two types of microparticulate system [103]

Micro particulate drug delivery system

Every drug has characteristic 'minimum effective concentration' below which no therapeutic effect is observed and a characteristic 'maximum safe concentration' above which undesired side effects may arise. This range is called 'therapeutic range' or therapeutic window which could be narrow for most of the drugs [43]. The optimum effect in medical treatments is achieved by maintaining the drug concentration in the therapeutic range through the delivery period of the drug. This is especially true in case of highly potent drugs like anti-viral drugs. By administration of the entire drug dose by conventional pharmaceutical dosage forms (e.g. Tablets), the whole amount is rapidly released in to the stomach, gets absorbed and enters into the systemic circulation. As there is no continuous drug supply the human body eliminates the active agent. So the drug concentration gets decreased. This results in fluctuating concentration of drug levels in the plasma and the therapeutic range is maintained only for very short time period.

Micro particulates are small solid spherical particles within the size range of 1-1000µm [44]. Based on the method of preparation, the drug is either dissolved or entrapped, and encapsulated to the micro particle matrix. Micro particles provide easy administration to deliver macromolecules by various routes and effectively control the release of drugs over the periods ranging from few hours to months. Effective protection of encapsulated drug by various polymers prevents its degradation in the body. It is important in novel drug delivery system as they are prepared for controlled drug delivery which improves bioavailability of the drug and to target the specific sites in the body [45- 48].

Microspheres also have **advantages** like [49, 50]

- Limiting the fluctuation within therapeutic range,

- Reduces side effects
- Reduces dosing frequency and improving patient compliance.
- Entrapment of drug is high.
- Drugs can be incorporated in to the system without any chemical reaction.
- Microcarriers can be administered through various routes like oral, parenteral,intra – ocular, nasal etc.
- Particle size is small and provides effective surface area of micro particles which helps to achieve drug targeting to the specific site in the body.

Limitations

- Handling of micro particles is difficult in liquid and dry forms.
- The particles may get aggregated because of small particle size and large surface charges.
- Small particle size limits drug loading and cause burst release effect.

Types of micro particulate carriers

Muco adhesive microspheres

Drug action can be improved by developing mucoadhesive microsphere drug delivery system. Mucoadhesive microspheres remain in close contact with the mucous membrane and release the drug at the site of action leading to increase in bioavailability and both local and systemic effects [51].Muco adhesion can be achieved by coupling bioadhesion characteristics to microspheres.

High surface to volume ratio mucoadhesive microspheres enables efficient absorption and enhanced bioavailability of the drugs. Intimate contact with the mucus membrane provides specific targeting of drugs at the absorption site. [52]

.

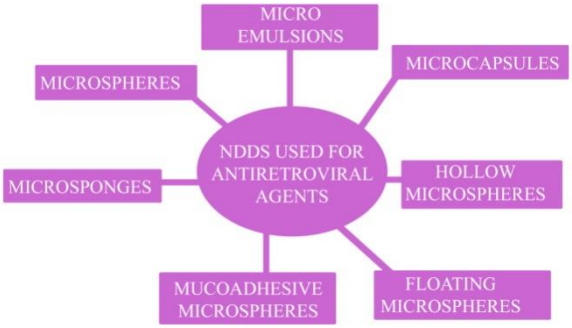

Fig.4: Schematic diagram of various microparticulate drug delivery approaches used for antiretroviral agents [104]

The term "bioadhesion" implies attachment of a drug carrier system to a specific biological membrane. The biological membrane can be epithelial tissue or the mucus coat on the surface of a tissue. The phenomenon of adhesive attachment to a mucous coat is referred to as "Mucoadhesion"[53]. Mucoadhesion has been widely promoted as a way of achieving site-specific drug delivery by incorporating of mucoadhesive polymers within pharmaceutical formulations along with the active pharmaceutical ingredient (API).

Mucoadhesive polymers are water-soluble and water insoluble polymers, having swellable networks, jointed by crosslinking agents. Mucoadhesive polymers possess optimal polarity to ensure that they allow sufficient wetting by the mucus and satisfactory fluidity that permits the mutual adsorption and inter penetration of polymer and mucus to take place [54].

All three polymers types can be used for drug delivery [55].

Anionic polymers [56]

Anionic polymers are the most widely used mucoadhesive polymers in pharmaceutical formulation due to their high mucoadhesive property and low toxicity. Typical examples include polyacrylic acid (PAA) and sodium carboxy methylcellulose (NaCMC). PAA and NaCMC have excellent mucoadhesive characteristics and enables the formation of strong hydrogen bonding interactions with mucin. Polycarbophil and Carbopol, PAA derivatives have been studied extensively as mucoadhesive polymers for delivering drugs to the GI tract. Polycarbophil is insoluble in aqueous media and have high swelling capacity under neutral pH conditions, promoting high levels of entanglement with the mucus layer

Cationic polymers [56]

Among the cationic polymers, chitosan is most widely used as mucoadhesive polymer. Chitosan is a cationic polysaccharide, produced by deacetylation of chitin. Chitosan has film-forming properties and is also used in cosmetics. Chitosan is gaining importance in recent mucoadhesive formulations due to its good biocompatibility and biodegradability. PAAs bind to mucus via hydrogen bonds but chitosan bind by ionic interactions between primary amino functional groups and the sialic acid and sulphonic acid substructures present in the mucus.

Novel second-generation mucoadhesive polymers [56]

The major disadvantage in traditional mucoadhesive systems is that adhesion may occur at sites other than those specified. However second-generation polymers are less susceptible to mucus turnover rates, binding directly to mucosal surfaces. More accurately it can be termed as "cytoadhesives".

Lectins [56]

Lectins are the natural proteins that play a fundamental role in biological recognition involving cells and proteins. By the use of appropriate cytoadhesives that can bind to mucosal surfaces, mucosal delivery can be enhanced. Lectins belong to a group of structurally diverse proteins and glycoproteins that can bind reversibly to specific carbohydrate residues. After the initial mucosal cell-binding,

lectins remain on the cell surface or the receptor mediated adhesion possibly become internalized by endocytosis. Such systems allow targeted specific attachment and additionally a method of controlled drug delivery of active agents by active cell-mediated drug uptake.

Thiolated polymers [56]

Thiolated polymers are the mucoadhesive polymers derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum. Chitosan– thioglycolic acid improved 10 folds of mucoadhesive properties, Polyacrylic acid–cysteine approximately improved 100-folds mucoadhesive properties, Chitosan–iminothiolane combination improved 250-fold mucoadhesive properties, Chitosan– thioglycolic acid improved 10 folds mucoadhesive properties, Chitosan–thioethylamidine improved mucoadhesive properties by 9folds,

Polyacrylic acid–homocysteine improved 20-fold mucoadhesive properties and Alginate– cysteine improved mucoadhesive properties by 4 folds etc. leading to increased residence time and improved bioavailability.

Floating drug delivery systems

Floating drug delivery systems is one of the most important approaches to achieve gastric retention [57]. This delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine to obtain sufficient drug bioavailability [58].

Non-effervescent Systems

Non-effervescent floating drug delivery systems are generally prepared by using gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides, matrix forming polymers like polymethacrylate, polyacrylates, polystyrene and polycarbonate. Drug delivery systems developed by intimate mixing of drug with a gel forming hydrocolloid after oral administration when come in contact with gastric fluid maintains a relative integrity of shape and a bulk density less than density of gastric fluid [59]. The air entrapped in the swollen polymer provides adequate buoyancy to these dosage forms. Hydroxypropyl methylcellulose (HPMC), polyacrylates, polyvinyl acetate, xanthangum, carbopol, agar, sodium alginate, sodium CMC, polyethylene oxide and polycarbonates are the most widely used excipients [60]. This system can be further divided into following sub-types:

Hydrodynamically balanced systems

The term 'hydrodynamically balanced systems' was first designated by Sheth and Tossounian [61]. These dosage forms contains drug with gel-forming hydrocolloids and remain buoyant on the stomach throughout the drug delivery period. Either alone or in combination of polymers are used to achieve the objective of formulation. commonly used polymers include hydroxyethyl cellulose (HEC), Hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polystyrene, agar, polycarbophil, polyacrylate, carrageenans or alginic acid [62, 63]. The mixture of drug and polymer forms a hydrodynamically balanced capsule. This capsule shell dissolves in contact with water and swells to form a gelatinous barrier. This imparts buoyancy to dosage form in gastric juice for a longer period. Because of continuous erosion of surface of the shell, it allows water penetration into the inner layers imparting surface hydration and buoyancy characteristics to the dosage form [63]. Drugs can be effectively delivered by the balancing drug loading and the monitoring the effect of polymer on release profile. Several strategies have been developed and investigated to improve efficiency of the floating drug delivery systems [63, 64].

Microballoons / Hollow microspheres

Microballoons / hollow microspheres were generally prepared by simple solvent evaporation or solvent diffusion or evaporation methods [65] to prolong the gastric retention time (GRT) of the dosage form. Eudragit S, cellulose acetate, polycarbonate, ethyl cellulose, calcium alginate, sodium alginate, agar,HPMC grades and low methoxylated pectin etc are the commonly used polymers. Buoyancy and drug release from dosage form depends on the drug polymer ratio, quantity of polymer, the solvent used and method of formulation. At present hollow microspheres are considered as one of the most promising buoyant systems due to the advantages of multiple-unit system and good floating beads. Talukdar and Fassihi [66] developed multiple-unit floating system based on cross-linked beads using Ca^{2+} and low methoxylated pectin (anionic polysaccharide) and sodium alginate by ionic gelation method. In this approach drug and sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated, dried by air convection and freeze drying, leading to porous system of the formulation which maintains the gastric retention for over 12 hrs [60, 67].

Microporous compartment system

In this approach the drug reservoir is encapsulated inside a microporous compartment with pores around its surface [68]. The peripheral walls of the microspheres were completely sealed to prevent any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber contains entrapped air which causes the delivery system to float in the gastric fluid [69]. Gastric fluid enters through the aperture present in the microspheres, dissolves the drug and the dissolved drug leach out for a prolonged period depending on the used polymer combination for a continuous transport across the intestine for drug absorption.

Effervescent (gas generating) systems

Floatation of dosage form can be achieved by generation of gas bubbles. These matrix type of buoyant systems can be prepared with swellable polymers such as effervescent components (sodium bicarbonate, citric acid or tartaric acid), polysaccharides (chitosan) [68]. The optimal ratio of citric acid and sodium bicarbonate used for gas generation is reported to be 0.76: 1 [70]. In this system when the sodium bicarbonate comes in contact with gastric fluid, carbon dioxide is released and causes the formulation to float in the stomach. Materials that have been reported to formulate this kind of system include, a mixture of sodium alginate and sodium bicarbonate, floating microspheres with a core of sodium bicarbonate and polyvinyl pyrrolidone (PVP) coated with hydroxypropyl methylcellulose (HPMC), multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, and floating system based on ion exchange resin technology etc [60].

In another approach Drugs and excipients can be formulated separately and the gas generating material can be incorporated in to any of the layers. The main difficulty in developing these formulations is achieving a good compromise between plasticity, elasticity and permeability of the polymers.

Recent approaches in novel drug delivery system for anti-HIV drugs

Several approaches are being investigated to develop strategies for the treatment of HIV infection. Effect of developed drug delivery systems on the efficacy and toxicity to improve the anti-HIV treatment are being evaluated. [71]. Percutaneous absorption has been one of the most studied routes for non-oral administration of antiretroviral agents [72]. Various scientists have made efforts on the delivery of anti -HIV drugs to avoid hepatic first-pass metabolism and intestinal degradation. Delivery of nucleoside analogues through nasal absorption, buccal permeation, intratracheal administration ,Percutaneous absorption, ,rectal administration, enteric-coated dosage form and co-administration with antacid are under research.

Controlled Drug Delivery of Anti-HIV Drugs

Controlled drug delivery system appeared to be the most effective drug delivery system in order to fulfil the need of a long-term treatment with antiretroviral agents. The main shortcomings in conventional dosage forms are frequent administration, low water solubility, drug-plasma concentration fluctuations, poor bioavailability and significant adjustment in the lifestyle. These drawbacks necessitated to develop controlled release drug delivery systems to improve the overall therapeutic benefit of anti-HIV drugs and to achieve effective therapy. By developing particulate drug carriers it is possible to achieve effective plasma concentration without significant fluctuation, to avoid sub-therapeutic or toxic plasma concentrations, to facilitate the drug release in a controlled manner, to achieve an effective therapy with low dosage of the drug, to reduce the dosage frequency, thus to improve patient compliance, and to prevent interference to the therapy with day-to-day lifestyle [73, 74].

Bio-adhesive and floating particulate drug carriers are designed to prolong retention in the stomach and to facilitate drug absorption over a prolonged period of time. Hence, the combination of both sustained release and floating or bio-adhesive properties in microcarriers system would further enhance therapeutic efficacy. Novel drug delivery carriers forms such as nanoparticles, liposomes, microparticles and others, has the advantage of overcoming the pharmacokinetic hurdles of anti-HIV drugs [75]. A study reported that administration of oral controlled release dosage forms leads to longer gastric residence time, lower the dosing frequency and constant maintenance of blood –drug levels [76]. A review discussed on the studies and progress on macromolecular pro-drugs in anti-

HIV therapy by using as carriers either natural and synthetic polymers showed good release properties in a prolonged time [77].The delivery of saquinavir, zidovudine, Lamivudine and zalcitabine, using microspheres as a drug carrier system could improve the delivery of antiviral agents to the mononuclear phagocyte system in-vivo, overcoming pharmacokinetic problems and increasing the efficiency of drugs for the treatment of HIV infection.

Table 5: List of retroviral drugs which are given as microparticulate drug carriers

Drug	Microcarriers	Polymer/method of preparation	Purpose/Results	Ref
Stavudine	Floating microspheres	Ethyl cellulose, Dibutyl phthalate/solvent evaporation	Prolongation of gastric retention time, sustain release	78
Lamivudine	Microspheres	Chitosan/ionic gelation	Controlled delivery of lamivudine	79
Zidovudine	Microspheres	Ethyl cellulose/dry-in-oil method	Sustain delivery of zidovudine	80
Stavudine	Microspheres	Ethyl cellulose / emulsion solvent diffusion	Sustain delivery of stavudine	81
Stavudine	Floating microspheres	Eudragit RS100/emulsion solvent diffusion	Prolongation of gastric retention time,sustain release	82
Lamivudine	Microspheres	Acryl coat, LSOD, S100/solvent evaporation	Controlled delivery of lamivudine	83
Zidovudine	Microspheres	HPMC/emulsification heat stabilizing	Sustain delivery of zidovudine	84
Indinavir	Microspheres	Eudragit E100/double emulsion solvent evaporation	Taste masking and control delivery of indinavir	85
Lamivudine	Microcapsules	Cellulose acetate phthalate, Ethyl cellulose/solvent evaporation	Sustain delivery of lamivudine	86
Stavudine	Microspheres	Eudragit RS100 and ethyl cellulose/emulsion solvent diffusion	Sustain delivery of stavudine	87
Zidovudine	Microspheres	Chitosan/ionic gelation	Controlled delivery of zidovudine	88
Stavudine	Microspheres	Eudragit/solvent evaporation	Sustain delivery of stavudine	89
Zidovudine	Microspheres	Eudragit RS 100,Eudragit RL 100/ emulsion solvent evaporation	Controlled release of Zidovudine	90
Zidovudine	Microspheres	Ethylcellulose/double emulsion solvent diffusion	Controlled release of Zidovudine	91
Zidovudine	Hollow Microspheres	Eudragit S100/Emulsion solvent diffusion	Prolong the gastric residence time, sustain release	92
Stavudine	Floating microspheres	Sodium Alginate/emulsion gelation	Prolong the gastric residence time, Improve bioavailability	93
WHI-07	Microemulsion		prevention of the sexual transmission of HIV	94
Lamivudine	Microcapsule	CAP, CAB, EC, HPMCP/solvent evaporation	Controlled release of lamivudine	95
Maraviroc	Mucoadhesive microspheres	Sodium alginate/Ionotropic gelation	Controlled release of maraviroc	96
Zidovudine	Microballoon	Eudragit S100/solvent diffusion and evaporation	Prolong the gastric residence time, sustain release	97
Tipranavir	Microemulsion		Bioavability enhanced	98
Efavirenz	Mucoadhesive Microspheres	HPMC, Carbopol/inversion microencapsulation	Enhancing Its Dissolution Rate and Bioavailability	99
Nelfinavir	Microcapsules	Cellulose Acetate/solvent evaporation	Sustain delivery of nelfinavir	100
Abacavir	Microspheres	Ethyl cellulose, HPMC K4M, Eudragit RSPO and Eudragit L 100/emulsion – solvent evaporation method	Controlled delivery of abacavir	101

CONCLUSION

Most of the anti-retroviral drugs have poor aqueous solubility and bioavailability. Also the half-life for several anti-HIV drugs are short, which requires frequent administration leads to poor patient compliance. Furthermore, HIV/AIDS treatment requires a long term treatment with high doses of the anti-HIV drugs and selective drug targeting to reduce the viral load. Therefore, the usage of Polymeric microcarriers could release the anti- retroviral drug at the target site in a sustained/ controlled manner for a prolong period of time, circumvent the shortcomings of conventional therapy and effectively treat the HIV infection.

The review embracing the need for microparticulate drug delivery and recent development in drug delivery of anti HIV drugs for better management of life threatening disease.

REFERENCES

1. Sosnik A, Chiappetta DA, Carcaboso ÁM. Drug delivery systems in HIV pharmacotherapy: What has been done and the challenges standing ahead. J Control Rel 2009; 138:2-15.
2. Piot P, Bartos M, Ghys PD, Walker N, Schwartlander B. The global impact of HIV/AIDS. Nature 2001; 410:968-73.
3. Smith KA. To cure chronic HIV infection, a new therapeutic strategy is needed. Curr Opin Immunol 2001; 13:617-24.
4. Yong HL, Patrick JS. Preface. Adv Drug Delivery Rev. 1999; 39:1–31
5. Khoo SH, et al. Intracellular accumulation of human immunodeficiency virus protease inhibitors. Antimicrob Agents Chemother 2002; 46(10): 3228–3235.
6. Geeraert L, Kraus G, Pomerantz RJ. Hide-and-seek: the challenge of viral persistence in HIV infection. Ann Rev Med 2008; 59:487-01.
7. Peralta G, Sanchez MB, Echevarria S, Valdizan EM, Armijo JA. P glycoprotein and human immunodeficiency virus infection. Enferm Infecc Microbiol Clin 2008; 26:150-59.
8. Petit F, Fromenty B, Owen A, Estaquier J. Mitochondria are sensors for HIV drugs. Trends Pharmacol Sci 2005; 26:258-64.
9. Hawkins T. Appearance-related side effects of HIV-1 treatment. AIDS Patient Care STDS 2006; 20:6-18.
10. Baert L, et al. Development of an implantable infusion pump for sustained anti-HIV drug administration. Int J Pharm 2008; 355:38-44.
11. Rossi JJ, Elkins D, Zaia JA, Sullivan S. Ribozymes as anti-HIV-1 therapeutic agents: principles, applications, and problems. AIDS Res Hum Retroviruses 1992; 8:183-89.
12. Helms RA, Quan DJ, Herfindal ET, Gourley DR. Infectious Diseases. Text Book of Therapeutics Drug and Disease Management. 8th edition. Lippincott Williams and Wilkins, USA Philadelphia, 2006, Section XIX: 2087–2136.

13. Ranjit mondol, sayon paul, somasree ray, sabyasachi maiti. Polymeric nanocarriers: a promising research avenue for the delivery of anti HIV drugs. International Journal of Applied Pharmaceutics 2010; 2 (2): 1-5.
14. Zeller JM, Swanson B. The pathogenesis of HIV infection. In: Durham JD, Lashley F, editors. The person with HIV/AIDS: nursing perspectives. 3rd ed. New York: Springer publishing company; 2000. p. 78-82.
15. Mitsuya H, Yarchoan R, Broder S. Molecular targets for AIDS therapy. Science 1990; 249:1533-44.
16. Schinazi RF, Mead JR, Feorino PM. Insights into HIV chemotherapy. AIDS Res Hum Retroviruses 1992; 8:963-90.
17. Johnston MI, Hoth DF. Present status and future prospects for HIV therapies. Science 1993; 260:1286-93.
18. Pozniak A. Tenofovir: what have over 1 million years of patient experience taught us? Int J Clin Practice 2008; 62:1285-93.
19. Wintergerst U, Hoffmann F, Jansson A, Notheis G, Huß K, Kurowski M et al. Antiviral efficacy, tolerability and pharmacokinetics of efavirenz in an unselected cohort of HIVinfected children. J Antimicrob Chemother 2008; 61:1336-39.
20. Bahal MS, Romansky JM, Alvarez FJ. Medium chain triglycerides as vehicle for palatable oral liquids. Pharm Dev Technol 2003; 8:111-15.
21. Starr SE, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. Pediatr Infect Dis J 2002; 21:659-63.
22. Cada DJ, Levien T, Baker DE. Etravirine. New drug information/continuing education. Hosp Pharm 2008; 43:498- 07.
23. Hochman JH, Chiba M, Nishime J, Yamazaki M, Lin JH. Influence of P glycoprotein on the transport and metabolism of indinavir in Caco² cells expressing cytochrome P 450 3A4. J Pharmacol Exp Therap 2000; 292:310-18.
24. Schiffman S, Zervakis J, Heffron S, Heald AS. Effect of protease inhibitors on the sense of taste. Nutrition 1999; 15: 767-72.
25. Boudad H et al. Combined hydroxypropyl β cyclodextrin and poly (alkylcyanoacrylate) nanoparticles intended for oral administration of saquinavir. Int J Pharm 2001; 218:113-24.
26. True AL, Chiu Y Y, DeMasi RA, Stout R, Patel I. Pharmacokinetic bioequivalence of enfuvirtide using a needle free device versus standard needle administration. Pharmacotherapy 2006; 26:1679-86.
27. Saksena NK, Haddad DN. Viral reservoirs an impediment to HAART: new strategies to eliminate HIV 1. Curr Drug Targets Infect Disord 2003; 3:179-06.
28. Dembri A, Montisci M J, Gantier JC, Chacun H, Ponchel G. Targeting of 3′azido 3′deoxythymidine (AZT) loaded poly(isohexylcyanoacrylate) nanospheres to the gastrointestinal mucosa and associated lymphoid tissues. Pharm Res 2001; 18: 467-73.
29. Palella, F.J. Jr, Delaney, K.M., Moorman . Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. New England Journal of Medicine 1998;338: 853-860.
30. Lalezari, J.P., Henry, K., O Hearn, . Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. New England Journal of Medicine. 2003; 348: 2175-2185.
31. Liu, R., Paxton, W.A. Homozygous defect in HIV- 1coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. Cell 1996; 86:367–377.
32. De Clercq, E. The bicyclam story. Nature Review Drug Discovery 2003; 2:581–587.
33. Hendrix, C.W., Collier. Safety,pharmacokinetics, and antiviral activity of AMD3100, a selective CXCR4 receptor inhibitor, in HIV-1 infection. Journal of Acquired Immune Deficiency Syndromes 2004; 37:1253–1262.
34. Este, J.A., Telenti, A. HIV entry inhibitors. Lancet; 370: 81-88.
35. Basavapathruni, A., Anderson, K.S. Reverse transcription of the HIV-1 pandemic. FASEB Journal 2007; 21: 3795-3808.
36. Turner, B.G., Summers, M.F. Structural biology of HIV. Journal of Molecular Biology 1999; 285:1-32.
37. Sekaly RP. The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development? Journal of Experimental Medicine 2008; 205: 7-12.
38. Scruggs, E.R., Dirks Naylor, A.J. Mechanisms of zidovudine-induced mitochondrial toxicity and myopathy. Pharmacology 2008; 82:83–88.
39. Mallewa, J.E., Wilkins, E. HIV-associated lipodystrophy: a review of underlying mechanisms and therapeutic options. Journal of Antimicrobial Chemotherapy 2008; 62: 648–660.
40. Mallon, P.W. Pathogenesis of lipodystrophy and lipid abnormalities in patients taking antiretroviral therapy. AIDS Reviews 2007; 9:3-15.
41. Inductivo-Yu, I., Bonacini, M. Highly active antiretroviral therapy-induced liver injury. Current drug safety 2008; 3: 4–13.
42. Strayer, D.S., Akkina, R.. Current status of gene therapy strategies to treat HIV/AIDS. Molecular Therapy 2005;11: 823-842.
43. Satheesh Madhav NV, Shivani Kala. Review of Microparticulate drug delivery system. Int. J.Pharm tech res 2011; 3(3): 1242 – 1254.
44. Abhey Padalha N, Sadhana Shahi R, Mahesh W. Micro particles: an approach for betterment of drug delivery system. Int. J. Pharm. Res&dev 2011; 3(1): 99 – 115.
45. Sudhamani T, et al. preparation and evaluation of ethyl cellulose microspheres of ibuprofen for sustained drug delivery. Int. J. pharma Res and dev 2010; 1:119-125.
46. Selvakumar Dhanasingh, Shanmuga Kumar Nalaperumal. Chitosan /Casein micro particles: Preparation, characterization and drug release studies. Int. Journal of engineering and applied sciences 2010; 6:4.
47. Morinto Y, Fujimoto S. Albumin microspheres as drug carrier. CRC critical reviews in therapeutic drug carrier systems 1985; (1)2:19-63.
48. Gupta P, Fung C. Targeted delivery of low dose doxorubicin hydrochloride administered via magnetic albumin microspheres in rats. J.microencap 1990; 7(1): 85-94.
49. Venkatesan P, Muralidharan C, Manavalan R, Valliyappan K. Selection of better method for the preparation of microspheres by applying analytic hierarchy process. J.pharm.sci & Res 2009; 1 (3): 64-78.
50. Yeo, Y. and Park, K. A new microencapsulation method using an ultrasonic atomizer J**.** Pharm**.** Biopharm 2004;59**:** 449–459.
51. Carvalho FC, Bruschi ML, Evangelista RC, Gremio MPD. Mucoadhesive drug delivery system. Brazilian Journal of Pharmaceutical Sciences 2010; 46(1): 1- 17.
52. Parmar H, Bakliwal S, Gujarathi N, Rane B, Pawar S. Different method of formulation and evaluation of mucoadhesive microsphere. International Journal of Applied Biology and Pharmaceutical Technology 2010; 1(3): 1157-1167.
53. Shaikh R, Singh TRR, Garland MJ, Donnelly RF. Mucoadhesive Drug Delivery Systems. Journal of Pharmacy and Bioallied Sciences 2011; 3(1): 89-100.
54. Asane GS, Nirmal SA, Rasal KB, Naik AA, Mahadik MS. Polymers for Mucoadhesive drug delivery system. Drug Development and Industrial Pharmacy 2011; 34: 1246-1266.
55. Gavin PA, Laverty TP, Jones DS. Mucoadhesive Polymeric Platforms for Controlled Drug Delivery. European Journal of Pharmaceutics and Biopharmaceutics 2009; 71: 505-518.
56. Hemlata Kaurav, S. L. HariKumar and Amanpreet Kaur. Mucoadhesive Microspheres as carriers in Drug Delivery: a Review. International Journal of Drug Development & Research 2012; 4 (2). 21- 34.
57. Sing BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Rel 2000; 63: 235-59.
58. Sungthongjeen S, Paeratakul O, Limmatvapirat S, Puttipupathachorn S. Preparation and in-vitro evaluation of multiple-unit floating drug delivery system based on gas formation technique. Int J Pharm 2006; 324: 136-43.
59. Hilton AK, Deasy PB. In vitro and in vivo evaluation of an oral sustained release floating dosage form of amoxicillin trihydrate. Int J Pharm 1992; 86: 79-88.
60. Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop. J Pharm Res 2008; 7(3): 1055-66.

61. Seth PR, Tossounian J. The hydrodynamically balanced system, a novel drug delivery system for oral use. Drug Dev Ind Pharm 1984; 10: 313-39.
62. Hwang SJ, Park H, Park K. Gastroretentive delivery systems. Crit Rev Ther Drug Carrier Syst 1998; 15(3): 243-84.
63. Reddy LH, Murthy RS. Floating dosage system in drug delivery. Crit Rev Ther Drug Carrier Syst 2002; 19(6): 553-85.
64. Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: overview and special case of Helicibacter pylori. J Control Release 2006; 111: 1-18.
65. Kawashima Y, Niwa T, Takenchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci 1992; 81: 135- 40.
66. 66 32. Talukdar R, Fassihi R. Gastroretentive delivery systems:hollow beads. Drug Dev Ind Pharm 2004; 30: 405-12.
67. Whiteland L, Fell JT, Collett JH. Development of gastroretentive dosage form. Eur J Pharm Sci 1996; 4: S182.
68. Harrigan RM. Drug delivery device for preventing contact of undissolved drug with the stomach lining. US Patent 405 5178; October 25, 1977.
69. Vyas SP, Khar RK. Gastroretentive systems. In: Controlled drug Delivery. Vallabh Prakashan, Delhi, India. 2006. p. 197-217.
70. Garg S, Sharma S. Gastroretentive drug delivery systems. Business Briefing: Pharmatech 2003: 160-66.
71. Mirchandani H, Chien YW. Drug delivery approaches for anti-HIV drugs. Int J Pharm. 1993; 95(1-3): 1-21.
72. Xiaoling L, William KC. Transport, metabolism and elimination mechanisms of anti-HIV agents. Adv Drug Deliv Rev 1999; 39(1-3): 81–103.
73. Devi KV, Pai RS. Antiretrovirals: Need for an Effective Drug Delivery. Indian J Pharm Sci 2006; 68(1): 1-6.
74. Ojewole E, Mackraj I, Naidoo P, Govender T. Exploring the use of novel drug delivery systems for antiretroviral drugs. Eur J Pharm. And Biopharm. 2008; 70(3): 697–710.
75. http://www.aidsreviews.com/files/2000_02_1_033-038.pdf
76. Ouriemchi EM, Vergnaud JM. Calculation of the plasma drug level with oral controlled release dosage forms. Effect of the dose frequency. Int. J. Pharm 1996; 127(2): 177–184.
77. Giammona G, Cavallaro G, Pitarresi G. Studies of macromolecular prodrugs of zidovudine. Adv Drug Delivery Rev 1999; 39(1-3): 153-164.
78. Rawal Tanvi, Diwan Anupama. Novel polymeric combinations for gastroretentive microspheres of Stavudine. Int.J. Drug Dev&Res 2011; 3(2): 211-216.
79. Dhanaraju MD, Mani Kumar R, Nithya P, Kishan JVVN, Thirumurugan G. controlled delivery of anti retroviral drug loaded chitosan cross- linked microspheres. Archives of applied Sci.Res 2009; 1(2): 279-286.
80. Jain S, Biswal I, Dinda A, Moitra SK, Kohli S. Modified sustained release chitosan - coated Zidovudine microspheres. Int. J.pharm &pharm.sci 2011; 3(4): 95 – 97.
81. Sanjay dey, Soumen Pramanik, Ananya Malgope. Formulation and optimization of sustained release Stavudine microspheres using response surface methodology. ISRN pharmaceuticals 2011; 1-7.
82. Josephine LJ, Mohul RJ, Wilson B, Shanaz B, Bincy R. formulation and in-vitro evaluation of floating microspheres of anti-retro viral drug as a gastro retentive dosage form. Int.J.Res.Pharm&Chem 2011; 1(3): 519-527.
83. Nayak Bhabani Shankar, Nayak Udaya Kumar. Lamivudine loaded microspheres for oral use: design development and establishment of in-vitro correlation. Asian J. Pharm & clinical Res 2009; 2(1): 55-60.
84. Phalguna Y, B. S. Venkateshwarlu, Ganesh Kumar Gudas, Subal Debnath. HPMC microspheres of Zidovudine for sustained release. Int.J.pharm & pharm.sci 2010; 2(4): 41-43.
85. Diego A. Chiappetta, Angel M. Carcaboso,Carlos Bregni, Modesto Rubio, Guillermo Bramuglia, and Alejandro Sosnik. Indinavir – loaded pH sensitive Micro particles for taste masking: toward extemporaneous pediatric Anti – HIV/AIDS liquid formulation with improved patient compliance. AAPS pharm sci.tech 2009; 10(1): 1-6.
86. Prakash K, Raju PN, Shanta KK, Lakshmi MN. Preparation and characterization of Lamivudine microcapsules using various cellulose polymers. Tropical J. Pharm. Res 2007; 6(4): 841-847.
87. Sanjay Dey, Bhaskar Mazumder, Mrinal Kanti Sarkar. Comparative study of Stavudine microspheres prepared using ethyl cellulose alone and in combination with Eudragit RS100. Malaysian J.Pharm.sci 2010; 8(2): 45 – 57.
88. Usha Yohendra Nayak, et.al. Glutaraldehyde cross – linked Chitosan microspheres for controlled delivery of Zidovudine. J.microencapsulation 2009; 26(3): 214-222.
89. Sunit kumar Sahoo, Abdul Arif Mallick, Barik BB, Prakash CH Senapati. Formulation and in-vitro evaluation of Eudragit microspheres of stavudine. Tropical J.Pharm. Res 2005; 4(1): 369 – 375.
90. Bipul Nath, Lila Kantanath, Pradeep Kumar. Preparation and in-vitro dissolution profile of Zidovudine loaded microspheres made of Eudragit RS100, RL100 and their combinations. Acta poloniae pham. Drug res 2011; 68(3): 409 – 415.
91. Rama Rao K, Prakash Senapati, Dos MK. Formulation and in-vitro evaluation of Ethyl cellulose microspheres containing Zidovudine. J.microencapsulation 2005; 22(8): 863 – 876.
92. Chetan patil, sunil bakliwal, sunil pawar, bhushan rane and nayan gujrathii. Preparation and evaluation of hollow microsphere drug delivery system of zidovudine. JPSR 2011; 2(10): 2669-2674.
93. Vikram, S. Firoz, D. Kishore, Yerram chandramouli, B. Rubia yasmeen, B. Mahitha, K.L.V Pavan kumar. Formulation and in-vitro characterization of floating microcarriers of stavudine. Asian j. Pharm. Res 2012;2(2) 70-75.
94. Osmond J. DCruz, Barbara Waurzyniak and Fatih M. Uckun. Antiretroviral Spermicide WHI-07 Prevents Vaginal and Rectal Transmission of Feline Immunodeficiency Virus in Domestic Cats.Antimicrobial agents and chemotherapy 2004; 48(4): 1082–1088.
95. 95.K Prakash, P N Raju, K K Shanta and M N Lakshmi. Preparation and characterization of Lamivudine microcapsules using various cellulose polymers. Tropical Journal of Pharmaceutical Research 2007; 6 (4): 841-847.
96. Sellappan velmurugan, mohamed ashraf ali. Formulation and evaluation of maraviroc mucoadhesive microsheres by ionotropic gelation method.Int j pharm pharm sci 2013; 5(4): 294-302.
97. Valquria Miwa Hanai Yoshida, Jose Martins de Oliveira Junior, Marcos Moises Goncalves Et.al. Development and Evaluation of a Floating Multiparticulate Gastroretentive System for Modified Release of AZT.AAPS PharmSciTech 2011; 12(2) : 658-664.
98. Chen, S., Gunn, J.A.: US20036555558 (2003).
99. KPR Chowdary and Annamma Devi GS. Preparation and Evaluation of Mucoadhesive Microspheres of Efavirenz for Enhancing Its Dissolution Rate and Bioavailability. RJPBCS 2012; 3(2):119-124.
100. Pheeba mary philip, ganesh shankar arya. Formulation and in vitro evaluation of nelfinavir mesylate microcapsules using cellulose acetate. Int J Pharmacy and Pharm Sci 2010; 2(3): 169-171.
101. Chandarsekaran N, Balamurugan M. Formulation, Characterization and *In-vitro* Evaluation of Abacavir Sulphate Loaded Microspheres.Research Journal of Pharmacy and Technology 2013;6(7):731-735.
102. Nelson Kenneth1, Varadarajan Parthasarathy, Rajappan Manavalan, Chikkanna Narendra. Advances in Drug Delivery of Anti-HIV Drugs - An Overview. Am. J. PharmTech Res. 2012; 2(6):231-244.
103. Pooja Sharma,Anuj chawala,sandeep arora,Pravin pawar.Novel delivery approaches on antiviral and antiretroviral agents.J.ADV.Pharm.Tech.Res 2012;3(3):147-159.
104. David lembo,Roberta cavalli.Naoparticulate delivery systems for antiviral drugs. Antiviral chemistry & chemotherapy 2010; 21:53-70