

A Review on Novel Formulation Approaches of Azidothymidine

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Abstract

Azidothymidine (AZT or ZVD), a Nucleoside Reverse Transcriptase Inhibitor (NRTI), is used as antiviral medication to treat Human Immunodeficiency Virus (HIV) which causes Acquired Immunodeficiency Syndrome (AIDS). It is the first approved anti HIV drug for AIDS used either in combination with other antiretroviral agents or as a single drug and is also included in WHO's national list of essential medicines 2011. Due to certain physico-chemical and pharmacokinetic constraints of the drug, various approaches are undertaken to improve the half life and bioavailability of ZVD. There are novel formulation approaches such as vaginal gels, bioadhesive film, niosomes, proniosomes, nanoparticles, microparticles etc. Certain researchers have reported different designs of ZVD with other antiretroviral drugs that are used for the combination therapy in the effective treatment of HIV. This review focus on the logistics of formulation designing along with an overview of report of the various analytical techniques employed for the estimation of the ZVD in pharmaceutical dosage forms.

Key Words: AIDS, HIV, novel formulation, Zidovudine.

INTRODUCTION

The Human Immuno Deficiency Syndrome (HIV) and Acquired Immuno Deficiency Syndrome (AIDS) statistics (World Health Organization and United Nations Educational Scientific Cultural Organization) has sketched more than 34.2 million populations surviving with HIV worldwide in 2011 approximately, 2.5 million people were newly infected with HIV and around 1.7 million people expire due to AIDS. [1] This focuses on the enormous counts of new HIV infections producing with time which alarms the significant magnification to the access to antiretroviral therapy so as to abate AIDS related mortality rates in the upcoming years. Women are the fastest growing population with sexually transmitted infections and acquired immune deficiency syndrome (Sexually Transmitted Infections (STIs) and AIDS) worldwide. With no possible cure, HIV continues to spread despite the availability of condoms and other preventive measures. Presently, there are 24 antiretroviral drugs available in market for the treatment of HIV type I infections which are approved by Food and Drug Administration (FDA). These drugs are categorized into six distinct classes based on their molecular mechanism: (1) Nucleoside/Nucleotide Analog Reverse Transcriptase Inhibitors (NRTIs), (2) Non-Nucleoside Analog Reverse Transcriptase Inhibitors (NNRTIs), (3) protease inhibitors (PIs), (4) fusion inhibitors, (5) integrase inhibitors and (6) co-receptor antagonists. ZVD is a NRTI, used as antiviral medication which is intended to inhibit the transmission of STIs and HIV which causes AIDS. [2] It is the first antiretroviral drug that was licensed for the cure of HIV in adult during 1987 by FDA, for paediatric use in 1990 and for pregnant women during 1994, especially for the avoidance of perinatal hauling of HIV from mothers to progeny. [3, 4] ZVD therapy was also observed to be very much efficient in the reduction of the viral infection, caused due to

occupational vulnerability hence the drug is mostly included in post pre-exposure prophylaxis regimens. [5]

ZVD is sparingly soluble in water and pKa is 9.68. The half life is 0.5-3 hours with protein binding of 30-38% showing oral bioavailability of 60-70%. [1, 2, 6] ZVD inhibits viral replication by inhibiting the viral reverse transcriptase by incorporating thymidine into viral DNA by the phosphorylated ZVD and thereby preventing the addition of phosphodiester link to the inert 3' azido group by termination of DNA chain. [7]

ZVD is available in tablet, capsule syrup and intravenous formulations. Fixed drug combinations (FDC) such as Combivir (ZVD and Lamivudine) and Trivizir (ZVD, Lamivudine and Abacavir) which includes a NNRTI or a protease inhibitor was found to have more sustained effect. [3] It is shown that antiretroviral combination therapy of ZDV was more effective in suppressing the viral load, delayed the complications by increasing the number of CD4 cells and perpetuating the survival of AIDS patients by many months and years compared to the use of ZVD alone. [3] Combination therapy of ZVD with Acyclovir or Castanospermene (recombinant β -interferon) showed synergistic impacts against HIV in T lymphocytes *in-vitro*, ZVD with Foscarnet showed activity against the virus in the mononuclear cells of peripheral blood and ZVD with granulocyte macrophage colony stimulating factor showed antiviral effects in monocytes. [7] ZVD and Stavudine in conjunction should never be administered as both are NRTIs hence intracellular phosphorylation takes place which causes interactions between the two drugs and cause harmful side effects. [8]

Adverse side effects are observed with combinations such as ZVD and Paracetamol, ZVD and Probenecid as well as ZVD and Dideoxycytidine possibly due to drug-drug interactions and reduced metabolism and excretion of ZVD. [7] Administration of ZVD and Acyclovir in combination

therapy caused side effects such as insomnia, headache, dry mouth, taste alterations, fatigue, lethargy and somnolence. [7] Hence drugs that cause cytotoxic, nephrotoxic or adverse haematological effect should not be administered in combination with ZVD. [7]

The main drawbacks of oral dose administration of ZVD include first pass metabolism, gastric intolerance and side effects such as myalgia, haematological abnormalities, bone marrow toxicity, confusions, seizures, neurological abnormalities, altered liver function, nail pigmentation, anaemia, neutropenia, hepatotoxicity, severe headache and abdominal discomfort. [2,7] Other side effects which resolve within first few weeks of the treatment include loss of appetite, nausea, vomiting, malaise, headache, weakness and dizziness. [9] In order to maintain therapeutic levels, high doses oral formulations of ZVD are needed to be administered multiple times a day, usually 300 mg twice a day or 200 mg thrice a day. [3]

To overcome the various side effects associated with the oral administration of ZVD, various novel approaches have

been extensively studied so as to make the drug available at the site of action with reduced side effects. This review focuses on the novel formulation approaches which have been designed and examined for its *in-vitro* characterization and *in-vivo* efficacy.

FORMULATION APPROACHES

Oral matrix tablets

Matrix tablets otherwise known as modified release tablets, are one of the interesting options whilst formulation of Controlled (CR) or Sustained Release (SR) oral formulations. These tablets can be prepared by a combination of hydrophobic and hydrophilic polymers that forms a matrix by embedding the drugs. A range of such matrix tablets of ZVD for oral route have been designed by different researchers employing polymers like Hydroxy Propyl Methyl Cellulose (HPMC), Ethyl Cellulose (EC), Sodium Carboxy Methyl Cellulose (Na CMC), Micro Crystalline Cellulose (MCC) etc., as shown in Table 1. Such formulations have been extensively studied due to its ease in manufacture and relatively low cost.

Table 1: Oral Matrix Tablets of Zidovudine

S. No.	Polymers used	Method employed	Reported Results	Authors
1	HPMC (4000, 15000, 100000 cps)	Wet granulation	HPMC 4000cps and HPMC 15000cps showed an initial release of 21-18% at 1 h and extended the release upto 16 h and 20 h respectively.	Ravi PR. <i>et.al.</i> 2008. [10]
2	HPMC K4M, Guar Gum and EC	Wet granulation	HPMC K4M and guar gum showed an initial release of 20-25% at 2 h and extended the release up to 12 h.	Kalyani Chithaluru <i>et.al.</i> 2009. [11]
3	Blend of natural (plant gum obtained from <i>Abelmoschus esculentus</i>) and synthetic polymer- Carbopol 71G (C71)	Direct compression	<i>Abelmoschus esculentus</i> and carbopol 71G showed an extended drug release upto 8 h.	Emeje M. <i>et.al.</i> 2010. [12]
4	HPMC K4M, EC and MCC	Direct compression, A2 ³ factorial design	Formulation with blend of HPMC K4M and MCC showed drug release of 82.49% at 12 h.	Kar RK. <i>et.al.</i> 2010. [13]
5	HPMC K15M and HPMC K100M, Eudragit RSPO and Eudragit RLPO	Direct compression	Low compression force (<100 Mpa) showed drug release profiles for 12 h.	Jucimary V Santos <i>et.al.</i> 2010. [14]
6	HPMC K15 and HPMC K4M as alone or in combination with EC	Direct compression	Formulation containing HPMC K15, HPMC K4M and EC showed sustained drug release of 23.12%-26.21% respectively for 12 h.	Gaurishyam Pasa <i>et.al.</i> 2011. [15]
7	Eudragit L100, Polyethylene Oxide (PEO) and Carbopol 971P	Wet and dry granulation method	Matrix tablets formulated by wet granulation (IPA) showed drug release of 60%-99% at 12 h with individual polymers.	Narayana Raju P. <i>et.al.</i> 2011. [16]
8	NaCMC, HPMC (ELV-15), Eudragit-L155, & Xanthan gum alone or in combination with EC	Wet granulation	NaCMC with Xanthan gum and EC showed sustained drug release of 79.16% and 65.21% respectively at 12 h.	Himansu Bhusan Samal <i>et.al.</i> 2011. [17]
9	HPMC K4M and HPMC K10M, Sodium CMC, EC	Direct compression	Matrix tablets prepared with HPMC and 4% EC showed drug release of more than 95% at 12 h.	Deepika V. <i>et.al.</i> 2011. [18]
10	HPMC K15M, HPMC K100M, EC, Eudragit RSPO and Eudragit RLPO	Direct compression	Formulation containing 5% of each of the polymer showed best drug release of 90% at 12 h.	Jucimary V. <i>et.al.</i> 2012. [19]
11	Eudragit RLPO, Eudragit RSPO and EC alone or in combination	Wet granulation	Eudragit formulated with EC and Eudragit alone gave a sustained drug release of 88.1% and 94.3% for 12 h and 6 h respectively.	Atul Kuksal <i>et.al.</i> 2006. [20]

In a comparative study between HPMC (semi synthetic) and acacia (natural), Sankar V. *et al.* 2010 proved that oral ZVD tablets formulated with HPMC by wet granulation process showed a slower and controlled drug release rate compared to tablets prepared with acacia. [21]

Oral dispersible tablets

ZVD has a very bitter taste and as its half life is very short, multiple dosing of the drug is followed which gives rise to reduced patient compliance. [22] In order to mask the taste of this bitter drug and enhance its solubility, taste masked dispersible tablets of ZVD were formulated by wet granulation method with Crosscarmellose Sodium (CCS) as a disintegrant. The results showed that Surelease clear (aqueous ethyl cellulose dispersion) in concentration order of 0.044 mL/tab to 0.052 mL/tab and 6% CCS masked the bitter taste of ZVD completely, hence giving it a pleasant taste, least disintegration time of 18.9 seconds as well as better dissolution profile compared to other commercially available ZVD tablets (Yash Paul *et al.* 2011). [22] Consequently, the same authors have performed a comparative study of oral dispersible tablets formulated with different super disintegrants and found that the tablets prepared with 6% CCS again showed the least disintegration time (12 second) and better dissolution profile (Yash Paul *et al.* 2011). [23] In order to overcome the problems related to incompatibility and instability of drug with the stomach acid and to increase the intestinal absorption of ZVD, Rasheed SH. *et al.* 2010 formulated enteric coated tablets of ZVD by wet granulation method where the formulations gave sustained release over 12 h. [24]

Particulated vaginal tablets

To mask the disadvantages associated with the conventional vaginal formulations such as gels which pose problems such as leakage and reduced retention of the formulation in the vaginal epithelium, sustained release bioadhesive vaginal tablets were formulated by direct compression using ZVD that was microencapsulated by solvent evaporation method. Tablets containing carbopol-934 and ZVD in 1:1 ratio were chosen as the optimized formulation (Amitava Ghosh *et al.* 2011). [25]

Oral tablets of Zidovudine in combinations

Multidrug therapy usually shows a delayed resistance towards HIV replication hence reduces pill burden and increases patient compliance to the Highly Active Antiretroviral Therapy (HAART). Few FDC for antiretroviral drugs in a single pill has been designed for its several advantages. Cytochrome P3A4 enzymes are responsible for metabolising ZVD due to which there is a decrease in the systemic availability of the drug. Hence ZVD in combination with a cytochrome P3A4 inhibitor proves as a very useful therapy against fungal infections that occurs during AIDS. SR matrix tablets were thus developed by wet granulation where ZVD was combined with Ketoconazole (cytochrome P inhibitor) using both hydrophilic (HPMC) and hydrophobic (EC) polymers and the optimized formulation was chosen as HPMCK4M and Ethyl cellulose in 1:1 ratio which provided a drug release for 12 h period. The pharmacokinetic boosting was hence proved by *in-vivo* studies on rabbits which showed that the above formulation with a 3:2 ratio of ZVD and

Ketoconazole produces an increase in the bioavailability (Pathak Jagriti *et al.* 2012). [26] Another combination of ZVD and Lamivudine was studied where in the tablets prepared by direct compression method was found to be better in comparison to wet granulation method. The optimized formulation (Lamivudine 300 mg, ZVD 150 mg) showed a very good drug release (100.2%) and were more stable in blister pack at varying temperature as well as relative humidity during the accelerated stability studies (Vikramjit Singh *et al.* 2012). [27] To reduce the frequent administration of the drugs, Sirisha VLN. *et al.* 2012 made an attempt to prolong the release of the antiretroviral drug (Lamivudine + ZVD) by coating them with a hydrophilic polymer (HPMC 100000 cps). The drugs were formulated by wet granulation method and two selected formulations were coated with 10% HPMC 100000 cps which showed a complete drug release for 8 h and hence considered as the optimized formulation for extended release of the drugs. [28]

Zidovudine loaded films

Transdermal route is one of the potential alternatives to oral route that bypass undesirable characteristics of oral administration of selective drugs. Hence to mask such disadvantages, Evrim Atalay Takmaz *et al.* 2009 developed monolithic films of ZVD by solvent evaporation method using Eudragit RL 100 and EC, in order to enhance the transdermal delivery of the drug. Results showed that the film containing 100% (w/w) of Eudragit RL 100 showed the best drug release at the end of 8 h which was close to free drug (2 mg/mL solution). [29] A new drug delivery system for the therapy and prevention of AIDS was successfully developed by Arkendu Chatterjee *et al.* 2010 where ZVD loaded bioadhesive vaginal film was prepared by solvent casting technique. The formulation comprising Acrycoat S 100: HPMC (4:1) and drug: polymer (1:5) was selected as optimized formulation because of higher drug content (87.44 ± 0.45 % w/w), folding endurance (321 ± 23 no. of times), swelling index (17.08 ± 67), % moisture content (1.23 ± 1.11), bioadhesive strength and *in-vitro* drug release kinetics when compared to standard oral conventional tablets. [30] In order to overcome the problems related to oral ZVD dosage forms, another approach was taken by Rakesh Reddy S. *et al.* 2012 by formulating mucoadhesive buccal patches by solvent casting method. These buccal patches were designed by employing certain film forming polymers such as HPMC 47cps, EC, Eudragit and Carbopol 934. The formulation containing HPMC and Carbopol 934 in 1: 1 and 1: 0.5 ratios were selected as the best formulations with respect to their bioadhesive strength, good drug release profile for 16.4 h and 14.7 h respectively, swelling index (45.65% and 44.00% increase in area), uniform thickness and other physical characteristics. [31]

Rectal Suppositories

In order to attain local or systemic effect of drugs, Takeo Kawaguchi *et al.* 1991 formulated rectal suppositories of ZVD for investigating the rectal absorption of the drug from the lower part of intestine. The *in-vivo* experiment on rats showed that the suppository containing 10 mg or 37.5 $\mu\text{mol/kg}$ of ZVD maintained constant plasma

concentration of above 1 μM for duration of more than 6 h. [32]

Transdermal Gels

Another conventional drug delivery system was developed as transdermal gel by incorporating various penetration enhancers in HPMC and *in-vivo* and *ex-vivo* study was conducted across rat skin, to examine the effect of the penetration enhancers on transdermal delivery of ZVD. The study revealed that 2.5%(w/w) methanol and oleic acid showed good enhancement in transdermal permeability of the formulated ZVD gel across rat membrane with decreased irritation on skin and a steady state flux of 2.26 $\text{mg cm}^{-2} \text{h}^{-1}$ was adequate to achieve the desired curative concentration (Narishetty ST. *et al.* 2004). [33] A similar study was performed by Pokharkar V. *et al.* 2010 by incorporating other penetration enhancers in HPMC. The gel containing cineole and menthol as penetration enhancers were selected as the optimized formulation based on parameters such as bioavailability, drug deposition, drug content, steady state flux (5.9 $\text{mg/cm}^2/\text{h}$ and 5.4 $\text{mg/cm}^2/\text{h}$ respectively), rheology, *in-vitro*, *in-vivo* and *ex-vivo* permeation of the drug across rat skin. [34] Mucoadhesive semisolid formulations facilitate very good contact with the absorption surface hence facilitating extended residence time of the formulation at the site of action hence improved patient compliance, bioavailability and reduce the side effects of drugs. Such studies were carried out by many researchers as listed in Table 2.

Intra nasal gels

In a study to find an alternative approach of delivering ZVD into the Cerebrospinal Fluid (CSF) and brain tissue,

an intra nasal formulation was prepared by mixing ZVD in phosphate buffer solution at pH 5.5 containing Poloxamer 407 as thermo reversible gelling agent and 0.1% n-Tridecyl- β -D-Maltoside (TDM) which facilitates the permeation of the drug across membrane. The *ex-vivo* studies on nasal mucosal membrane of rabbit unveil an accretion in permeability of ZVD by 53%. *In-vivo* study exhibited bioavailability of 29.4% that showed four times delayed absorption achieving a T_{max} of 20 min and the drug level in CSF and brain post intranasal administration of the gel were found to be 4.7–5.6 times greater than the IV injections. This proved that transfer of ZVD through Olfactory lobe after intranasal administration could transfer the drug into CSF and brain tissues (Parag M Ved *et al.* 2011). [40] Mucoadhesive *in-situ* gelling stimuli-sensitive drug delivery system for nasal administration of ZVD was employed by formulating liquid crystal precursors containing PPG-5-CE- TETH-20, oleic acid and water in the concentration range of 55, 30, 15% w/w. The formulation administered through nasal route showed gel formation in contact with artificial liquid nasal mucous resulting in a rigid liquid crystal matrix formation showing a promising novel tool for sustained delivery of ZVD and other antiretroviral drugs. *In-vivo* study of the formulation was conducted on male Wistar rats of 250–300 g where nasal and intravenous administration of the formulation was compared in which the plasma concentration curve of nasal administration showed a better profile compared to intravenous administration (Flavia Chiva Carvalho *et al.* 2012). [41]

Table 2: Intravaginal Gels of Zidovudine

S. No.	Derived compound	Activity/Method	Polymers used	Reported Results	Authors
1	ZVD loaded bioadhesive vaginal gel	Cold mechanical stirring	Carbopol 940p-HPMCK4M	The formulation with carbopol 940p and HPMC K4M in 1:3 ratio showed drug release profile of 90.18% up to 24 h.	Arkendu Chatterjee <i>et al.</i> 2011. [35]
2	ZVD loaded microencapsulated vaginal gel	O/O single emulsion solvent evaporation, Cold mechanical stirring	HPMC and Carbopol 940p	The ZVD microencapsulated vaginal gel containing 407 mg of the optimized microparticles and 100 mg of carbopol 940P showed a constant drug release of 63.41% upto 28 h.	Arkendu Chatterjee <i>et al.</i> 2010. [36,37]
3	Phenyl phosphate derivative of Bromo-Methoxy ZVD (WHI-05)	Anti-HIV as well as spermicidal activity	Xanthan gum and Carrageenan (0.5–2.0% viscosity)	Repeated application of the WHI-05 gel emulsion did not cause any adverse effects or toxicity <i>in-vivo</i> in mice (active ingredient of vaginal contraceptives for women).	Osmond J. D'Cruz <i>et al.</i> 2000. [38]
4	Aryl phosphate derivative of Bromo-Methoxy ZVD (WHI-07)	Anti-HIV as well as spermicidal activity	Seaspan, Xanthan gum and Carrageenan (0.5–2.0% viscosity)	2% WHI-07 gel microemulsion through intravaginal route before artificial insemination inhibited pregnancy rate in the rabbits by 81-85% provided by inhibiting fertility by more than 90%	Osmond J. D'Cruz <i>et al.</i> 2000. [39]

Hydrogels and Emulgels

In another approach to mask the side effects associated with the oral administration of ZVD, Sushil Raut *et al.* 2012 formulated hydrogel and emulgels of ZVD for transdermal application. Based on some evaluation parameters such as viscosity, spreadability, drug release kinetics and other physical properties, the emulgels were found to exhibit very good partition in both oil and aqueous phases hence found to be an effective drug delivery system for ZVD. [42]

Microemulsions

Nasal route of administration of drugs suffer with certain disadvantages among which mucociliary clearance possess various problems with the intranasal absorption of drugs. To circumvent such problems, microemulsion of ZVD with mucoadhesive property was developed using PPG-5-CETETH-20 as a surfactant, oleic acid and water. Results show that formulated microemulsion when in contact with simulated aqueous nasal mucous had the ability to form a gelatinous and viscid crystalline matrix due to phase transition of the microemulsion to a lamella phase. Hence the formulation showed very good mucoadhesive force as well as increase in elasticity hence prolonging the duration of ZVD in the rhinal cavity. (Flavia Chiva Carvalho *et al.*, 2010). [43, 44]

Polymeric Nanoparticles

Biodegradable solid lipid nanoparticles of ZVD were formulated by Singh S. *et al.* 2010 and its entrapment efficiency was investigated. The nanoparticles were prepared by double-emulsion solvent-evaporation method (w/o/w) with different triglycerides using 3² factorial design. The study showed that fatty acids with 621 nm particle size and 27% entrapment efficiency have possible advantages over triglycerides in solid lipid nanoparticles hence a blend of PLA-PEG can be used as carrier for the delivery of ZVD by the intranasal route. [45] Another study was performed by Mara Mainardes *et al.* 2010 to assess the pharmacokinetics of ZVD loaded biodegradable PLA-PEG nanoparticles in mice models. It was observed that the mean half life of ZVD was increased approximately by 7 h for the PLA-PEG nanoparticles in comparison to aqueous solution of ZVD and hence proving that nanoparticles were suitable for intranasal delivery of ZVD. [46] Chitosan,

possessing potential advantages over the other available polymers, was used for a study where ionic gelation method was used for preparing cross linked chitosan (ionic cross linking) nanoparticles with tripolyphosphate anions. The nanoparticles of ZVD with core: coat ratio of 1:2 was selected as the optimum formulation which exhibited drug release for 24 h (Adlin Jino Nesalina J. *et al.* 2012). [47] In another study, Diana P Callender *et al.* 1999 verified the pharmacokinetics of ZVD entrapped biodegradable nanospheres made of polylactide-coglycolide matrix (50:50) when administered through oral route in 15 female *Oryctolagus cuniculus* (2.5 to 3.0 kg). The study revealed that bioavailability of the nanosphere preparation was higher (76%) compared to the conventional dosage forms as well as the drug concentrations sustained in the plasma for a longer time which will be useful when administered in humans. [48]

Microparticulate systems

In a recent study, a natural biomaterial was isolated from the pulp of fruit *Artocarpus heterophyllus* and ZVD loaded microparticles in different ratios were formulated using this biopolymer. Two formulations comprising 100 mg of the drug and 150 mg of biopolymer showed good content uniformity (85.38% and 84.34%) and mucoadhesivity with retention time of 3 hours 30 min and 4 h 20 min respectively (Satheesh Madhav NV. *et al.* 2011). [49] For controlled release of ZVD, Raghavendra C. *et al.* 2011 developed ZVD loaded microparticles by spray drying technique using polymers such as PLGA and PLA-PEG in which the formulation containing PLGA showed a controlled drug release upto 125 h whereas 30 h was required for the release of drug from PLA-PEG microparticles. [50] Khawla Abu Izza *et al.* 1996 formulated ZVD microspheres employing factorial design using Surface response methodology where low concentrations of the Sodium Dodecyl Sulfate with ethyl acetate with drug: polymer ratio in moderation produced optimum ZVD microspheres. [51] Different microsphere preparations have also been reported by various scientists by employing enormous polymers which have been listed in Table 3.

Table 3: Microspheres of Zidovudine

S. No.	Polymers	Method	Reported Results	Authors
1	EC	Double emulsion solvent diffusion method	Drug entrapment of 41-55% and <i>in-vitro</i> drug release upto 18-20 h was observed.	Rao KR. <i>et al.</i> 2005. [52]
2	EC	Double emulsion solvent diffusion method	54% drug entrapment was observed at polymer-drug ratio from 1:0.25 to 1:0.50 at 1000 rpm. 100 % drug release was found at 1:1 drug polymer ratio by 10 h.	Das MK. <i>et al.</i> 2007. [53]
3	Chitosan	Suspension cross linking method	Drug entrapment of 60% was obtained with microspheres in size range 60–210 µm. Glutaraldehyde cross linked microspheres (35%) with 1:6 drug-polymer ratio showed a drug release of 75% upto 12 h.	Usha Yogendra Nayak <i>et al.</i> 2009. [54]
4	Chitosan	Emulsification method	Microspheres with 1:2 drug-polymer ratios prepared at 1500 rpm showed drug entrapment efficiency of 93.54% and an <i>in-vitro</i> drug release of 96% upto 12 h.	Kesari Asha <i>et al.</i> 2012. [55]

Tarun K Mandal *et al.* 1996 developed biodegradable microcapsules of ZVD in to enhance the encapsulation ability of ZVD in PLGA (50:50). This was obtained by modification and change in pH of secondary aqueous phase by partial saturation using calcium chloride. The particle (8-18 μ m) surface was found to be wrinkled with change in pH of aqueous phase (pH=10) and a boost in the particle size (78-140 μ m) was observed due to the partial saturation of aqueous phase with ZVD. An increase in encapsulation efficiency (17%) was subsequently found due to partial saturation of aqueous phase with 0.75% of the drug hence showing a sustained drug release of 15-34% within the first 24 hours which continued the release upto 60 days. [56] In another similar study, the same authors formulated the above said ZVD loaded biodegradable microcapsules and investigated the effect of formulation and processing factors on the characteristics of the microcapsules. It was found that encapsulation efficiency reduced when ZVD powder was mixed into the organic solvent directly instead of adding an aqueous solution (Tarun K. Mandal *et al.* 1996). [57]

Vesicular systems

An attractive approach for the targeted delivery of ZVD to the lymphoid organs was performed by formulating surface engineered nanosized liposomes by incorporating charges (stearylamine and dicetyl phosphate) and site specific ligand (mannose). It was observed that the surface engineered liposomes (120 +/- 10 nm) were found to be highly localized in spleen and lymph nodes ($p < 0.05$) (Kaur CD. *et al.* 2008). [58] Another approach for the lymphatic targeting of ZVD was undertaken by formulating PEGylated elastic liposomes. The *ex-vivo* evaluation of the PEGylated liposomes through rat skin showed a transdermal flux of 119.5 \pm 5.2 μ g/cm²/hr, biodistribution as 27-fold higher in the lymphoid tissues, high cellular uptake (88.9 \pm 8.7%) by the lymphoid cells (MT-2 cell line) compared to the free drug (Jain S. *et al.* 2008). [59] Hence these works represented novel approaches for targeting ZVD delivery for sustained action thus proving a promising anti-HIV therapy. Niosomal drug delivery system has been studied for the intravenous delivery of ZVD. The niosomes were developed by thin-film hydration technique and proniosomes (slurry form) was formulated using beta-cyclodextrin as a carrier molecule. For niosomes formulated with Tween 80 surfactant (without dicetylphosphate), there was very good drug distribution in lungs, kidney, heart, liver and spleen of mice post intravenous bolus injection. Pharmacokinetic study of Tween 80 formulation with dicetylphosphate in rabbits showed $T_{1/2}$ of 202 min and a mean residence time of 212.1 min. The stability study (90 days) showed leakage of drug from Tween 80 formulation which was overcome by encapsulation of the drug in proniosomes (Ruckmani K. *et al.* 2010). [60] The study was extended by the same authors, where ZVD niosomes were formulated and optimized by changing the ratios of the surfactants (Tween 80, Span 80, cholesterol) and the process variables (% hydration, sonication time, charge inducing agent, alteration in osmotic shock, viscosity and its related effects, etc.). The study showed that Tween 80 with dicetylphosphate entrapped higher amounts of ZVD in the

niosomes with drug release of 88.72% over 12 h which was fickian diffusion controlled obeying first order release kinetics (Ruckmani K. *et al.* 2010). [61] Hence the results of the above experiments demonstrate niosomes as a promising vehicle for targeted delivery of ZVD.

Chemical Delivery Systems

Since there was rapid systemic elimination and poor uptake of ZVD observed in parenteral route of administration, Marcus E Brewster *et al.* 1997 developed a chemical delivery system named Redox trapping (covalent attachment of a target molecule 1-methyl-1, 4-dihyronicotinate to ZVD) for targeting ZVD to brain. By administering an aqueous formulation of ZVD chemical delivery system, it resulted in rapid penetration through blood brain barrier and conversion of the target molecule to its quaternary salt subsequently releasing the drug. Results reveal an exacerbation in the drug level in brain (1.75- to 3.3-fold higher than the conventional ZVD) when the formulations were tested upon dogs and other animals, hence the pharmacokinetic and tissue distribution behaviour of the ZVD chemical delivery system was proved. [62]

CONCLUDING REMARKS

The continuing need to affray the existing and emerging HIV infections, alarms upcoming pharmaceutical researchers to identify and develop newer drug delivery systems of the existing drugs to minify its related secondary effects. The novel drug delivery systems offer improved protection and an effective means of therapy over conventional multidose therapy, much of which is focussed on sustained release technology to deliver drug in a controlled manner. The intent of this review was to focus on ZVD with respect to its formulation aspect and to highlight all the possible efforts which are being undertaken by various researchers for the administration of this antiviral drug through different possible routes, to deliver the drug in such a manner so as to reduce the drug related side effects and to obtain optimum benefits of the therapy. Few of the research has also led to the discovery and development of some polymers derived from natural sources and the efficiency of the same has also been studied when compared to the synthetic polymers which is also been discussed. Hence from a global health perspective, various novel and redesigned approaches are to be undertaken in future to deliver ZVD to the target site so as to improve its permeability, minimize side effects like localization of drug hence decrease the frequency of dosage.

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