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Abacavir Sulphate: AnAntiretroviral drug with multiple clinical potential, manifestations and applications.

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ABSTRACT
Abacavir sulphate is Nucleoside reverse transcriptase inhibitor (NRTI) which are mainly used to treat HIV. It is a 2′-deoxyguanosine nucleoside analogue that is carbocyclic. Intracellularly, it is converted to a 2′-deoxyguanosine nucleoside analogue that inhibits HIV reverse transcriptase and stops proviral DNA chain expansion. The reductions in HIV RNA levels in patients receiving abacavir in conjunction with other antiretroviral medications were larger and lasted longer in double-blind trials in antiretroviral therapy-experienced or -naive patients than in patients receiving placebo in combination with the same agents. Furthermore, in a proportion of patients, abacavir in combination with lamivudine and zidovudine lowered viral load to levels below detectable levels, similar to the protease inhibitor indinavir in combination with lamivudine and zidovudine. Antiretroviral therapy-naive patients had the greatest decreases in viral load. Preliminary findings suggest that the viral suppression achieved with a protease inhibitor plus two nucleoside reverse transcriptase inhibitors can be maintained just as well with abacavir in combination with two NRTIs as it does with the protease inhibitor-containing treatment regimen. Initial virological data from studies of abacavir and protease inhibitor combinations show promising, but bigger controlled trials are needed to confirm these findings. The current review was prepared by compiling pharmacokinetics, Pharmacodynamics properties, mechanism of action, drug interactions, toxicity, and drug resistance.

Keywords: Antiretroviral agent, Abacavir Sulphate.

INTRODUCTION

Abacavir is chemically {(1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl] cyclopent-2- en-1-yl} methanol sulphate. It has molecular formula (C14H18N6O) 2. H2SO4 and Molecular weight of 260.7 Daltons. Abacavir sulphate is the enantiomer with 1S, 4R absolute configuration on the cyclopentene ring. It is a white to off-white solid freely soluble in water [1].The general profile of Abacavir sulphate is given in (Table No. 1).

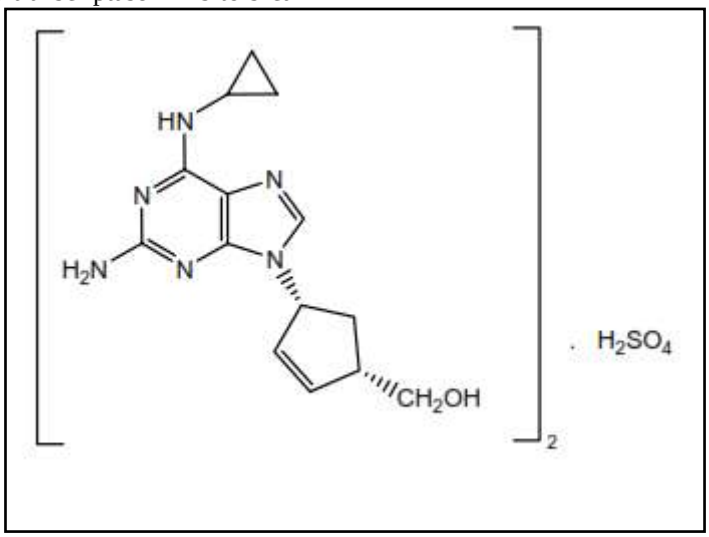

Fig. 1: Structure of Abacavir Sulphate

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Table No. 1: General profile of Abacavir Sulphate.

Category	Antiretroviral (Nucleoside Reverse Transcriptase Inhibitor)
Chemical Name	[(1S, 4R)-4-[2-Amino-6(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-] methanol sulphate
Molecular Formula	(C14H18N6O) 2. H2SO4
Molecular weight	670.7 Daltons
Appearance	White to almost white powder.
BCS Class	Class-III (High Solubility, Low Permeability)
Solubility	Freely soluble in water
pKa	15.41 (Acidic) 5.8(Basic)
Melting Point	165-167 ^{o}C
Storage	Abacavir sulphate should be kept in a well-closed container
Standards	Not less than **99.0 %** and not more than **101.0 %** of (C14H18N6O) 2. H2SO4 calculated with reference to the dried substance

1.2 Mechanism of action

Abacavir is an antiviral drug that is a carbocyclic synthetic nucleoside analogue. Intracellularly, abacavir is transformed to carbovir triphosphate, an analogue of deoxyguanosine-5'-triphosphate, by cellular enzymes (dGTP). By competing with the natural substrate dGTP and incorporating itself into viral DNA, carbovir triphosphate inhibits HIV-1 reverse transcriptase (RT). Because the integrated nucleotide lacks a 3'-OH group, which is required to create the 5′ to 3′ phosphodiester linkage required for DNA chain elongation, viral DNA growth is stopped. Abacavir is a weak inhibitor of the following cellular DNA polymerases α, β and γ [1], [2].The detail mechanism of cation of abacavir is given in (Fig. No. 2).

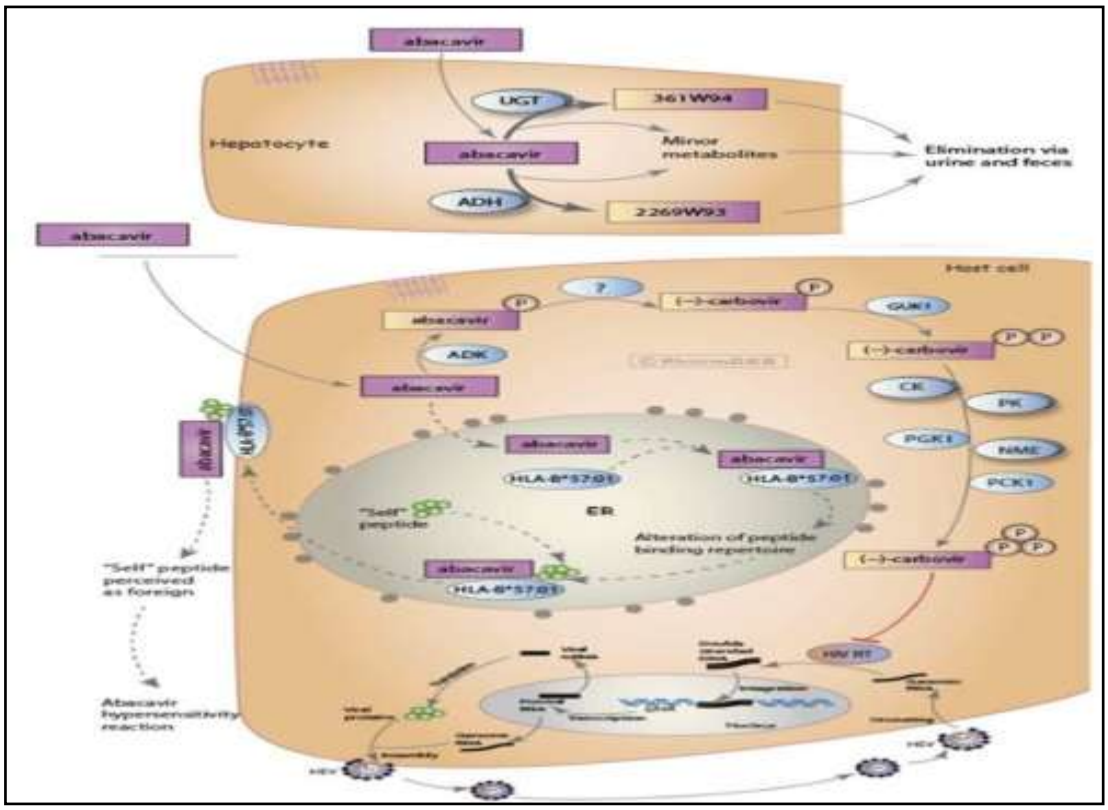

Fig. No. 2 Mechanism of action of Abacavir[3]

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1.3 Pharmacokinetics

a) Absorption and Bioavailability

After oral treatment, abacavir was immediately and thoroughly absorbed. The tablet's geometric mean absolute bioavailability was 83 %. The steady-state peak serum abacavir concentration (Cmax) was 3.0 ± 0.89 mcg/mL (mean ± SD) and AUC (0-12 hr) was 6.02 ± 1.73 mcg.hr/mL in 20 patients after oral administration of 300 mg twice daily. Abacavir tablet bioavailability was tested in both fasted and fed conditions. Because there was no significant change in systemic exposure (AUC) between the fed and fasted phases, ZIAGEN Tablets can be taken with or without food. After administration of ZIAGEN Oral Solution and ZIAGEN Tablets, systemic abacavir exposure was equivalent. As a result, these products can be utilised interchangeably.

b) Distribution

After IV administration of abacavir, the apparent volume of distribution was 0.86 0.15 L/kg, indicating that abacavir is distributed extravascularly. The ratio of CSF AUC (0-6 hr) to plasma AUC (0-6 hr) ranged from 27% to 33% in three patients. Abacavir binds to human plasma proteins at a degree of about 50%. The concentration of abacavir did not affect its binding to plasma proteins. Abacavir distribution into erythrocytes is demonstrated by the fact that total blood and plasma drug-related radioactivity concentrations are similar.

c) Metabolism

In humans, cytochrome P450 enzymes do not appreciably metabolise abacavir. Abacavir is primarily eliminated through alcohol dehydrogenase (to produce 5′-carboxylic acid) and glucuronyl transferase (to produce 5′-glucuronide). The metabolites have no antiviral properties. Abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant dosages, according to in vitro tests.

d) Elimination

Following the administration of a 600-mg dose of 14C-abacavir, a mass balance study revealed that 99 % of the radioactivity was recovered, 1.2 % was excreted in the urine as abacavir, 30% as the 5′-carboxylic acid metabolites, 36% as the 5′-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. 16 percent of the dosage was eliminated through faeces. The reported elimination half-life (t1/2) in single-dose experiments was 1.54 0.63 hours. Total clearance after intravenous treatment was 0.80 0.24 L/hr/kg (mean SD)concentrations.

1.4 Pharmacodynamic

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) that inhibits the replication of the Human Immunodeficiency Virus Type 1 (HIV-1) (HIV-1). Phosphorylation of abacavir produces active metabolites that compete for viral DNA integration. They function as a chain terminator of DNA synthesis by competitively inhibiting the HIV reverse transcriptase enzyme. Against HIV-1IIIB and HIV-1BaL, the medication concentration required to inhibit viral replication by 50% (EC50) ranged from 3.7 to 5.8 M (1 M = 0.28 mcg/mL) and 0.07 to 1.0 M, respectively, and was 0.26 0.18 M against 8 clinical isolates. In cell culture, abacavir had synergistic activity with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the protease inhibitor (PI) amprenavir, as well as additive activity with the NRTIs didanosine, emtricitabine, lamivudine, stavudine[2].

1.5 Side Effects

The most commonly reported adverse reactions of at least moderate intensity (incidence ≥10%) in adult HIV-1 clinical trials were nausea, headache, malaise and fatigue, nausea and vomiting, and dreams/sleep disorders. Serious hypersensitivity reactions have been associated with abacavir which has been strongly linked to the presence of the HLA-B*57:01 allele.

1.6 In Vitro Antiviral Activity:

- **Abacavir Alone:**

The concentration of abacavir inhibiting replication by 50% (IC50) in human T lymphocyte cell lines (CD4+ CEM, CD4+ HeLa, MT-4) or human peripheral blood mononuclear cells (PBMC) infected with the laboratory HIV-1 strain IIIB ranged from 3.7 to 5.8 mol/L. [4] Abacavir was about four times as active as didanosine (IC50 16 mol/L), slightly less active than zalcitabine (IC50 0.23 mol/L), and significantly less active than zidovudine (IC50 0.09 mol/L). Abacavir, on the other hand, showed similar efficacy to zidovudine (IC50 0.26 and 0.23 mol/L, respectively) in experiments with clinical isolates in PBMC culture, was about twice as effective as didanosine (IC50 0.49 mol/L), but was 9 times less potent than zalcitabine (IC50 0.03 mol/L) [4]. In vitro, abacavir has action against latently HIV-infected cells [5]. Selective death of active cells with an anti-CD25 immunotoxin produces a population of latently infected cells that can then be activated with an anti-CD3 monoclonal antibody or

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co-cultured with PHA-activated PBMCs in the presence of medication. In both the anti-CD3 system and the coculture experimental systems, abacavir was more active than zidovudine or lamivudine. In MT4 cells, abacavir had activity against HIV-2 that was similar to its action against HIV-1 (IC50 4.1 mol/L). In two independent test techniques, the medication demonstrated some activity against human hepatitis B virus (IC50 4.7 to 7 mol/L) and showed weak activity against human cytomegalovirus but not the other herpes viruses [4].

- **Abacavir in Combination with Other Agents:**

Abacavir has been studied in combination with other NRTIs or medicines from other classes (table I) in a number of studies [4, 6-12]. There have been no reports of abacavir antagonistic combos. The triple NRTI combination of abacavir, lamivudine, and zidovudine was the only triple combination of medicines studied [11]. In both zidovudine-sensitive and zidovudine-resistant HIV-1 isolates, this combination showed synergistic efficacy (table I). When compared to other abacavir combinations, abacavir in combination with mycophenolic acid, a lymphocyte proliferation inhibitor, demonstrated the most synergistic effectiveness against HIV-1[9]. In vitro, mycophenolic acid is hypothesised to limit HIV-1 replication by lowering the pool of guanosine nucleotides in the host cell. In PBMCs, the combination of abacavir (0.25 to 4 mol/L) and mycophenolic acid (0.25 to 1 mol/L) exhibited substantial synergy against HIV-1 IIIB [10]. This combination (and, to a lesser extent, abacavir alone) proved effective against lamivudine-resistant HIV clones with the M184V mutation as well as zidovudine-resistant clones with numerous mutations. Mycophenolic acid and didanosine demonstrated synergism against HIV-IIIB in PBMCs, but lamivudine and zalcitabine were just additive, and stavudine and zidovudine showed antagonism [10]. The clinical implications of these findings are still unknown.

1.7 Resistance:

- **Monotherapy:**

In order to determine the optimum antiretroviral drug combination regimens for both initial and salvage therapy, it is necessary to characterise patterns of resistance and cross-resistance (genotypic and phenotypic). The resistance mutations occurring in vivo were basically the same as those found duringmany in vitro passage tests [13], according to genotypic data acquired from 43 patients taking abacavir monotherapy [14]. Abacavir, at doses of 100, 300, or 600 mg twice daily, selected for resistance mutations at locations 184 [methionine (M) to valine (V)], 74 [leucine (L) to V], 65 [lysine (K) to arginine (R)], and 115 [tyrosine (Y) to phenylalanine (F)] in the reverse transcriptase coding area[14].Only one mutation was discovered within the first 12 weeks of treatment, indicating that mutations were acquired slowly. At the most recent time point (range 6 to 48 weeks, median 20 weeks), 21 of 43 (49%) abacavir monotherapy patients had genotypic alterations that had not been present at baseline. M184V plus L74V was the most often found mutational pattern (n = 11). Four patients had single mutations that were evenly split between M184V and L74V. Other double and triple mutations (2 and 4 cases, respectively) involved M184V in combination with L74V, K65R, and/or Y115F. The occurrence of these mutations was linked to an increase in viral load over time.

Increased phenotypic resistance to abacavir was linked to an increase in the number of mutations in the reverse transcriptase genome. According to previously determined phenotypic-viral-load correlations, sensitive (8-fold increase) phenotypic outcomes were defined [15]. At baseline, phenotypic data for 29 individuals on abacavir monotherapy were obtained [14]. At baseline, all 29 isolates examined were wild-type abacavir susceptibility, but following 12 to 48 weeks of abacavir monotherapy (100, 300, or 600 mg twice daily), 10 of 28 (36 percent) isolates (from 24 patients) showed reduced Abacavir susceptibility [14]. The presence of a single mutation had no effect on abacavir susceptibility, while the presence of two or more mutations was linked to intermediate resistance (6 isolates) and the presence of three or more mutations was linked to high resistance (9 isolates) Table- I. Activity in a variety of cell lines and mononuclear cells from the peripheral blood [4, 6-12]. Patients with intermediate or resistant phenotypes still exhibited viral load decreases to 4-fold increase in IC50) to didanosine when lamivudine and zidovudine were added. This was linked to a pair of M184V and L74V mutations (9 isolates). Dual mutations of M184V and L74V or M184V and K65R (10 isolates) were found to be related with phenotypic cross-resistance to zalcitabine [14]. Abacavir and lamivudine share the M184V mutation, which is one of the earliest mutations to develop in vivo; hence the risk of cross-resistance appears to be

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particularly high.When viral replication is not completely reduced, lamivudine rapidly selects for the M184V mutation, which provides phenotypic resistance to lamivudine (IC50 >100-fold increase) [16]. During the 16-week double-blind comparative phase of clinical trial CNA3003, researchers discovered that the triple combination of abacavir, lamivudine, and zidovudine was more effective than lamivudine plus zidovudine dual therapy at delaying the appearance of genotypic mutations, particularly the M184V mutation (4 vs 50 %, respectively) [17]. In vitro, adding abacavir to a stable background treatment (SBG) regimen led in reductions in HIV RNA levels (10-fold increase over wild-type IC50) for 50 patients who previously had the M184V mutation (but no additional reverse transcriptase mutations) (fig. 2) [19].Patients with HIV strains that are resistant to numerous NRTIs are much more likely to have abacavir resistance than those who are just resistant to one. In vitro, clinical isolates resistant to just didanosine, stavudine, lamivudine, or zidovudine, as well as isolates resistant to both zidovudine and lamivudine (fig. 2), remained sensitive to abacavir. Susceptibility to abacavir was much more likely to be reduced in patient HIV isolates that were phenotypically resistant to two NRTIs (excluding the combination of zidovudine and lamivudine) (fig. 2) [19, 20]. In addition, Lanier et al. [18] found that baseline phenotypic and genotypic indications of multiple NRTI resistance were linked to significant decreases in virological response to abacavir treatment [18]. Abacavir was added to all of the patients' background antiviral medication, and the majority of them had viruses with NRTI related mutations at the start of the study (135 of 156 patients). Only 13 % of individuals with virus phenotypically resistant to two NRTIs at baseline obtained undetectable HIV levels after a mean treatment duration of 22 weeks. However, viral load responses (a drop in viral load of 0.5 log10 copies/ml or a viral load of 10-fold increase) were >4-fold higher than wild-type IC50 for didanosine (DDI) and stavudine (D4T). IC50 is the concentration of a medication that inhibits replication by 50%.

1.8 Cytotoxicity:

During exposure to abacavir, minimal cytotoxicity (IC50 >100 mol/L) was detected in a range of human leukaemia cell lines of the T, B, and monocyte lineages (IM-9, CEM, CD4+ CEM, U-937) as well as liver tumour cell lines (2.2.15, HB611). The Molt-4 cell line, on the other hand, showed increased susceptibility (20 mol/L) and was thus utilised to assess the impact on mitochondrial DNA synthesis. At the highest dosage tested (100 mol/L), abacavir did not affect mitochondrial DNA synthesis, whereas zalcitabine, a medication linked to peripheral neuropathy, exhibited a significant reduction in mitochondrial DNA synthesis in the same assay. In CD4+ CEM cells, clinically relevant abacavir doses (10 mol/L) had no effect on intracellular deoxynucleoside triphosphate pools or DNA synthesis.Abacavir revealed modest toxicity to human bone marrow progenitor cells (BFU-E, CFU-GM; IC50 110 mol/L for both assays), indicating a reduced risk of haematopoietic toxicity than zidovudine (comparative IC50 values for BFU-E and CFU-GM, respectively) [4]. At dosages of 5000 g/plate, abacavir exhibited no evidence of mutagenicity in the Ames salmonella microsome experiment, with or without metabolic activation [21]. Abacavir, on the other hand, caused chromosomal aberrations in human cells in an in vitro investigation, both with and without metabolic activation[22].It was similarly mutagenic without metabolic activity in an L5178Y mouse lymphoma assay, but not with metabolic activation.

1.9 Drug Interactions:

The possibility for alcohol to interact with abacavir was explored in 24 HIV-infected male patients [23, 24] because abacavir is metabolised by alcohol dehydrogenase. When 0.7 g/kg of alcohol was combined with a single 600mg dose of abacavir, the AUC of abacavir increased by 41% and the abacavir t1/2 increased by 26% [24]. The pharmacokinetics of alcohol was unaffected, and no indication of a disulfiram-like effect was found. It was determined that the increase in plasma abacavir concentrations was not clinically significant. As a result, alcohol is not contraindicated in abacavir patients, and no dosage adjustments are required [25]. Methadone and abacavir coadministration showed no effect on abacavir absorption, whereas abacavir marginally enhanced methadone elimination [26].

Patients on methadone programmes can therefore utilise abacavir, however modest methadone dose adjustments may be required. Many of the currently available protease inhibitors and NNRTIs, as well as some antituberculosis medicines, are metabolised by the human liver microsomal cytochrome P450 (CYP) enzymes (CYP3A4, CYP2C9, and CYP2D6). As a result, no clinically relevant pharmacokinetic interactions are expected with these medicines. Abacavir has been found to have no clinically relevant

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pharmacokinetic interactions with the following antiretroviral agents: adefovir [27], amprenavir [28], indinavir [27], zidovudine [29], and/or lamivudine [30, 31].Some of the most often used medications to treat opportunistic infections, such as cotrimoxazole, ketoconazole, and tuberculosis treatments, do not share common elimination pathways with abacavir (e.g., rifampicin, rifabutin). As a result, clinically significant pharmacokinetic interactions between these medications and abacavir are unlikely.

1.10Therapeutic Efficacy:

In clinical trials of antiretroviral treatments, the achievement of a persistent reduction in plasma HIV viral load is the widely acknowledged measure of biological efficacy [32, 33]. Increases in CD4+ cell counts are used as indicators of immunological advantage. Positive changes in these markers are thought to be sufficient for obtaining an early indication of HIV therapy success. Abacavir efficacy data based on these surrogate markers can be found in controlled studies lasting up to 48 weeks. Antiretroviral treatment-naive and -experienced individuals were included in the studies [34, 35]. Additional nonblind follow-up data for up to 72 weeks of therapy is available [36, 37]. All data from controlled phase III research is only available as meeting abstracts and posters, and is thus preliminary.There are currently no results from clinical end-point trials or controlled investigations of longer-term viral suppression available. The ‘standard' viral load assays [limit of detection (LOD) roughly 400 to 500 copies/ml] and the newer 'ultrasensitive' assays (LOD approximately 5 to 50 copies/ml) were used to measure viral load in several of the abacavir trials. Where results from both types of assays are available, they are provided. The therapeutic importance of these various assays is unknown, but plasma viral load reductions below the 'ultrasensitive' assays' cut-off have been linked to a longer-lasting virological response than reductions between 50 and 500 copies/ml [38]. The data are mostly given for the intention-to-treat (ITT) population, which includes all randomly assigned patients. This is the most thorough examination, and it more accurately reflects the situation in a clinical context. Only data for patients who are still on randomised treatment is included in 'as treated' (AT) or 'on-treatment' analysis, giving a notion of the best results that may be achieved with a given therapeutic regimen. Abacavir's use in triple NRTI treatment regimens, often in conjunction with zidovudine and lamivudine, in antiretroviral therapy-naive and/or -experienced patients, has received the most attention in clinical trials. Abacavir (300 mg), zidovudine (150 mg), and lamivudine (300 mg) were all given twice daily in controlled trials in adults. The sole exception was a trial in which the abacavir dosage was raised to 600mg twice daily in patients with AIDS-dementia complex [39,40]. Zidovudine and lamivudine were given together in several studies (150mg lamivudine, 300mg zidovudine) [35, 41-44]. Other NRTIs were given at the recommended therapeutic doses. Abacavir 8 mg/kg, zidovudine 180 mg/kg, and lamivudine 4 mg/kg were given twice daily to paediatric patients with HIV infection (aged >3 months) [22]. Abacavir has also been studied in 'intensification' studies [39, 40, 45, and 46] and as’ salvage' regimens in conjunction with medications from both therapeutic classes (NNRTIs and protease inhibitors) [47-50]. Only modest trials in antiretroviral-naive patients have looked at abacavir in conjunction with protease inhibitors [47, 51]. In nonblind dose-finding studies in 139 antiretroviral treatment-naive individuals with HIV infection, abacavir monotherapy at doses of 600 to 1800 mg/day led in reductions in plasma HIV RNA levels at week 4 and increases in CD4+ cell counts that were sustained for 12 to 24 weeks [52, 53].After 4 weeks of treatment, adding zidovudine [53] or zidovudine and lamivudine after 24 weeks [52] led in even further reductions in plasma viral load. Furthermore, these reductions were maintained for 72 weeks in the latter research. The median reduction in HIV RNA from baseline for the 55 patients who entered the open label phase of the research was 2.9 log10 copies/ml at this time. Reductions in plasma HIV RNA levels to below the LODs of 400 and 50 copies/ml occurred in 74 and 50 percent of patients, respectively [37].

1.11 Hypersensitivity Reactions:

The most prevalent reason for early abacavir therapy cessation is a hypersensitivity reaction to abacavir, which is characterised by symptoms indicating multiorgan involvement. It has been documented in roughly 3% to 5% of patients undergoing abacavir therapy. The incidence of hypersensitivity was 3.8 percent in a study of 26 769 people who took part in clinical trials or expanded access protocols [55]. Fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhoea, or abdominal pain), and weariness and malaise are the most prevalent symptoms (fig. 5).The difficulty in making a diagnosis has been highlighted. Patient percentage 40 30 20 20 0 50 Fatigue and malaise Headache Vomiting and

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nausea Diarrhoea Feeding issues Infection of the ear, nose, and throat Nausea ABC/ZDV/LAM is an acronym for ABC, ZDV, and LAM (0-15 wk) ABC/ZDV/LAM (0-16 wk) PL/ZDV/LAM (0-16 wk) (16-48 wk) Figure 4 More than 5% of patients taking a triple nucleoside reverse transcriptase inhibitor regimen with abacavir experienced adverse effects [54]. Adverse events (all grades) reported for all treated patients during the first 16 weeks of trial CNA3003: a randomised, double-blind study in antiretroviral therapy-naive patients of abacavir, zidovudine, and lamivudine (ABC/ZDV/LAM; n = 83 in this analysis) or placebo, zidovudine, and lamivudine (PL/ZDV/LAM;When the first presentation includes respiratory symptoms, follow-up adverse event data (weeks 16 to 48) for patients staying on the triple regimen is also shown. These symptoms were reported in 18% of patients, but no one symptom was reported in more than 6% of instances; tachypnoea, cough, and pharyngitis were the most common. In patients with hypersensitivity to abacavir, wheezing and bronchospasm, which are linked with some allergic reactions, have occurred infrequently. The hypersensitive reaction's underlying mechanism is unknown, and risk factors are only now beginning to emerge. The predictor with the strongest predictive value for hypersensitivity in a stepwise logistic regression model including 84 completely documented cases of hypersensitivity among 2402 abacavir-treated patients was antiretroviral therapy naive status (odds ratio = 1.95, p = 0.0042).Furthermore, Caucasian race was only marginally associated with an elevated risk (p = 0.06). After stopping abacavir, the hypersensitive reaction normally goes away within 24 hours. Rechallenge, on the other hand, causes a quick return of symptoms (within hours of injection) that are often more severe (fig. 5) and have included life-threatening hypotension [58-60] and death [54, 55, 58]. As a result, reintroducing abacavir after a hypersensitivity reaction is always dangerous. Continuing to take abacavir in the presence of a hypersensitivity reaction might exacerbate symptoms and even be fatal [54, 56]. Patients who were misdiagnosed as having acute respiratory disease with an initial presentation of flu-like sickness, pneumonia, or bronchitis have occasionally died. If the clinical manifestation of an acute respiratory disease cannot be distinguished from a hypersensitivity reaction, abacavir should be discontinued permanently [56].

1.12 Marketed Formulation:

Abacavir alone:

Formulations	Brand Name	Manufacturer
Abacavir Tab (300 mg)	A-Bec	Emcure
Abacavir Sulphate Tab (300 mg)	Abamune	Cipla
Abacavir Film coated Tab (300 mg)	Ziagen	GlaxoSmithKline
Abacavir Oral Sol^{n} (20 mg/mL)	Ziagen	GlaxoSmithKline

Abacavir Combination:

Formulations	Combination	Brand Name	Manufacturer
Film coated Tab	Abacavir (600 mg) + Lamivudine (300 mg)	ABEC-L/ EPZICOM/ ABAKAST-L/	Emcure/ GlaxoSmithKline/ APRAZER/ Zydus
Tab	Abacavir (600 mg) + Lamivudine (300 mg)	ABALAM/ ALBAVIR	Hetero Healthcare/ Mylan
Tab	Abacavir (600 mg) + Lamivudine (300 mg) + Zidovudine(50 mg)	TRIZIVIR	GlaxoSmithKline
Film coated Tab	Abacavir (600 mg) + Lamivudine (300 mg) + Dolutegravir (50 mg)	Triumeq/ INBEC	GlaxoSmithKline/ Emcure

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1.13 Recent research related to Abacavir:

- Development & Characterization of Abacavir sulphate loaded Microspheres.
- Development of Albumin- based Nanoparticles for delivery of Abacavir.
- Novel semi-interpenetrating Microspheres of Dextran-grafted-Acrylamide and poly (vinyl alcohol) for controlled release of Abacavir Sulphate.
- A novel vaginal drug delivery system: anti-HIV bioadhesive film containing Abacavir.

- **Microspheres of Carboxymethyl Guar Gum for In Vitro Release of Abacavir Sulphate: Preparation and Characterization**

Carboxymethyl guar gum (CMGG), an anionic semi-synthetic GG derivative, was produced by incorporating the CM group into the GG chain. Abacavir sulphate (AS) was loaded into microspheres using water-in-oil (w/o) emulsion method. Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), X-ray diffraction (XRD), thermogravimetry (TGA), differential scanning calorimetry (DSC), and scanning electron microscopy were used to characterise the formulations (SEM). The in vitro release profiles of GG and CMGG loaded with AS performed in pH 1.2 and 7.4 buffer media at 37^{o}C revealed the different drug release profiles in stomach and intestinal conditions. The drug was released for up to 28 hours in both the GG and CMGG matrices, but the burst release observed in the GG matrix was reduced in the CMGG matrix. The kinetics of in vitro release was analyzed using the empirical equations.

Guar gum (GG), also known as poly-galactomannan gum, is a natural polysaccharide whose chain is made up of D-mannose units with 1–4 linkages, while the D-galactose unit is linked 1–6 on average to every second D-mannose unit; it has a cyclic neutral structure with numerous hydroxyl groups (an average of three per sugar unit), and it is extracted from the seeds of Cyamopsis tetragon Previously, some reports on GG drug delivery applications[62–64] and GG structure modification for CR applications [65–67] were published. Rubinstein [68], for example, described CR systems of GG cross-linked with glutaraldehyde (GA) and phosphate for colon targeting. Water transport and drug release characteristics of cross-linked polyacrylamide-grafted GG hydrogel microspheres were investigated by Soppimath and Aminabhavi[61]. Kumar et al. [69] Chitosan–carboxymethyl GG (CMGG)-based interpolymer complexes for fluticasone colon delivery were reported. Bajpai and Sharma [70] investigated the pH-sensitive swelling and vitamin B12 release behaviour of barium alginate/CMGG hydrogel beads. Thimma and Tammishetti22 developed barium and calcium-cross-linked CMGG beads for gastrointestinal drug delivery of protein to observe that BaCl2-crosslinked beads protect the protein from low pH conditions to deliver in the simulated intestinal fluid. In this paper, we describe the synthesis of CMGG polymer by inserting a carboxymethyl (CM) group into GG and characterising its structure using Fourier transform infrared (FTIR) and 13C-NMR methods.

- **Novel Semi-interpenetrating Microspheres of Dextran-grafted-Acrylamide and Poly (Vinyl Alcohol) for Controlled Release of Abacavir Sulphate**

By emulsion cross-linking, semi-interpenetrating (semi-IPN) microspheres of Dextran-grafted-acrylamide (Dex-g-AAm) and poly(vinyl alcohol) (PVA) in the size range of 80-100 m were prepared for investigating controlled release (CR) of an anti-HIV agent, Abacavir sulphate. Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry were used to confirm the graft copolymer (DSC). To demonstrate the effect of drug release in acidic and alkaline conditions, the microspheres were characterised for morphology, swelling, and in vitro release of Abacavir sulphate in pH 1.2 and 7.4 buffer media. To understand the nature of the release mechanism, the kinetics of in vitro release were analysed using empirical equations [71].

Dex, a glucose homo-polysaccharide, has a significant number of consecutive -(1f6) interconnections in the backbone, accounting for more than half of the total linkages. These -D-glucans have side chains that originate from -(1f2), -(1f3), or -(1f4) branch linkages. Dex has been widely used as a drug carrier in the biomedical field due to the excellent biocompatibility[72, 73]. but its uncontrolled rate of hydration and low mechanical strength limit its long-term application. As a result, Dex must be modified in order to be useful as a drug delivery device. Previously, Rokhade et al.[74] formed semi-IPN microspheres of acrylamide grafted onto Dex and Chitosan used in the CR of acyclovir to demonstrate that the nature of the polymeric carrier affects the percent cumulative release rates. Cascone et al. [75] demonstrated dexamethasone release from PLGA nanoparticles encapsulated in a Dextran/poly (vinyl

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alcohol) (Dex/PVA) hydrogels matrix. Previously, we developed a number of interpenetrating network (IPN)-based formulations as CR devices for a variety of drugs[76, 77]. In continuation of these investigations, we present here the synthetic methods for the preparation of semi-IPN microspheres of Dextran-grafted-acrylamide (Dex-g-AAm) and PVA as an effective CR device for Abacavir sulphate, an antidepressant of the antiviral/reverse transcriptase inhibitor class. The drug's chemical formula is (1S, 4R)-4-[2- amino 6(cyclopropylamino)-9H-purin-9-yl]. HIV-preventive -2-cyclopentene-1-methanolthe drug has a plasma half-life of 1.45 h, necessitating the development of a CR formulation. As a result, semi IPN microspheres were prepared using the water-in-oil (w/o) emulsion cross-linking method in this study and characterised using Fourier transform infrared (FTIR) spectroscopy, X-ray diffraction (XRD), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM). In vitro release studies in pH 1.2 and 7.4 buffer media were carried out to better understand their in vitro release kinetics.

- **A novel vaginal drug delivery system: anti-HIV bioadhesive film Containing Abacavir:**

Women are especially vulnerable to AIDS and other sexually transmitted diseases (STDs), owing to unprotected heterosexual vaginal intercourse and a variety of other social and economic disadvantages. Our goal was to develop and optimise a vaginal film of Abacavir, a powerful nucleoside reverse transcriptase inhibitor used to treat AIDS and HIV. Abacavir films were created using a solvent evaporation method with sodium alginate (Na-alginate) as the main polymer, Hydroxypropyl Methylcellulose E 15 (HPMC E 15) as the copolymer, and glycerol as the humectant. Abacavir sulphate (ABC) was used as a medication in this case. Tensile strength, percent elongation at break, swelling capacity, drug content (mg/cm2), thickness, folding endurance, bio-adhesion, pH, moisture content, and SEM were all optimised in the films.FTIR Spectra was used to investigate the drug-polymer interaction. The drug release experiment was carried out in a dissolution apparatus. An in vivo study was also conducted. This newly formed film was a type of sustained release and can be thought of as a novel drug carrier system for the treatment of AIDS and other STDs. It was appropriate for both local and systemic effects. The films demonstrated good physicochemical properties as well as aesthetic appeal [78].

REFERENCES:

[1]. International pharmacopoeia monograph on Abacavir Sulphate, Working document QAS/05.144, Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland.
[2]. https://go.drugbank.com/drugs/DB01048.
[3]. Barbarino et al.PharmGKB summary: abacavir pathway. Pharmacogenetics and Genomics 2014, 24 (5): 276-81.
[4]. Daluge SM, Good SS, Faletto MB, et al. 1592U89, A novel carbocyclic nucleoside analog with potent, selective antihuman immunodeficiency virus activity. Antimicrob Agents Chemother 1997 May; 41: 1082-93.
[5]. Saavedra J, Johnson C, Koester J, et al. Comparative antiviral effect of zidovudine, lamivudine and 1592U89 on latently HIV-infected cells [abstract I-59]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1997 Sep28; Toronto, 253.
[6]. Bilello JA, Bilello PA, Symonds W, et al. Amprenavir (141W94) in combination with 1592U89 is highly synergistic in vitro [abstract]. 38th Inter-science Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep; 369: 24-27.
[7]. Drusano GL, D'Argenio DZ, Symonds W, et al. Nucleoside analog 1592U89 and human immunodeficiency virus protease inhibitor 141W94 are synergistic in vitro. Antimicrob Agents Chemother 1998 Sep; 42: 2153-9.
[8]. Hill E, TaylorN, Borroto-Esoda K, et al. In vitro synergy studies withMKC-442, a non-nucleosideHIV-1 reverse transcriptase inhibitor [abstract 49]. Antiviral Res 1998 Mar; 37: 54.
[9]. Margolis D, Heredia A, Gaywee J, et al. Abacavir and mycophenolic acid, an inhibitor of inosine monophosphate dehydrogenase, have profound and synergistic anti-HIV activity. J Acquir Immune DeficSyndrom Hum Retrovirol 1999 Aug15; 21: 362-70.
[10]. Margolis DM, Heredia A, Hazen DJ, et al. The in vitro synergy of abacavir (Ziagen) and mycophenolic acid (Cellcept) suggests a novel approach to HIV therapy [oral presentation]; 39th Interscience Conference on Antimicrobial Agents andChemotherapy; 1999 Sep 26-29; San Francisco.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 678-690 www.ijprajournal.com ISSN: 2456-4494

[11]. Tremblay C, Merrill DP, Chou TC, et al. 1592U89 as a component of 2- and 3-drug regimens against zidovudine-sensitive and zidovudine-resistant HIV isolates in vitro [abstract 632]. 5th Conference on Retroviruses and Opportunistic Infections; 1998 Feb 1-5; Chicago.
[12]. Cherrington J, Mulato AS. Adefovir (PMEA) and PMPA show synergistic or additive inhibition of HIV replication in vitro in combination with other anti-HIV agents [abstract 41195].12thWorld AIDS Conference; 1998 Jun 28-Jul 3; Geneva, 781.
[13]. TisdaleM, Alnadaf T, Cousens D. Combination of mutations in human immunodeficiency virus type 1 reverse transcriptase required for resistance to the carbocyclic nucleoside 1592U89. Antimicrob Agents Chemother 1997 May; 41: 1094-8.
[14]. Miller V, Ait-Khaled M, Stone C, et al. HIV-1 reverse transcriptase (RT) genotype and susceptibility to RT inhibitors during abacavir monotherapy and combination therapy. AIDS 2000; 14: 163-71.
[15]. Lanier ER, Stone C, Griffin P, et al. Phenotypic sensitivity to 1592 (abacavir) in the presence of multiple genotypic mutations: correlation with viral load response [abstract 686]. 5th Conference on Retroviruses and Opportunistic Infections; 1998 Feb 1-5; Chicago.
[16]. Kavlick MF, Shirasaka T, Kojima E, et al. Genotypic and phenotypic characterization of HIV-1 isolated from patients receiving (-)-2',3'-dideoxy-3'-thiacytidine. Antiviral Res 1995; 28: 133-46.
[17]. Ait-Khaled M, Rakik A, Griffin P, et al. Low prevalence of the HIV-1 RTM184V mutant in antiretroviral therapy-naiveHIV-1 infected patients following 16 weeks of abacavir/lamivudine/ zidovudine combination therapy [abstract 29]. 2nd International Workshop on HIV Drug Resistance and Treatment Strategies; 1998 Jun 24-27; Lake Maggiore.
[18]. Lanier ER, Scott J, Steel H, et al. Multivariate analysis of predictors of response to Ziagen (1592, abacavir, ABC): comparison of prior antiretroviral therapy, baseline HIV RNA, CD4 count and viral resistance. 3rd InternationalWorkshoponHIV Drug & Treatment Strategies [poster 82]; 1999 Jul 23-26; San Diego.
[19]. Mellors JW, HertogsK, Peeters F, et al. Susceptibility of clinical HIV-1 isolates to 1592U89 [abstract 687]. 5th Conference on Retroviruses and Opportunistic Infections; 1998 Feb 1-5; Chicago.
[20]. Pauwels R, Hertogs K, Peeters F, et al. Susceptibility profile (AntivirogramTM) of 945 clinical HIV-1 isolates to abacavir [abstract 41226]. 12thWorld AIDS Conference; 1998 Jun 28-Jul 3; Geneva, 787.
[21]. Ching SV,AyersKM,Dornsife RE, et al.Nonclinical toxicology and in vitro toxicity studies with the novel anti-HIV agent (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl] - 2-cyclopentene-1-methanol (1592U89) succinate [abstract 188]. 34th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1994 Oct 4-7; Orlando, 92.
[22]. Glaxo Wellcome. Ziagen® (abacavir sulfate). Product information (USA). Jan 2000.
[23]. Ravitch JR, Walsh JS, Reese MJ, et al. In vitro studies of the potential for drug interactions involving the antiretroviral abacavir (1592) in humans [abstract 634]. 5th Conference on Retroviruses and Opportunistic Infections; 1998 Feb 1-5;Chicago.
[24]. McDowell JA, Chittick GE, Pilati Stevens C, et al. Pharmacokinetic interaction of abacavir (1592U89) and ethanol in human immunodeficiency virus-infected adults. Antimicrob Agents Chemother 2000 Jun 44 (6): 1686-90.
[25]. Glaxo Wellcome. Ziagen (abacavir sulfate) - Product monograph (USA). August 1999.
[26]. Sellers E, LamR,McDowell J, et al. The pharmacokinetics (pk) of abacavir (ABC) and methadone (M) following co-administration: CNAA1012 [abstract 663]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29; San Francisco, 26.
[27]. Morse G, Squires K, Hammer S, et al. Abacavir (ABC) and efavirenz (EFV) pharmacokinetics in adefovir (ADV) containing salvage regimens. 7th Conference on Retroviruses and Opportunistic Infections [abstract 85]; 2000 Jan 30-Feb2; San Francisco, 30.
[28]. McDowell JA, Sadler BM, Millard J, et al. Evaluation of potential pharmacokinetic drug interaction between 141W94 and

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 678-690 www.ijprajournal.com ISSN: 2456-4494

1592U89 in HIV+ patients [abstract A-62]. 37th Inter-science Conference on Antimicrobial Agents and Chemotherapy; 1997 Sep 28-Oct 7; Toronto, 13.

[29]. McDowell JA, Symonds WT, LaFon SW. Single-dose and steady-state pharmacokinetics of escalating regimens of 1592U89 with and without zidovudine [abstract 1140]. 11th International Conference on AIDS; 1996 Jul 7-12;Vancouver, 79.

[30]. Wang LH, Chittick GE, McDowell JA. Single-dose pharmacokinetics and safety of abacavir (1592U89), zidovudine, and lamivudine administered alone and in combination in adults with human immunodeficiency virus infection. Antimicrob Agents Chemother 1999 Jul; 43: 1708-15.

[31]. Symonds WT, McDowell J, Chittick G, et al. The safety and pharmacokinetics of GW1592U89, zidovudine and lamivudine (3TC) alone and in combination after single-dose administration in HIV-infected patients [abstract P19]. AIDS 1996 Nov; 10 Suppl. 2: 23.

[32]. Pozniak A, Gazzard BG, Churchill D, et al. British HIV association (BHIVA) guidelines for the treatment of HIV infected adults with antiretroviral therapy. http:// www.aidsmap.com/bhiva/bhivagd1299.htm Issued Dec 1999. Last updated Jan 28 2000.

[33]. Fauci AS, Bartlett JG, Goosby EP, et al. Guidelines for the useof antiretroviral agents in HIV-1 infected adults and adolescents. http://www.hivatis.org.guidelines/adult/text. Issued 1998. Last updated Jan 28 2000.

[34]. Clumeck N, Fischl M, Greenberg S, et al. Triple nucleosidetherapy with abacavir plus 3TC/ZDV provides a potent anddurable antiretroviral response through 48 weeks in antiretroviraltherapy-naive adults (CNA3003) [poster 209]. 7thEuropean Conference on Clinical Aspects and Treatment of HIV-Infection. 1999 Oct 23-27; Lisbon, 20.

[35]. Staszewski S, Keiser P, Gathe J, et al. Comparison of antiviral response with abacavir/combivir to indinavir/combivir in therapy-naive adults at 48 weeks (CNA3005) [abstract 505]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29; San Francisco, 472.

[36]. Staszewski S, Katlama C, Harrer C, et al. 96 Week experience with a class sparing triple, reverse transcriptase nucleoside therapy regimen containing abacavir (1592,ABC) [abstract 446]. Clin Infect Dis 1998 Oct; 27: 1005.

[37]. Staszewski S, Katlama C, Harrer T, et al. Long-term, 72 week experience with a class sparing, triple, reverse transcriptase nucleoside therapy regimen containing abacavir: a follow up of protocol CNA2002 [abstract P69]. AIDS 1998 Nov; 12 Suppl. 4: 34.

[38]. Raboud JM, Montaner JSG, Conway B, et al. Suppression of viral load below 20 copies/ml is required to achieve a long term response to therapy. AIDS 1998; 12: 1619-24.

[39]. Brew BJ, Brown SJ, Catalan J, et al. Safety and efficacy of abacavir in AIDS dementia complex [abstract 561]. 12th World AIDS Conference. 1998 Jun 28-Jul 3; Geneva, 559.

[40]. Brew BJ, HalmanM, Catalan J, et al. Abacavir in AIDS dementia complex. Efficacy and lessons for future trials. 2000 GlaxoWellcome Inc. North Carolina. Data on file.

[41]. Rozenbaum W, Katlama C, Massip P, et al. Treatment intensificationwith abacavir in HIV-1 infected adults with previous3TC/ZDV antiretroviral treatment – 48 week results(CNAB3009) [abstract 466]. 7th European Conference onClinical Aspects and Treatment of HIV-Infection; 1999 Oct23-27; Lisbon, 91.

[42]. Cooper D, Perrin L, Kinloch S, et al. Intervention with quadruple HAART (Combivir/Abacavir/Amprenavir) Interventionduring primary HIV-1 infection is associated with rapid viremiaclearance and decrease of immune activation. 7th Conferenceon Retroviruses and Opportunistic Infections[abstract 552]; 2000 Jan 30-Feb 2; San Francisco.

[43]. Opravil M, Yerly S, Lazzarin A, et al. Protease inhibitor classsparingmaintenance therapy with abacavir + lamivudine +zidovudine in patients with long term suppression of HIV-1RNA[abstract 457]. 7th Conference on Retroviruses and OpportunisticInfections; 2000 Jan 30-Feb 2; San Francisco.

[44]. Opravil M, Yerly S, Staszewski S, et al. Prior treatment withmono or dual NRTIs before HAART as predictor of

virologicalfailure in simplified abacavir-based triple NRTI regimens:results from the simplified maintenance trial (SMT)and CNA30017 [abstract and poster]. 4th International Work.

[45]. Rockstroh J, Clotet B, Katlama C, et al. The role of abacavir (ABC, 1592) in antiretroviral therapy-experienced patients: preliminary 48-week results from a randomized double-blind trial [abstract]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29; San Francisco, 518.

[46]. Katlama C, Clotet B, Plettenberg A, et al. Intensification of stable background antiretroviral therapy with abacavir: preliminary 16 week data [abstract OP2.3]. AIDS 1998 Nov; 12 Suppl. 4: 9.

[47]. Mellors J, Lederman M, Haas D, et al. Durable activity of Ziagen (Abacavir, ABC) combined with protease inhibitors (PI) in therapy naive adults [abstract 625]. 6th Conference on Retroviruses and Opportunistic Infections; 1999 Jan 31-Feb 4; Chicago.

[48]. Squires K, Hammer S, DegruttolaM, et al. Randomized trial of abacavir (ABC) in combination with indinavir (IDV) and efavirenz (EFV) in HIV-infected patients with nucleoside analog experience [abstract 529]. 7th Conference on Retroviruses and Opportunistic Infections; 2000 Jan 30-Feb 2, San Francisco.

[49]. Carr A, Cooper D. Arandomized, multicenter study of protease inhibitor substitution in aviremic patients with antiretroviral (ARV) lipodystrophy syndrome [abstract 205]. 7th Conference on Retroviruses and Opportunistic Infections; 2000 Jan 30-Feb 2; San Francisco.

[50]. Hammer S, Squires K, Degruttola V, et al. Randomized trial of abacavir & nelfinavir in combination with efavirenz and adefovir dipivoxil as salvage therapy in patients with virologic failure receiving indinavir [abstract 490]. 6th Conference on Retroviruses and Opportunistic Infections; 1999 Jan 31-Feb 4;Chicago.

[51]. Rizzardi GP, Bart P-A, ChapuisA, et al.Quantitative normalization of CD4+ T cells in blood and lymph node of HIV-1 infected therapy-naive adults at an early stage of chronic infection treated with abacavir plus amprenavir. 39th Inter-science Conference on Antimicrobial Agents and Chemotherapy [poster 1822]. 1999 Sep 26-29, San Francisco.

[52]. Staszewski S, Katlama C, Harrer T, et al. Adose-ranging study to evaluate the safety and efficacy of abacavir alone or in combination with zidovudine and lamivudine in antiretroviral treatment-naive subjects. AIDS 1998 Nov 12; 12: F197-202.

[53]. Saag MS, Sonnerborg A, Torres RA, et al. Antiretroviral effect and safety of abacavir alone and in combinationwith zidovudine in HIV-infected adults. AIDS 1998 Nov 12; 12: F203-9.

[54]. Steel H, Hetherington S, Pearce G, et al. Abacavir safety and tolerability: experience from over 25,000 adults and children [Poster/abstract 599]. 7th European Conference on Clinical Aspects and Treatment of HIV Infection; 1999 Oct 23-27; Lisbon.

[55]. Hetherington S, Steel HM, Lafon S, et al. Safety and tolerance of abacavir alone and in combination therapy of HIV infection [abstract 12353]. 12th World AIDS Conference; 1998 Jun 28-Jul 3; Geneva.

[56]. Glaxo Wellcome. Fatal hypersensitivity reactions, respiratory symptoms and Ziagen (Rm). Dear Health Care Provider letter, Jan 2000; Glaxo Wellcome Inc. Media Release.

[57]. Hetherington R, Steel H, Naderer O, et al. Hypersensitivity reactions during therapy with abacavir: analysis of 636 cases for clinical presentation and risk factors [abstract and poster. 60]. 7th Conference on Retroviruses and Opportunistic Infections; 2000 Jan 30-Feb 2; San Francisco.

[58]. Weiner SM, Handke M, Usadel S, et al. Anaphylactic shock in a HIV infected patient receiving abacavir (1592U89). AIDS 1998 Nov; 12 Suppl. 4: S58.

[59]. Walensky RP, Goldberg JH, Daily JP. Anaphylaxis after rechallenge with abacavir. AIDS 1999 May 28; 13: 999-1000.

[60]. Escaut L, Liotier JY, Albengres E, et al. Abacavir rechallenge has to be avoided in case of hypersensitivity reaction. AIDS 1999 Jul 30; 13: 1419-20.

[61]. Soppimath, K. S.; Aminabhavi, T. M. Eur J Pharm Biopharm 2002, 53, 87.

[62]. Toti, U. S.; Aminabhavi, T. M. J Control Release 2004, 95, 567.

[63]. George, M.; Abraham, T. E. Int J Pharm 2007, 335, 123.

[64]. Li, X.; Wu, W.; Wang, J.; Duan, Y. CarbohydrPolym 2006, 66,473.

[65]. Sen, G.; Mishra, S.; Jha, U.; Pal, S. Int J Biol Macromol 2010,47, 164.
[66]. Huang, Y.; Yu, H.; Xiao, C. CarbohydrPolym 2007, 69, 774.
[67]. Thakur, S.; Chauhan, G. S.; Ahn, J. H. CarbohydrPolym 2009,76, 513.
[68]. Rubinstein, A. Biopharm Drug Dispos 1990, 11, 465.
[69]. Kumar, V.; Tiwary, A. K.; Kaur, G. Int J Drug Deliv 2010, 2,242.
[70]. Bajpai, S. K.; Sharma, S. J. Macromol Sci Part A 2006, 43, 1513.
[71]. Anita G. Sullad, Lata S. Manjeshwar,*, and Tejraj M. Aminabhavi. Novel Semi-interpenetrating Microspheres of Dextran-grafted-Acrylamide and Poly(Vinyl Alcohol) for Controlled Release of Abacavir Sulfate. Ind. Eng. Chem. Res. 2011, 50, 11778–11784.
[72]. Cascone, M. G.; Maltinti, S. Hydrogels based on chitosan and dextran as potential drug delivery systems. J. Mater. Sci.: Mater. Med. 1999, 10, 301–307.
[73]. Jeong, Y. I.; Choi, K. C.; Song, C. E. Doxorubicin release from core-shell type nanoparticles of poly(DL-lactide-co-glycolide)-grafteddextran. Arch. Pharmacal Res. 2006, 29, 712–719.
[74]. Rokhade, A. P.; Patil, S. A.; Aminabhavi, T. M. Synthesis and characterization of semi interpenetrating polymer network microspheres of acrylamide grafted dextran and chitosan for controlled release of acyclovir. Carbohydr. Polym. 2007, 67, 605–613.
[75]. Cascone, M. G.; Pot, P. L.; Lazzeri, L. Release of Dexamethasone from PLGA nanoparticles entrapped into dextran/poly(vinyl alcohol) hydrogels. J. Mater. Sci.: Mater. Med. 2002, 13, 265–269.
[76]. Sullad, A. G.; Manjeshwar, L. S.; Aminabhavi, T. M. Controlled release of theophylline from interpenetrating blend microspheres of poly(vinyl alcohol) and methyl cellulose. J. Appl. Polym. Sci. 2010, 116, 1226–1235.
[77]. Sullad, A. G.; Manjeshwar, L. S.; Aminabhavi, T. M. Polymeric blend microspheres for controlled release of theophylline. J. Appl. Polym. Sci. 2010, 117, 1361–1370.
[78]. Kajal Ghosal, Alok Ranjan, BenoyBrata Bhowmik. A novel vaginal drug delivery system: anti-HIV bioadhesive film containing abacavir. J Mater Sci: Mater Med (2014) 25:1679–1689.