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FORMULATION, CHARACTERIZATION AND EVALUATION OF ZIDOVUDINE NANOPARTICLES PREPARED BY CO-PRECIPITATION METHOD

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ABSTRACT

The prevailing research was aimed at developing Zidovudine (AZT) -loaded Eudragit RS 100-based nanoparticles via Co-precipitation which could have sustained launch of the drug. Nanomedicine opens new healing avenues for attacking viral illnesses and for enhancing treatment success. Nanoparticulate-primarily based systems would possibly alternate the discharge kinetics of antivirals, growth their bioavailability, improve their efficacy, restriction unfavourable drug side effects and reduce treatment expenses. Moreover, they could permit the delivery of antiviral drugs to specific target sites and viral reservoirs in the body. Zidovudine (AZT) is normally used to deal with sufferers with AIDS, but it is confined with the aid of toxicity and high doses. The organized nanoparticles had been subjected to various assessment parameters inclusive of surface morphology, particle length distribution, drug loading, entrapment efficacy, scanning electron microscopy, *in-vitro* release studies, release kinetics and stability studies. The dimensions of the nanoparticles is 720.1nm. The entrapment efficacy changed into as much as 68.42% and drug loading became 26.25%. The drug release changed into up to 96.59% and release become extended as much as 24 hrs.

KEYWORDS

Nanoparticle, Zidovudine, Co-precipitation and Extended release.

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INTRODUCTON

Human immunodeficiency virus (HIV) infection maintains to pose a chief infectious sickness threat worldwide. It is characterised via the depletion of CD4 T cells, persistent immune activation, and increased susceptibility to secondary infections. Advances in the improvement of antiretroviral (ARV) drugs and aggregate ARV remedy have led to excellent fall in HIV-associated morbidity and mortality. Antiretroviral therapy which consists of mixture antiretroviral therapy can successfully sup-

press HIV replication via concentrated on more than one specific steps within the viral replication cycle. The requirement for lifelong management of ART provides a regular venture for financial affordability and patient compliance and management of secondary effects. New procedures are wanted for developing much less toxic anti-retroviral drugs (ARVs) and therapeutic regimens consisting of reduced dosage and frequency. (Yavuz *et al*, 2018)[1] One of the finest challenges of ART is to develop drug-shipping systems with high efficacy and healing selectivity. Nanotechnology permits the development of novel systems that would convey adjustments on this scenario. Over the past years, nano-constructions have been designed as prophylactic dealers in conflict to HIV (Chiodo *et al*, 2014)[2]. Nanoparticles are strong, stable colloidal particles which include macromolecular fabric and varying in size from 10 to at l000 nm. Drugs can be adsorbed on the particle floor or may be entrapped or dissolved inside the particle matrix (Bender *et al*, 1996)[3]. Traditional chemotherapy is not very effective as the drug does no longer attain the goal site in effective concentrations. For this reason, powerful treatment demands an elevated dose size, which may lead to undue toxicity. In past, several of polymeric substances had been used for the preparation of nanoparticles. Currently, polysaccharides had been investigated for the developing nanoparticles due to their notable physicochemical properties and biocompatible nature which are useful for biomedical use (Subudhi *et al*, 2015)[4]. The solubility of drug molecules is a vital thing to consider during the development and design of new drug products. Eudragits are normally appeared as trustworthy and non-irritant substances. A daily consumption of 2 mg/kg frame-weight in humans is regarded as essentially secure. It is blanketed inside the FDA Inactive components manual (oral capsules and tablets), non-parenteral medicines certified inside the united kingdom, Canadian list of ideal non-medicinal components. Eudragit S 100 is an anionic copolymer based totally on methacrylic acid and methyl methacrylate. The ratio of the unfastened carboxyl groups to ester groups is approx. 1:2 (Subudhi *et al*, 2015)[4]. It is utilized in design of transdermal patch, nanoparticles, microparticles, microballons, solid dispersions and spherical crystals. It's been used for various claims together with colon unique drug transport, sustain launch, bioavailability enhancement, development in micromeritic properties and so forth (Patra *et al*, 2017)[5]. Zidovudine (3'-azido-3'-deoxythymidine; AZT) is a nucleoside reverse transcriptase inhibitor (NRTI) that deters the replication of the human immunodeficiency virus type 1. AZT is phosphorylated by cellular enzymes to a5'-triphosphate form that restricts with the viral RNA dependent DNA polymerase (reverse transcriptase) and chain elongation of the viral DNA, thereby obstructing viral replication. It drops the incidence and severity of opportunistic infections, progresses neurologic feature, rapidly recovers CD4 T-lymphocyte counts, and drops the serum concentration of HIV antigen (Peter Christoper *et al*, 2014)[6]. AZT is classed beneath Biopharmaceutical Classification System (BCS) as a category III drug, has a short biological half -life, and undergoes vast first pass metabolism. Due to first pass metabolism common bioavailability is about 63%. Greater than 75% of administered dose of zidovudine is metabolized by liver via glucuronidation which is inactive in nature and closing 20% excreted unchanged in urine (Purvin *et al*, 2014)[7]. Long term use of AZT can have intense consequences which include bone marrow toxicity resulting in granulocytopenia and anemia (Banerjee *et al*, 2013)[8]. These consequences are dose structured, the toxicity can be reduced through lowering the dose and minimizing the plasma level fluctuation. Nanoparticles are promising drug delivery for water soluble drugs to enhance bioavailability (Banerjee *et al*, 2013)[8]. The drug selected for the observe is Zidovudine (AZT). AZT is normally administered orally as capsules or tablets. The half-life of the drug is about 1 to 3 hour, which calls for the frequent administration of the drug. The prevailing work to affirm progressed safety, bioavailability and pharmacokineics of AZT encapsulated in Eudragit RS100 nanoparticles (Kumar *et al*, 2015)[9].

MATERIAL AND METHODS

Zidovudine acquired as present sample from Micro Labs. Bangaluru, Tween 80 acquired from Rolex Laboratory Reagent Bombay, Eudragit RS 100 and Acetone of HPLC grade were purchased from Yarrow Chem products, Mumbai. All of the chemical compounds and solvents used have been of analytical grade

Drug polymer compatibility

The compatibility of drug and polymer broke down utilizing FT-IR Spectrophotometer. In this technique 3 mg of test and 300 mg of potassium bromide turned out to be finely ground utilizing mortar and pestle. A little amount of blend put underneath a hydraulic press compressed at 10 kg/cm2 to shape a conspicuous pellet. The pellet kept in test holder and glance at from 4000 cm-1to 400 cm-1 in Shimadzu toes-IR spectrophotometer.

DSC studies

DSC studies were finished for drug and with polymer. DSC sweeps have been performed by methods for computerized thermal analyzer device. (DSC60 Shimadzu enterprise, Japan). Aluminum dish have been utilized in the analyses for every samples. Temperature alignments finished with indium as standard. The whole samples had been kept running at a checking cost of 10°C/min from 50-300°C.

Preparation of standard graph of Zidovudine.

Preparation of Standard solution

1º Stock

Precisely gauged 100 mg of zidovudine transferred into 100ml volumetric flask and dissolved with 7.4 pH phosphate buffer and volume was made upto 100ml with 7.4 pH phosphate buffer.

2º Stock

10 ml of 1º solution was pipetted into 100ml volumetric flask and the volume was made 100ml with 7.4 pH phosphate support. (i.e.: 100µg /ml). Beer's law range: 2 - 20µg.

Preparation of working standard solution

From 2º Stock solution 0.5ml, 1ml, 1.5ml, 2ml, 2.5ml, 3ml, 3.5ml and 4ml were pipetted into 25 ml volumetric flasks. The volume was made up with pH 7.4 phosphate buffer. The range of this solution was kept running in 200 to 400 nm extend in UV-Visible Spectrophotometer. The λmax of the zidovudine was observed to be 266nm. The absorbance of every focus was estimated 266 nm utilizing pH 7.4 phosphate buffer.

Preparation of Zidovudine loaded nanoparticles:

Nanoparticles, stacked with Zidovudine were set up by Co-precipitation technique. Different concentration of eudragit RS 100 and drug were dissolved in acetone (5ml). Polymer drug mixture (organic phase) included drop wise into 10ml of aqueous phase containing 1% of tween 80 under magnetic stirring at room temperature prompts unconstrained arrangement of nano particles and furnished the solution over to smooth colloidal suspension. Organic phase was excluded by persistent stirring for overnight at room temperature. Formulation optimization was pursued to obtain nanoparticles of desired physical properties. Impact of different polymer drug proportions from 1:1, 1:2, 1:3, 1:4 and 1:5 and the stabilizer concentration 1%w/v were surveyed on drug encapsulation capability and molecule size and poly dispersibility index.

Characterization of Eudragit RS100 nanoparticles

Particle size analysis

The particle size was dictated by dynamic light scattering, utilizing a Malvern framework, with vertically polarized light provided by an argon-particle laser (Cyonics) operated at 40 mW. Trials were performed at a temperature of 25.0 ± 0.1ºC at an measuring angle of 90º to the incident beam.

Surface charge analysis

The zeta-potential of the nanoparticles was estimated in 0.1mM sodium chloride utilizing a Malvern Zetasizer.

Surface morphology

Morphology of the particles was analyzed utilizing scanning electron microscopy (SEM) (Jeol Jem 1010, Japan), nanoparticles suspension was diluted with a solution of phosphotungstic corrosive (3% w/v, pH 4.7) and observed under SEM.

Determination of process yield

The procedure yield of Eudragit RS100 nanoaprticles of drug Zidovudine was resolved from weight percentage of conclusive product subsequent

to drying, concerning introductory measure of drug, polymer and different materials utilized for the preparation.

Process yield = Practical yield/Theoretical yield × 100

Determination of drug loading capacity

The percent drug stacking was dictated by extricating the drug totally from known measure of drug stacked nanoparticles utilizing pH 7.4 phosphate buffer. The drug content was resolved spectrophotometrically at a wavelength of 266 nm against blank.

Drug Loading percentage = Actual drug content /Weight of powdered nanoparticles × 100

Determination of percentage entrapment efficacy

To decide Zidovudine ensnarement in nanoparticles, identical 10.0mg of nanoparticles suspended in 10.0 ml containing PBS (Phosphate buffer) pH 7.4. Nanoparticles suspensions were exposed to cold rotator at ~4 0 c and 10,000 rpm utilizing Remi axis (Remi gear Pvt. Ltd., Mumbai) for 10 minutes. From the supernatant 2.5ml solution was moved into 25ml volumetric flask and makes the volume using methanol. The subsequent solutions were examined for Zidovudine concentration utilizing double beam UV-spectrophotometer and percentage entrapment viability was determined utilizing following formula.

Percentage Entrapment = Free drug/Theoretical drug loaded × 100

***In-vitro* drug release studies**

The drug discharge studies were completed by dialysis method. Nanoparticles equivalent to 1mg of drug was set in a cellulose dialysis sack (cut-off 5 kDa, Himedia, India), and to this a little proportion of dissolution media was incorporated, which was then fixed at the two ends. The dialysis sack was dove into the receptor compartment containing the dissolution medium, which was mixed incessantly at 100rpm kept up at 37°C. The receptor compartment was closed to avoid dissipation of the dissolution medium. Tests were drawn at standard time and a comparative volume was replaced with new dissolution medium. The examples were assessed by UV Spectrophotometer at a wavelength 266 nm against blank

Stability studies

Zidovudine containing nanoparticles were secured at raised temperature and relative moistness (25±2□C/60%±5% RH, 40±2□C/75%±5% RH) in a stability examination chamber over a period of 3 months. Recently arranged nanoparticles were secured at 5±3□C used as control. Tests and control are were kept for 90 days for stability analysis and succeeding 90 days, drug stacking of nanoparticles were contrasted with the control.

RESULTS AND DISCUSSION

Preformulation studies

FTIR studies

In the primary examination, the drugs were exposed to preformulation study, for example, the drug-polymer compatibility. Drug-polymer association was examined utilizing FT-IR examination and demonstrated that there were no changes in the IR spectra of pure drug zidovudine in presence of eudragit RS100 (Tables No.1 to 3 and Figures No.1 to 3), which demonstrates that the polymer don't change the presentation qualities of drug thus revealing compatibility of the selected drug with the polymer.

DSC studies

The DSC thermograms of Zidovudine and physical blend of zidovudine and polymer demonstrated no characteristic peaks of polymers. Zidovudine peaks were as yet present however somewhat moved from their unique positions. The DSC for drug zidovudine (Figure No.4) demonstrates that is taken to ponder its properties at higher temperature has shown softening peak at 120ºC.

Standard Plot:

The standard calibration curve of Zidovudine was acquired by plotting Absorbance vs. Concentration. (Table No.4). The standard curve is shown in Figure No.5. The curve was found to be linear in the concentration range of 8-24µg/ml (Beer's range) at 266 nm. The calculations of drug content, *in-vitro* release and stability studies are based on the calibration curve.

Preparation of nanoparticles

In this present study, eudragit RS100 nanoparticles of drug zidovudine were prepared by Co-

pecipitation technique with different drug polymer ratio. The system utilized for the planning of nanoparticles created great yield, which shows least loss of nanoparticles during the preparation and recuperation.

Characterization of the nanoparticles

Particle size

The particle size was determined by dynamic light scattering, using a Malvern system. The mean molecule size of eudragit RS100 nanoparticles of drug zidovudine was observed to be in the scope of 720.1-800nm (Figure No.6). The capacity of nanoparticles to change the bio circulation and pharmacokinetics of drugs, have significant in-vivo curative applications. In this regard, the size and surface qualities of nanoparticles are of prime importance, nanoparticles of less widths with hydrophilic surface have longer dissemination in blood. Such frameworks drag out the length of drug movement and furthermore increment the focusing on efficiencies to explicit destinations

Surface charge

The zeta potential of the nanoparticles was estimated in 0.1mM sodium chloride utilizing a Malvern Zetasizer. Zeta potential of Eudagit RS100 nanoparticles containing drug zidovudine was found to be -28.5. (Figure No.7). The zeta potential is a proportion of the charge of the particles, thusly the bigger the total estimation of the zeta potential the bigger the measure of charge of the surface It might be said, the zeta potential speaks to a file for molecule stability. For the instance of charged particles, as the zeta potential expands, the frightful connections will be bigger prompting the development of progressively stable particles with increasingly uniform size dispersion.

Surface morphology

The surface morphology of drug stacked nanoparticles was examined by Scanning electron microscopy and the investigation uncovered that the nanoparticles were discrete and uniform in size Figure No.8.

Determination of Process Yield, Drug Loading Capacity and Percentage Entrapment

Procedure yield went between 82.32 to 91.28% w/w relying upon the drug polymer proportion. Entrapment feasibility ranges from 55.82 to 68.42 %. The organised nanoparticles demonstrated a high drug loading limit, which went from 8.36% to 26.25% (Table No.5).

***In-vitro* drug release studies**

The *in-vitro* drug arrival of drug zidovudine from the different nanoparticles formulation was completed by utilizing dialysis film in 7.4 pH phosphate buffer for 24 hr. The aggregate percentage discharge of zidovudine from the readied nanoparticles was shifted from 77.60% to 97.69% relies on the drug polymer proportion for 24 hr (Table No.6). The aggregate level of drug discharged from nanoparticles diminished with augmented concentration of eudragit RS100 (Figure No.9).

Selection of an ideal batch

Among the varied zidovudine nanoparticles formulation, the plan F1 (drug polymer proportion 1:1) was chosen as the perfect , in the wake of considering its ideal mean particle size, better drug stacking limit and furthermore drug discharge at supported way as long as 24 hours.

Stability Studies

F-1 formulation is subjected for stability studies at 25±2□C/ 60%±5% RH and at 400 ± 20C, 75 ± 5% and also at 50C as control. The stability data's were shown in Table No.7. It was discovered that there was no such contrast in entrapment ability. This show the equipped nanoparticles were firm.

Table No.1: Characteristic peaks of Zidovudine

S.No	Peak (cm-1)	Functional group
1	3463.19	NH
2	2936.10	CH
3	1316.59	C-N
4	1515.14	C=C
5	1665.50	-C=O-

Table No.2: Characteristic peaks of Eudragit

S.No	Peak (cm-1)	Functional group
1	3446.99	NH
2	2949.69	CH
3	1559.02	C=C
4	1734.11	-C=O-

Table No.3: Characteristic peaks of Zidovudine and Eudragit physical Mixture

S.No	Peak (cm-1)	Functional group
1	3463.08	NH
2	2935.85	CH
3	1316.44	C-N
4	1515.02	C=C
5	1681.99	-C=O-

Table No.4: Absorbance values for the calibration curve of Zidovudine

S.No	Concentration in µg/ml	Absorbance	Standard deviation
1	5	0.153	0.0051
2	10	0.304	0.0020
3	15	0.455	0.0015
4	20	0.615	0.0109
5	25	0.795	0.0043
6	30	0.909	0.0018

Table No.5: Data of Process yield and drug loading capacity (%) of Zidovudine loaded Eudragit RS100 nanoparticles for F1-F5

S.No	Batch code	Entrapment Efficacy	Process Yield (%)	Drug loading (%)
1	F1	55.82	82.32	8.36
2	F2	61.51	84.23	13.78
3	F3	62.24	88.99	17.28
4	F4	64.19	90.64	23.82
5	F5	68.42	91.28	26.25

Table No.6: *In-vitro* release profile of Eudragit RS100 nanoparticles of drug zidovudine with different drug polymer ratio

S.No	Time (hrs)	Batch code				
		F1	F2	F3	F4	F5
1	1	11.79	10.28	8.17	8.22	6.84
2	2	13.75	22.73	16.41	16.39	13.53
3	3	26.56	30.88	25.34	24.76	21.80
4	4	37.78	37.93	33.87	30.14	30.34
5	5	44.53	45.85	42.67	42.13	39.09
6	6	53.55	56.25	52.17	50.96	47.84
7	12	76.73	76.25	74.54	72.93	68.26
8	24	96.59	88.99	85.08	80.38	77.60

Table No.7: Stability studies data for F-1 formulation

S.No	Entrapment efficacy (%)			
	Time (days)	5±3ºC Control	25±2^{0}C/60%±5%RH	40±2^{0}C/75%±5%RH
1	Initial	26.25	26.25	26.25
2	15	26.14	26.02	25.92
3	30	26.04	25.67	25.24
4	45	25.89	25.24	24.76
5	60	25.43	24.87	23.84
6	90	25.12	24.29	22.52

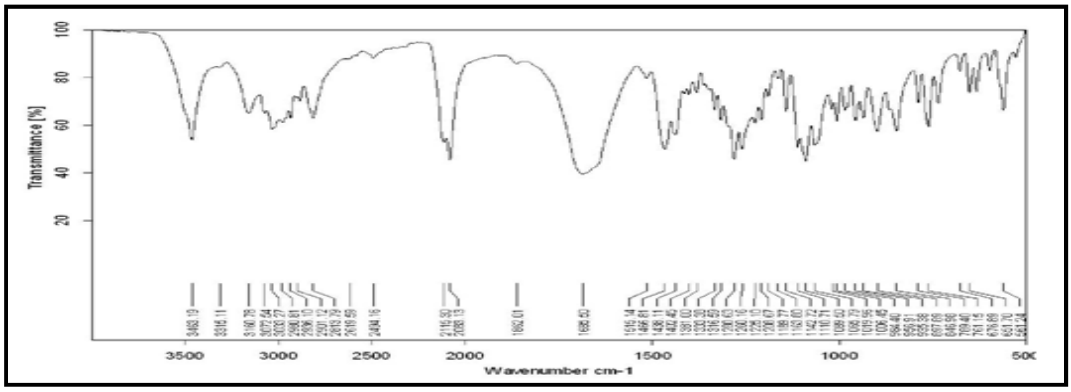

Figure No.1: IR spectrum of zidovudine

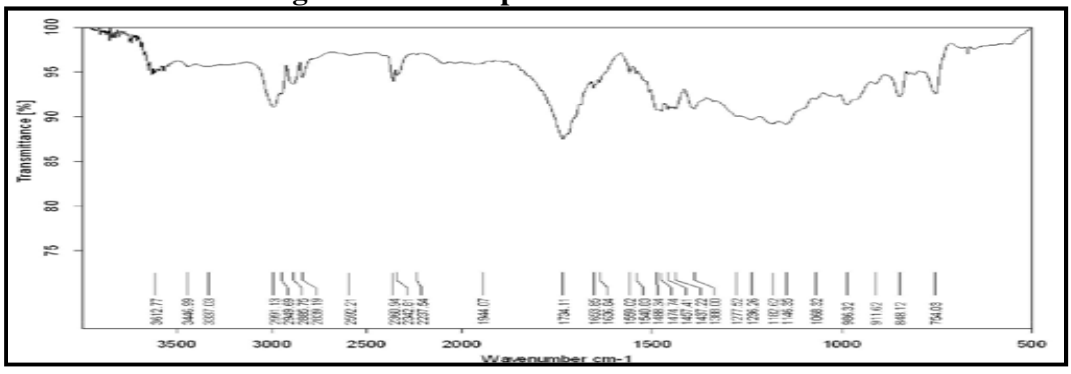

Figure No.2: IR spectrum of Eudragit RS100

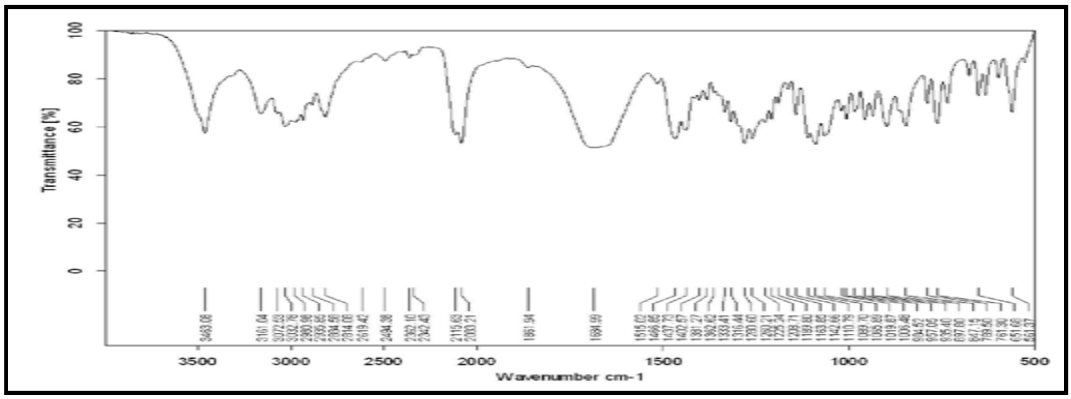

Figure No.3: IR spectrum of zidovudine + Eudragit RS100

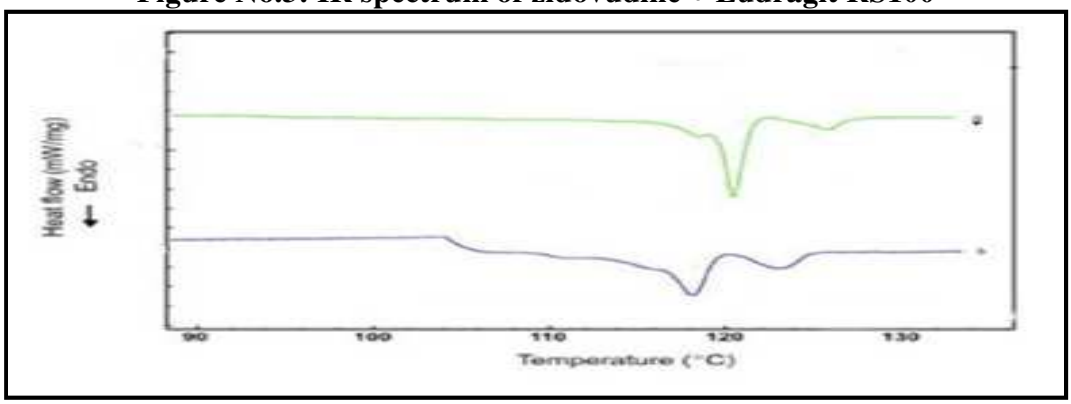

Figure No.4: DSC spectra of pure zidovudine

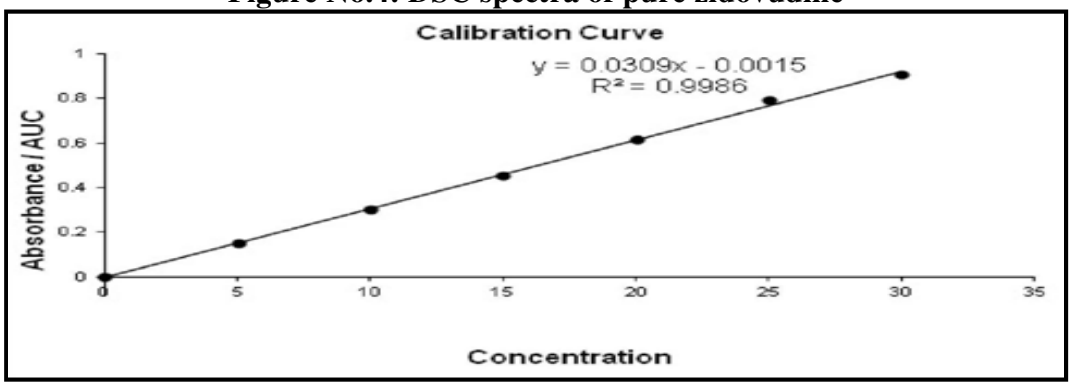

Figure No.5: Calibration curve for Zidovudine in phosphate buffer pH 7.4 at266nm

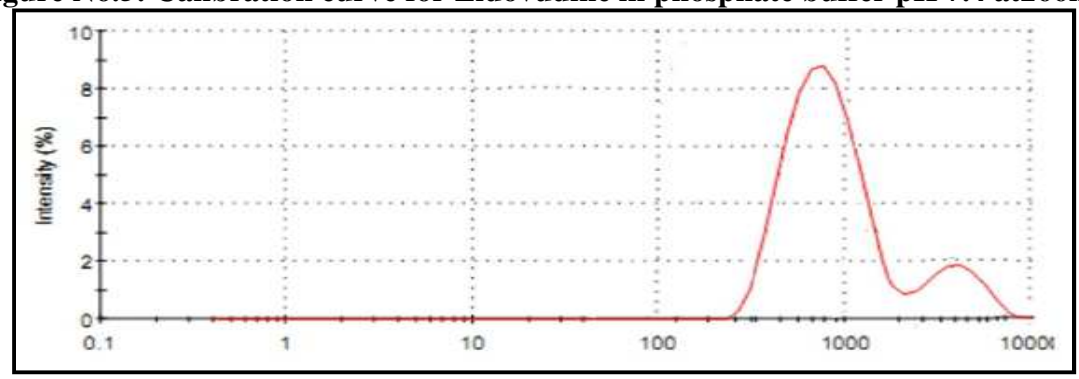

Figure No.6: Particle size distributions of Zidovudine nanoparticles (F1)

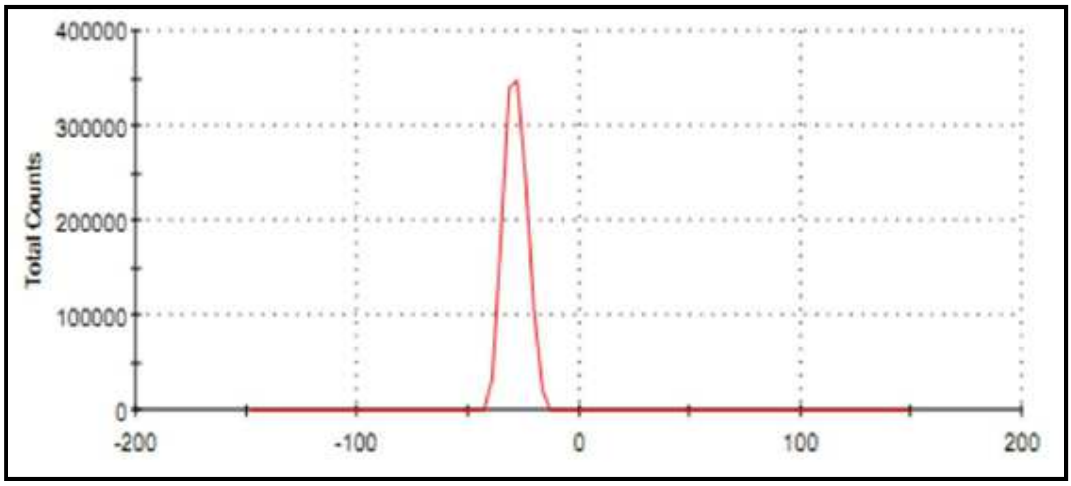

Figure No.7: Zeta potential distributions of Zidovudine nanoparticles (F1)

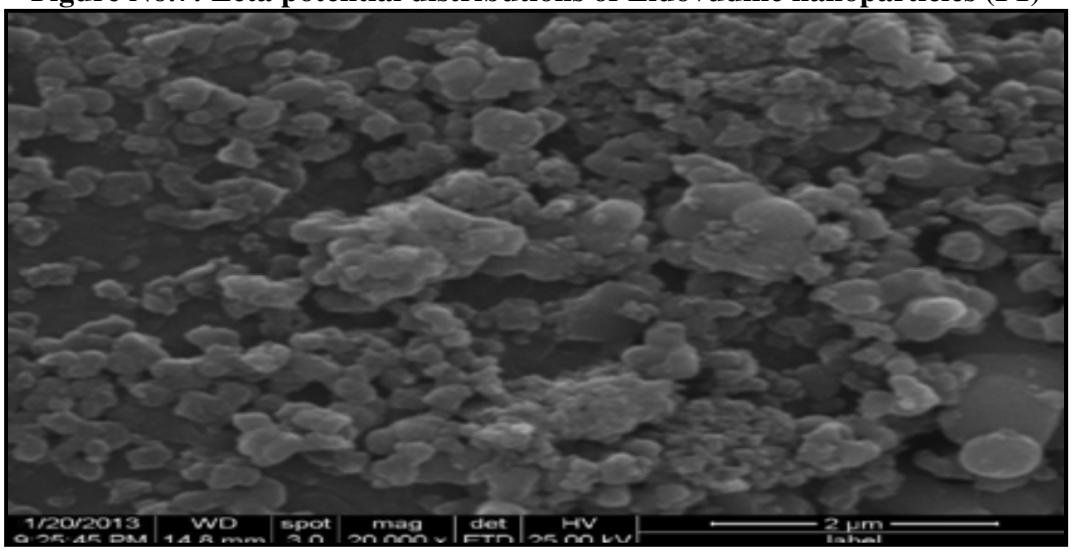

Figure No.8: Scanning electron microscopy (SEM) images of Zidovudine nanoparticles (F1)

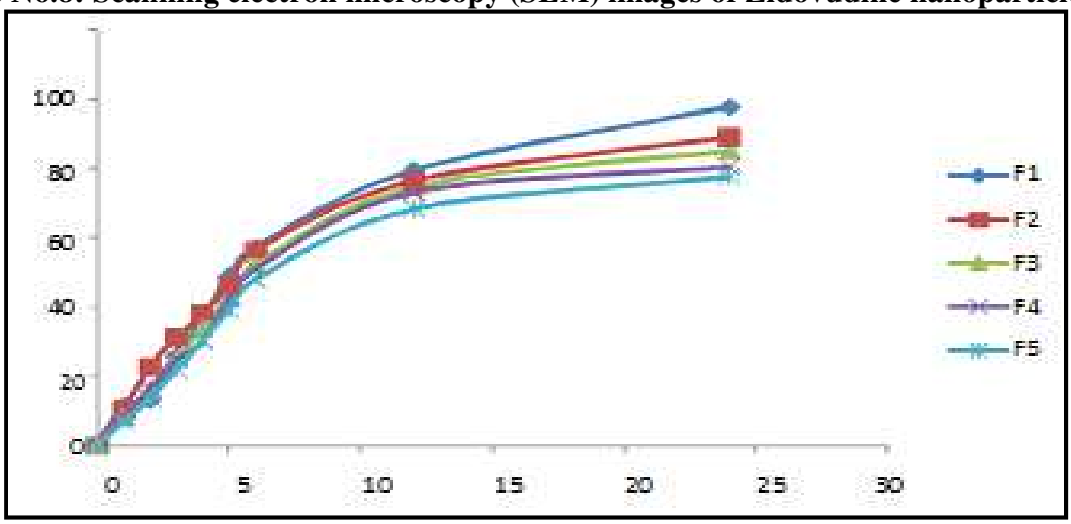

Figure No.9: *In vitro* release profile of Eudragit RS100 nanoparticles of drug Zidovudine with different drug polymer ratio

CONCLUSION

In the present investigation, a venture was made to create nanoparticulate delivery framework for water dissolvable medication zidovudine. FT-IR studies uncovered that there was no interaction between the chosen medication and polymer. EudragitRS100 nanoparticles of zidovudine were set up by co-precipitation procedure produces discrete, free flowing and uniform estimated particles. Among the various groups, Formulation F1 (Drug polymer proportion 1:1) was chosen as the perfect plan, in the wake of considering their better medication loading and *in-vitro* medication discharge. Molecule size investigation demonstrated that the framed particles were in nano size and has a negative surface charge. In light of the perceptions, it very well may be inferred that the defined nanoparticulate delivery arrangement of water dissolvable medication zidovudine utilizing generally acknowledged and physiologically safe polymer was fit for displaying continued discharge properties for a time of 24 h. They are subsequently might be lessen recurrence of dosing, along these lines limiting the event of adverse reactions, improve bioavailability and increment the adequacy of the medication.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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