EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 10
Issue: 5
225-230
Year: 2023

COMPOSITE ALGINATE HYDROGEL MICROPARTICLEDELIVERY SYSTEM FOR ZIDOVUDINE BASED ON COUNTERION-INDUCED AGGREGATION: INFLUENCE OF VARIOUS GRADES OF POLYACRYLATE AND HYPROMELLOSE POLYMERS

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Article Received on 28/02/2023 **Article Revised on 19/03/2023** **Article Accepted on 09/04/2023**

ABSTRACT
In the present research endeavor, Zidovudine Microparticles were attempted to reduce the frequency of dosing and to attain steady-state drug levels. Zidovudine an anti-retroviral drug was selecte dasanovel drug for the experiment. Different batches of zidovudine microsphere formulation Fl to Fl6 were developed using different polymers like eudragit RS-100, eudragit RL-100, andhydroxylpropyl methyl cellulose (HPMC K4m premium) propyl methyl cellulose (HPMCK 15M), swelling agent like sodium alginate and crosslinking agents like calcium chloride ($cacl_2$), bariumchloride($bacl_2$) at variousratios. Allthebatchesof theformulated zidovudine microparticles from Flto Fl6 were evaluate for various physic chemical parameters like mean particle size distribution, percentage yield, and drug entrapment efficiency. The entrapment efficiency of the formulations F1 to F16 ranges from 52.43% to 62.35%. Invitro release studies were carried out on all the formulation using pH7.4phosphate buffer as the dissolution medium. Thed uration of the drug release was 12hours. Based on the results of the physic chemical characterization and in vitro drug release studiesof all the batches of the formulated microspheres from Fl to FI6 formulation F11 was chosenas the most satisfactory formulation as it possessed all the required physic chemical characters and prolonged duration of the drug release up to 8hours.

KEYWORDS: Zidovudine, Microparticles, Ionotropicgelationtechnique, Polymer, FTIR Studies, In vitro drug release studies.

INTRODUCTION
Microparticulate drug delivery systems are most promising strategy based system for controlled drug delivery. They are the most reliable controlled drug delivery system and could be employed as oral drug delivery system or implantable devices. A basic objective indosage form design is to optimize the delivery of medication so as to achieve a measure ofcontrol of the rapeutic effect in the face of uncertain fluctuation in the in vivo environment in which drug release takes place. This is usually accomplished by maximizing drug availability, i.e., by attempting to attain a maximum rate and extent of drug absorption, however the control of drug action through formulation also implies controlling bio availability to reduce drug absorption rates. Microparticulate drug delivery systems are most promising strategy based system for controlled drug delivery. They are the most reliable controlled drug delivery system and could be employed as oral drug delivery system or implantable devices. Zidovudine, a nucleoside analogue of thymidine. Zidovudine triphosphate inhibits the activity of HIV reverse transcriptase both by competing with the natural substrate deoxythymidine triphosphate, andby its incorporation into viral DNA causing a termination of DNA chain elongation because zidovudine lacks the essential 3'-OH group. Researches have been carried on the use of sodium alginate as network forming or gelling agent because of lesser cost, naturally occurring polysaccharide, biodegradability, non-toxicity, provides protection against mucous from irritation and high swelling capacity on contact with gastric fluid. In order to provide stability and protection against the external environment several researchers reported concomitant use of hypromellose or hyroxypropyl methylcellulose (HPMC) and pH independent polymers like polyacrylates (Eudragit RS and RL [ERS and ERL]). Recently, biocompatible polysaccharides-based microparticles for intranasal protein delivery were successfully developed. Lyophilized polysaccharide

based lysozyme microparticles were also prepared and tested for stability. Hence, in the present study an attempt has been made to zidvudine sustained releae microspheres by using various polymer like sodium alginate and ethyl cellulose by using iontropic gelation technique. To characterize different evaluation parameters.

MATERIALS

Zidovudine was obtained from Ranbaxyfine chemicals, Sodium alginate, Hydroxyl propyl methy cellulose, EudragitRS 100, EudragitRL100were purchased from from Ranbaxy fine chemicals and other chemicals, and the reagents used were of analytical grade.

METHODOLOGY

FTIR analysis

The IR spectra were recorded for pure drug sample zidovudine, and physical mixture of the drug Zidovudine and polymers Eugrad it RS100, Eudrag it RL100, HPMCK 4m, HPMCK 15m, Sodium alginate and Barium chloride. Samples were prepared in KBr disks (2mg sample in 200mg KBr) with hydrostatic pressata forceof5.2cm-2for3min.

Differential Scanning Calorimetry

Physical mixture of the drug Zidovudine and the polymers Eudragit RL100, HPMC K4m, HPMC K15M, Bacl2 were prepared. After powder sieving, the mixture was analysed by DSC. The ther mogram obtained was compared with the thermogram of the pure drug. The instrument was calibrated using indium standards. Accurately weighed samples (10mg) were hermetically sealed inflat bottom aluminiumpans. The scanning was carried out at atemperature ranging from 40°C to 300°C at a rate of 20°C/min under an atmosphere of nitrogen.

FORMULATION DEVELOPMENT

Table 1: Formulation development.

F.No.	Drug (mg)	INGREDIENTS						
		Sodium Alginate (%)	HPMCK 4M (mg)	HPMCK1 5M (mg)	Eudragit RS 100(%)	Eudragit RL100 (%)	Bacl 2	Cacl 2
F1	300mg	1.5%	100mg	-	3%	-	10%	-
F2	300mg	2.5%	75mg	25mg	3%	-	10%	-
F3	300mg	3.5%	25mg	75mg	3%	-	10%	-
F4	300mg	3.5%	50mg	50mg	3%	-	10%	-
F5	300mg	1.5%	100mg	-	3%	-	-	10%
F6	300mg	2.5%	25mg	75mg	3%	-	-	10%
F7	300mg	3.5%	75mg	25mg	3%	-	-	10%
F8	300mg	3.5%	50mg	50mg	3%	-	-	10%
F9	300mg	1.5%	100mg	-	-	3%	10%	-
F10	300mg	2.5%	75mg	25mg	-	3%	10%	-

Preparation of Zidovudine Micropaticles using Eudragit RS100

Microparticles containing zidovudine were prepared employing sodium alginateby ionicgelation method. Sodium alginate were dissolved in sufficient quantity of distilled water to form homogenous polymer solution. When sodium alginate was uniformly mixed then specified quantity of HPMC K4and HPMC K15 was added andsonicate it for short period of time. Another beaker was taken in that Zidovudine were dissolved in little amount of methanol add Eudragit RS 100. Finally, core materialzidovudine was added to the polymer solution and mixed thoroughly to form a smoothviscous dispersion. The dispersion were taken into syringe then added drop wise byusing needlein 100ml of 10% barium chloride and calcium chloride Filtrate the microspheres and product was dried at 40 in hot airoven.

Characterization of Formulated Microparticles

Particle Size Analysis

The particle size of all the batches of the formulated microparticles in a sample was measured with an optical micrometer fitted with a calibratedeye piece. Calibration of the microscope was done piror to particle size measurement of the microparticles. Them ean of 100 particles was noted as particle size.All the readings of the three±SD.

Encapsulation efficiency

50 mg Equivalent weight of microparticles were accurately weighed. They were taken in to motor and pestletriturate until it get powder dissolved in 10 ml of methanol for one hour andaliquot from the filterate was analyzed spectro photo metrically, after suitable dilution, they were analyzed using SHIMADZU UV-VIS at 266 nm. Reliability of method was judge by conducting recovery analysis using known amount of drug with or with out polymer. Encapsulation efficiency was calculated using following formula:

Encapsulation efficiency(%)=Actual drug content/Theoretical drug content×100

Particle Size and Surface Morphology

The shape and surface topography of the microparticles were studied by scanning electronmicroscopy(SEM). Scanning electron microscopy (SEM, Philips- XL-20) was performed tocharacterize the surface of formed microparticles. Microparticles were mounted directly on to the samples tuband coated with gold film(200nm) under reduced pressure.

In-Vitro Drug Release Studies

The *In - Vitro* release of drug from microparticles were carriedoutfor 9 hours using paddletype containing 900ml of dissolution medium maintaine dat37±0.5ºCand speed of agitation at 75rpm. Anaccurately weight sample was respond edind is solution media consisting 900mlof pH0.1 NHCl buffer solution and dissolution was done for 2hours then the dissolution medium was changed to pH7.4 phosphate buffer solution and dissolution was studied for further 7 hours. At prefixed time (every 1 hour); 5 ml of solution were with drawn. After suitable dilution, samples were assayed spectro photometrically for the drug content at 266nm using UV-Visible spectro photometer. The volume of the dissolution medium was adjusted to 900 ml at every sampling time by replacing 5 ml with same dissolution medium. The released data obtained were fitted into various mathe matical models like zero order, Higuchi, Korsmeyer-Peppas to know which mathematica lmodel is best fitting the obtained release profile.

Stability Study

The purpose of stability is to provide evidence on how the quality of a drug substance or drugproduct varies with time under the influence of a variety of environmental factors such as temperature and humidity and to formulations of Zidovudine loaded microparticles was carried out by storing 1gm of microparticles in an amber colored screw capped bottle for a period of 1months at 40 2°Ctemperature and 75 5% RH using stability chamber (Thermolab, Mumbai). Sampling was carried out at 1month intervaland examined forpercent entrapment.

RESULTS AND DISCUSSION

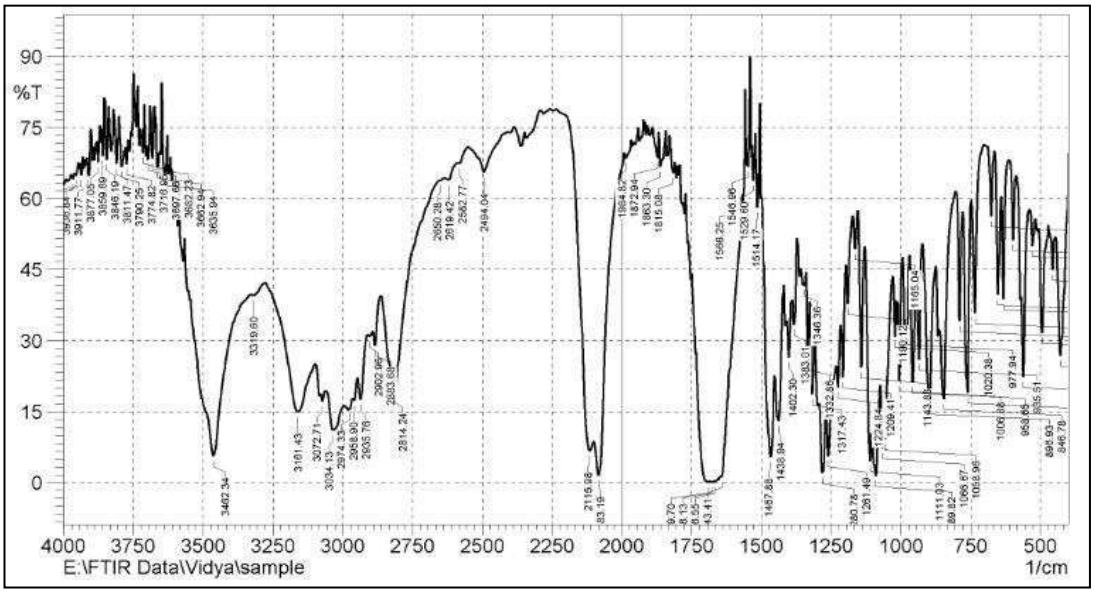

Fig. 1: FTIR Spectra of Zidovudine Pure Drug.

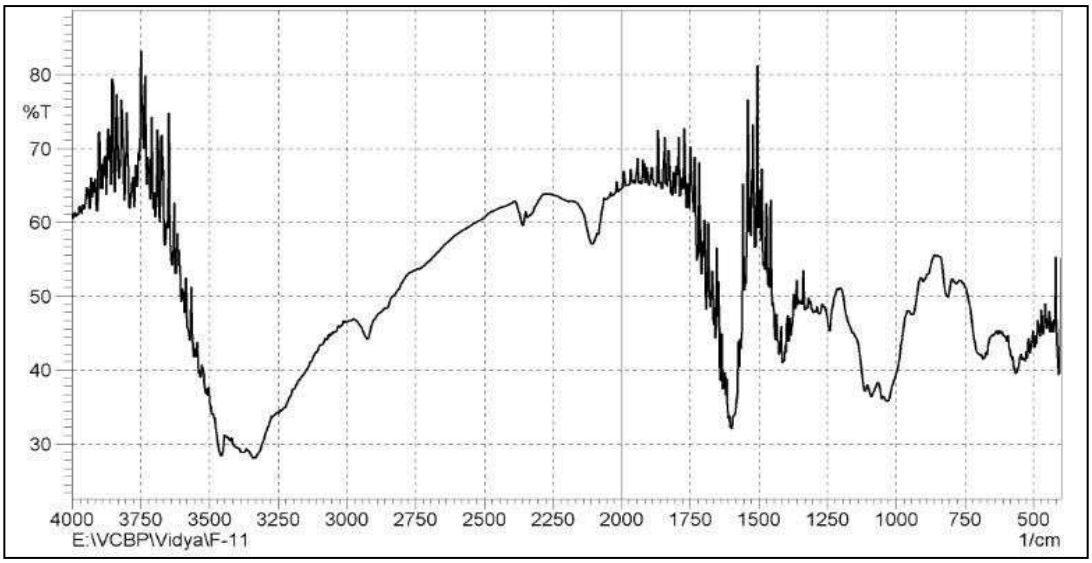

Fig. 2: FTIR Spectra of F-11.

Differential Scanning Calorimetry

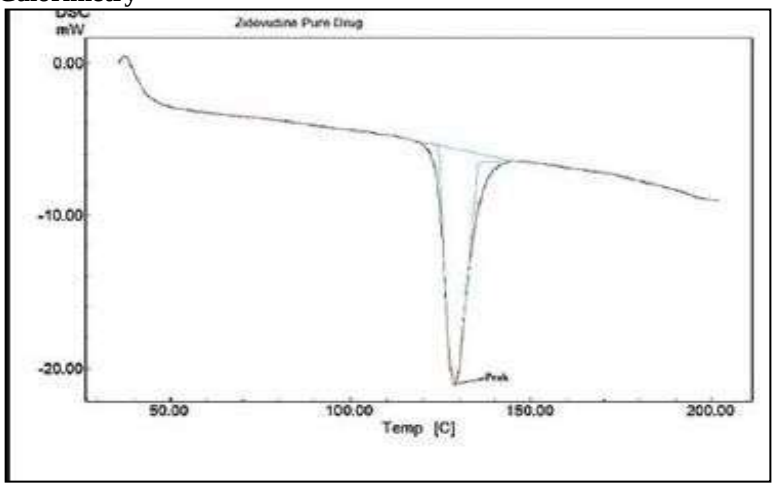

Fig-3: DSC Analysis of Pure drug.

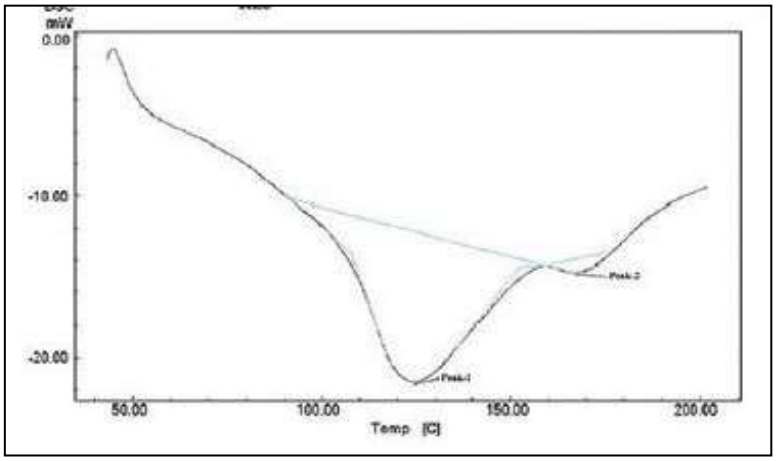

Fig-4: DSC Analysis of Optimized formulation.

SEM Analysis

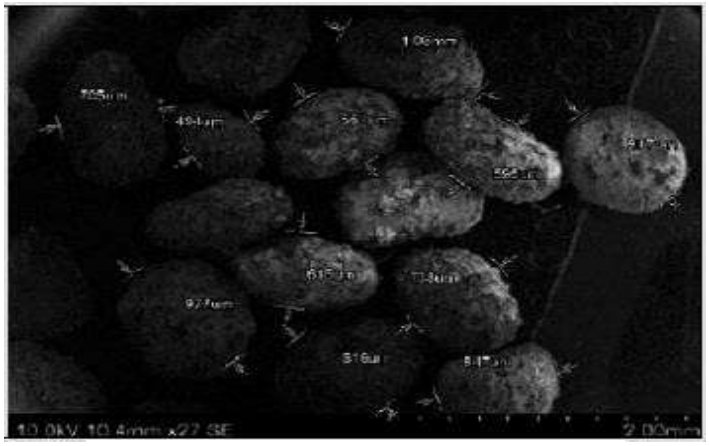

Fig. 5: SEM Analysis of optimized formulation.

Table 2: Drug entrapment efficiency and particle size containing microparticles of zidovudine(F1-F16).

Formulationcode	%drugentrapmentefficiency	Particlesize±SD
F1	44.1±0.24	531±09.21
F2	30.52±0.54	632±14.61
F3	21.05±0.56	734±20.48
F4	34.47±0.45	842±16.21
F5	23.68±0.47	736±13.21

F6	21.93±0.40	633±10.21
F7	35±0.46	542±10.65
F8	51.84±0.57	645±09.54
F9	49.47±0.57	739±08.21
F10	72.10±0.88	789±11.21
F11	79.21±0.87	836±14.23
F12	47.2±0.81	884±12.32
F13	47.2±0.81	936±11.32
F14	72.3±0.68	996±21.32
F15	75±0.59	852±18.91
F16	46.84±0.90	996±13.56

In-Vitro Drug Release Profile

Table 3: Vitro Drug Release Profile Containing Microparticles of Zidovudine(F1-F8).

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.25	16.25±2.12	30.27±1.56	33.34±3.24	32.17±2.46	24.6±3.23	24.61±3.18	19.42±2.45	28.24±1.34
0.5	18.65±4.12	31.26±4.12	34.29±4.17	32.84±3.25	25.46±4.68	25.57±2.11	19.71±3.59	29.68±2.57
0.75	19.59±2.38	32.11±3.59	35.56±4.36	34.27±1.05	25.77±3.84	26.36±4.29	20.81±2.41	29.98±4.28
1	19.87±1.92	35.97±4.98	37.28±3.85	36.98±2.94	26.4±2.58	27.14±3.45	21.32±3.26	31.2±3.49
1.5	20.12±3.67	36.28±3.28	38.49±4.04	36.03±1.76	27.4±3.56	28.01±4.28	21.81±3.4	32.27±2.84
2	21.37±4.38	36.97±4.37	39.45±3.27	38.45±3.32	28.15±4.38	38.12±3.85	22.84±4.19	34.18±2.97
3	27.26±3.59	43.65±3.56	48.58±3.75	38.49±3.47	38.46±3.28	44.53±4.05	34.69±3.27	40.23±3.58
4	33.67±2.57	53.27±3.67	47.49±4.25	45.49±2.74	40.21±4.23	51.58±3.67	35.48±4.28	49.24±4.19
6	50.56±4.12	66.48±4.16	68.38±3.57	55.36±2.76	58.29±3.67	63.67±4.10	51.97±3.28	52.48±3.27
8	61.29±3.4	78.34±3.72	79.56±4.1	67.38±4.64	65.35±4.36	64.58±3.67	63.28±2.17	68.35±4.65

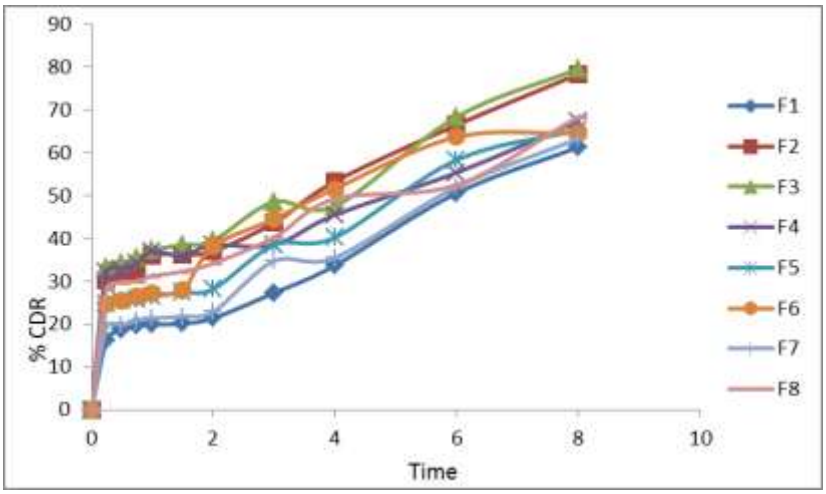

Fig-6: Vitro Drug Release Profile Containing Microparticles of Zidovudine (F1-F8).

Table 4: Vitro Drug Release Profile Containing Microparticles of Zidovudine(F9-F16).

Time	F9	F10	F11	F12	F13	F14	F15	F16
0	0	0	0	0	0	0	0	0
0.25	21.64±4.23	30.11±2.64	30.15±2.36	27.66±2.35	19.95±2.56	32.14±3.25	32.34±2.34	38.56±2.85
0.5	22.66±4.12	32.44±5.12	40.21±4.24	37.63±3.18	22.12±3.73	34.07±2.56	35.75±3.57	42.83±3.57
0.75	24.56±2.36	33.95±3.68	47.46±2.56	41.46±4.29	23.69±3.82	36.42±4.06	38.01±3.87	44.35±3.45
1	25.05±3.45	35.34±4.27	52.19±3.17	43.92±3.78	24.32±4.05	40.65±3.84	40.39±4.03	48.65±4.13
1.5	26.87±2.56	38.37±2.67	56.38±4.12	43.99±4.32	23.39±2.46	47.31±3.12	42.51±3.59	52.35±3.29
2	27.77±4.38	39.07±4.18	63.4±3.72	49.19±3.56	26.37±3.57	57.15±3.17	50.23±3.37	57.06±2.79
3	35.68±4.21	47.62±3.27	72.17±3.71	52.62±3.14	32.56±1.97	63.58±4.05	65.12±4.22	68.12±4.04
4	49.35±3.56	62.33±8.49	78.63±2.35	63.76±2.28	44.45±4.1	71.77±2.48	77.58±3.37	72.42±3.76
6	65.27±3.64	72.98±3.35	85.12±3.68	67.52±2.17	58.48±3.58	87.36±3.58	79.23±2.56	79.57±3.57
8	68.95±2.68	85.32±2.45	98.82±3.87	78.75±3.63	63.59±4.35	92.35±2.95	86.35±2.58	86.39±4.02

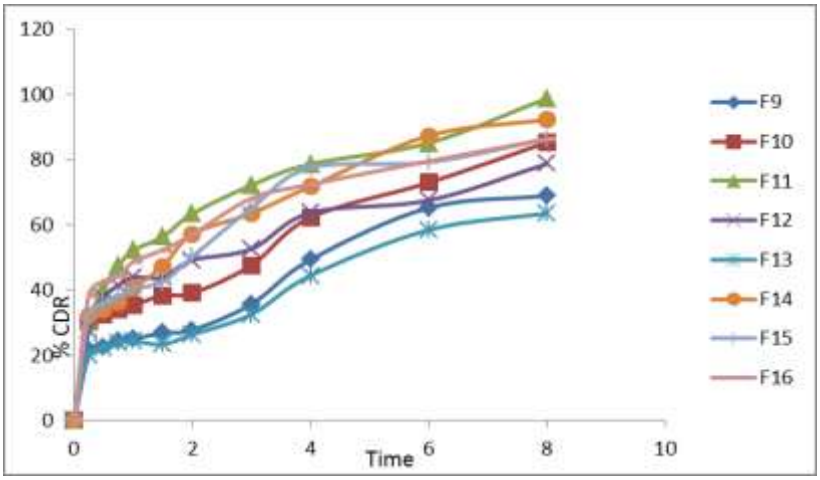

Fig. 7: Vitro Drug Release Profile Containing Microparticles of Zidovudine (F8-F16).

Stability Studies

Table 5: Stability data of zidovudine microparticles.

Sampling time (months)	Entrapment efficiency
0	79.21±0.87
1	78.25±0.85
2	77.21±0.82
3	75.21±0.80

CONCLUSION

FTIR studies and therm alanalysis can be used to in vestigate and predictany physicochemical interactions between compounds in a physical mixture and therefore can be applied to the selection of suitable chemically compatible excipients. pure drug zidovudine exhibited an endothermic peak atabout 130°C, which started to melt at 128.8°C, which corresponds to the melting pointof the drug. F11 exhibited an endothermic peak at about 124.4°C, which is corresponds to theme lting point of the drug. Microparticles containing the drug it may indicate that the drug was uniformly dispersed at the molecular level in the microparticles. F-11showed maximum of drugentrapment(79%) and F-11showed maximum of drugrelease (98.82±3.87). From the scanning electron microscopy, it was observed that particles were spherical. The surface of thedrug loaded all the microparticles manifested the presence of drug particles. All the microparticles had small pores on their surface, which is responsible for therelease. Among all the F-11 formulation showed maximum drug release in 8 hours. The stability study was performed for theselected formulation for 3 months suggested that all the formulation were stable, withno physical change and also the drug content was unchanged.

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