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Preparation and Characterization of Swellable Polymer based Gastro-Retentive Zidovudine Superporous Hydrogel Composite

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Abstract

The main objective of this research work was to prepare and characterize zidovudine superporous hydrogel composite (sphc). Zidovudine is an anti retroviral agent well absorbed from stomach belongs to the class of narrow therapeutic window so there is a need to prepare a gastro retentive dosage form. Superporous hydrogel composite is a second generation sph. For this preparation acrylic acid, acrylamide monomers were used which shows high water absorbing affinity, N,N methylene bisacylamide was used as a crosslinking agent, N,N,N[1],N[1]Tetrametylethyelenediamine, ammoniumpersulphate as a polymerization initiator pair. Sodiumbicarbonate was used as a gas blowing agent which aids in formation of pores in the structure of sphcomposite. In sphC Ac-Di-Sol was used as a composite material which enhances the mechanical strength of sphC. To characterize the prepared zidovudine sph composite evaluation tests which include swelling ratio, swellingtime, scanning electron microscopy (SEM) analysis were performed, and dissolution studies were carried out to assess release characteristics.

Keywords: Superporoushydrogels, superporoushydrogel composite, swelling time.

Introduction

General problem for all the oral dosage forms that are encountered is the gastric residence time. For this, researchers attracted towards the novel drug delivery technologies to enhance drug residence time by formulating various gastro retentive systems. Dosage form retention in the stomach with the intention of prolonging oral gastro intestinal (G.I) transit time to achieve and improve drug bioavailability is the current target. The rigid crystalline structure and low elasticity in polymer leads to slow swelling of hydrogels and they take few hours to days for complete swelling. Diffusion of water through glassy matrix structure of hydrogel is the reason for its slow swelling. This property of hydrogel is responsible to make a controlled release dosage form. When faster swelling was required these may not serve the purpose. This is the reason behind the development of a new generation hydrogels, namely a super porous hydrogel[1].

A superporous hydrogel is a 3-dimensional net-work of a hydrophilic polymer which absorbs a large amount of water in a very short period of time because of the presence of interconnected microscopic pores[2].

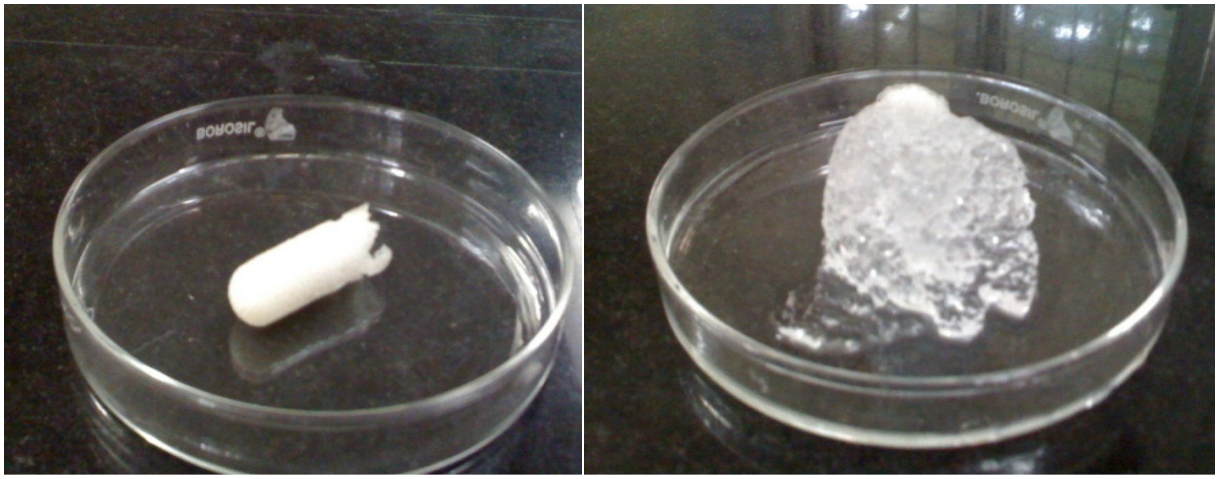

Figure-1
Sphc in dried form and in swelled form

Classification of Superporoushydrogels: these superporous hydrogels are classified into 3 types

i. The First generation SPH named as conventional SPHs. ii. Second generation SPH named as SPH composite (sphcomposite). iii. Third generation SPH named as superporous hydrogel hybrids**.**

In this research work sphc was prepared using zidovudine (0.5 to 3 hours half life).To prolong the therapeutic efficacy of the drug it can be prepared as a zidovudine superporoushydrogel composite. Super porous hydrogel composite is a second generation sph, which shows high mechanical strength than conventional sph. Ac-di-sol, composite material which gives mechanical strength to sph composite structure[3].

Material and Methods

Zidovudine was obtained as a gift sample from Aurobindo laboratories, Hyderabad. Acrylic acid from Loba Chemie pvt Ltd Mumbai, Acryl amide was obtained from Thermo Fisher Scientific India pvt Ltd, Mumbai, N, Nmethylene bisacrylamide was obtained from Loba Chemie pvt Ltd, Mumbai, N, N, N^1, N^1Tetrametylethyelenediamine was obtained from Hi Media Laboratories, Mumbai, ammonium persulphate, sodium bicarbonate were obtained from Fine chemicals, Mumbai.

Construction of standard calibration curve for zidovudine using uv-visible spectrophotometry method:

Preparation of stock solution: 10mg of pure zidovudine was weighed and dissolved in small volume of methanol in a10ml volumetric flask. After shaking the flask vigorously the volume was made up to the mark with distilled water to give a solution containing 1000µg/ml (stock solution 1). From this stock solution 1, 1ml of solution was pipette out and placed in 100 ml volumetric flask. Adjust the volume up to the mark with distilled water, which gives a solution containing 10 µg/ml (stock solution 2).

Preparation of analytical concentration ranges: From the above stock solution 2 of zidovudine, appropriate samples were pipette out 2ml, 4ml, 6ml, 8ml, 10ml, into 10ml volumetric flasks. And then distilled was added up to the mark in order to prepare 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml. By using uv-visible spectrophotometer the absorbance of these solutions were measured at 267.8nm.and plot was showed in Figure-5.

Construction of standard calibration curve for zidovudine using RP-HPLC method:

Instruments: The present work was investigated on gradient high pressure liquid chromatography [Shimadzu HPLC] with LC-20 ATProminence solvent delivery system for constant flow and constant pressure delivery. SPD – M20, a prominence diode array detector was connected to software LC solution class M20A for controlling the instrumentation as well as processing the data generated was used.

Preparation of mobile phase: The Water and acetonitrile in the ratio of 65:35 having pH 3.5 was prepared and was degassed done by sonication.

Preparation of diluent: Water and acetonitrile in the ratio of75:25 with pH 3.5(adjusted with dilute orthophosphoric acid) was prepared and degassed by sonication.

Preparation of Standard solutions: The stock solution zidovudine having concentration of 100µg/ml each was prepared and was measured at room temperature. The standard solutions were prepared by proper dilutions of the primary stock solution with water and Acetonitrile (75:25) to obtain working standards in the aliquots ranges as 30,45,60,75 and 90µg/ml of Zidovudine. The calibration plot was obtained as in figure 7.

Recording of chromatogram: Mobile phase ratio of 65:35 (Water: Acetonitrile), pH3.5 (adjusted with dilute Orthophosphoric acid), wave length272 nm, flow rate1.0ml/min. After getting a steady baseline, the standard solution was injected and chromatogram was recorded until the reproducibility of the peak areas was found.

Preparation of zidovudine superporous hydrogel composite: SPHC were synthesized using various vinyl monomers. The monomers used in this study were acryl amide (AM), acrylic acid (AA), (2.5%) bisacrylamide as cross linker, span- 80 as foam stabilizer. Initially all the ingredients were added sequentially into a test tube: 50%(w/v) AM and 50%AA(v/v) as monomers, (2.5%w/v) Bisacrylamide as cross linker, span-80 (10%v/v) as foam stabilizer, 20%(w/v) APS, and 20% (v/v) TEMED(tetra methyl ethylene di amine) as polymerization initiator pair, double distilled water (DDW), and 150 mg of sodium bicarbonate. The test tube was shaken to mix the solution after each ingredient was added. The pH of the AA was adjusted to pH5 by using 2 M NaOH. Before addition of sodium bicarbonate zidovudine 300mg was added into the reaction mixture Ac-Di-Sol was used as composite material. Sodium bicarbonate was added to the monomer solutions and whole mixture was stirred using a spatula for several seconds to properly distribute the gas bubbles. Sodium bicarbonate was used as a foaming or gas blowing agent which increases the pH of the solution and accelerated the polymerization reaction. The synthesized SPH was removed from the test tube by adding 2 ml of absolute ethanol. The absence of monomers was ensured spectrometrically by ensuring that the water of the washings did not contain any trace of monomers. The formed zidovudine sphcomposite was dried in an oven at 60°C for 6 hours[4].

Table-1
Composition of zidovudine sph composite

S.no	Ingredients	F1	F2	F3	F4	F5	F6
1	Acrylic acid(µl)	200	200	200	200	20	20
2	Acryl amide(µl)	300	300	300	300	300	300
3	N,Nmethylene Bisacrylamide(µl)	50	50	100	150	200	250
4	N,N,N^{1},N^{1}Tetrametyl Ethyelenediamine(µl)	20	20	20	20	20	20
5	Ammoniumpersulphate(µl)	50	50	50	50	50	50
6	Span -80(µl)	50	50	50	50	50	50
7	Double distilled water(µl)	400	400	400	400	400	400
8	Ac-Di-Sol(mg)	--	30	45	60	75	90
9	Sodium bicarbonate(mg)	150	150	150	150	150	150
10	Zidovudine(mg)	300	300	300	300	300	300

Evaluation of zidovudine superporous hydrogels composite: Swelling property of SPHs: Swelling studies:

Swelling studies were measured for F6. In this swelling ratio, swelling time was measured by adding distilled water and 0.1N Hcl individually to sphcomposite. After adding solvents hydrogels were swelled, size of hydrogels was increased. Swelling is the main property shown by all the hydrogels when Placed in contact with water. They undergo swelling within 20 minutes or less in stomach and escapes from premature emptying through house keeper waves there by act as gastro retentive System. By using this swelling parameter equilibrium swelling time and equilibrium swelling ratio were determined[5,6].

Equilibrium swelling time: Equilibrium swelling time is the time taken by the superporous hydrogel to attain its equilibrium swelling point. After this point the swelling of hydrogel was no more occurs. To measure the swelling time, the hydrogel was immersed in distilled water, 0.1NHcl and measure the time at which equilibrium in swelling process occurs[7,8].

Equilibrium swelling ratio: For this dried super porous hydrogel was taken and measured its weight and then it was allowed to hydrate in distilled water at room temperature. At various time intervals measured the swollen hydrogel weight. The Equilibrium swelling ratio was calculated by using the formulae

$$Qs = Ws – Wd/Wd \times 100$$

Ws -weight of the swelled hydrogel, Wd - weight of the dried hydrogel and Qs- Equilibrium swelling ratio.

Mechanical strength: In order to withstand the pressure exhibited by gastric contents and its contractions, any hydrogel must require showing mechanical strength. Mechanical strength was measured by using bench comparator and gastric simulator. Conventional super porous hydrogels showed low mechanical strength when compared with sph composite[9].

In vitro dissolution studies: 0.1N Hcl was used as dissolution medium for in vitro dissolution studies of zidovudine sphc used and the study was carried out for up to 12 hours. The rotational speed was maintained at 50 rpm and the temperature at 37 ± $0.^{0}$c. Aliquots of dissolution medium were withdrawn periodically and were analyzed using UV-Visible spectrophotometer (Shimadzu, UV-1700) at 267.8nm[10].The results were mentioned in Table4.

Drug Release kinetics of all formulations: The drug release profiles of all formulations were put into drug release kinetics equations, in order to know the pattern of drug release from the formulations. Those formulations F6 was optimized as a best one due to release of more amount of drug than remaining formulations. And correlation coefficient values of F6 zero order (R^2 = 0.976), first order (R^2 =0.941), higuchi model (R^2 =0.909), Korsemeyer-Peppas equation (R^2 =0.815) were showed in Figure7-Figure10.comparison of all formulations drug releases where clearly shown in Figure 11. From these values the in vitro drug release kinetics of F6 followed zero order and the best fitted to the Higuchi model indicating that the drug release is diffusion controlled.

Results and Discussion

FT-IR studies reveal that there is no incompatibility was observed between pure zidovudine and polymers. The drug release kinetics was applied to all the formulations. In those formulations F6 follows zero order higuchi kinetics.SEM analysis shows the formation of numerous pores in its structure. In evaluation studies, it was observed that on increasing the concentration of composite material (ac-di-sol) swelling ratio decreases and was mechanical strength increased and these are mentioned in table 5. So F6 follows all the ideal requirements of a superporoushydrogel composite.

FT-IR studies: The FT-IR spectrum was taken for pure zidovudine and also the physical mixtureof polymers like acrylamide, BIS acrylamide, ammonium persulphate with drug. In this method 3mg of sampleand 300mg ofpotassium

bromidewas finely ground using mortar and pestle. A small amount of mixture was placed under hydraulic presscompressed at10kg/cm to form a transparent pellet. The pellet was kept in the sample holder and scanned from 4000cm to 400cm in Shimadzu FT-IR spectrophotometer.

The study of the FTIR spectra of Zidovudine demonstrated that the characteristic absorption peaks for the carbonyl group at 1675 cm -1, C-N (amine) stretching at 1221 cm -1 and azido group stretching at 2082 cm -1. This further confirms the purity of zidovudine. And this spectra was compared with the spectra of polymer mixture which reveals that here is no incompatibility was observed between zidovudine and polymers and peaks were showned in figure2,3.

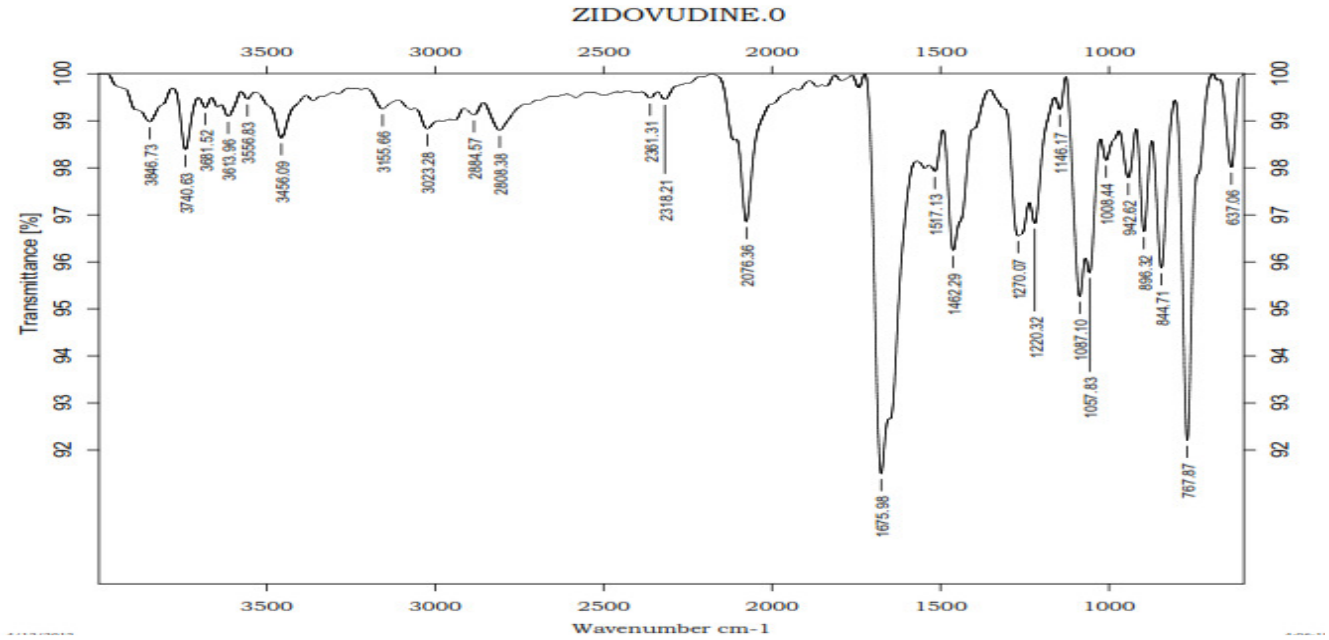

Figure-2
FT-IR graph of Zidovudine

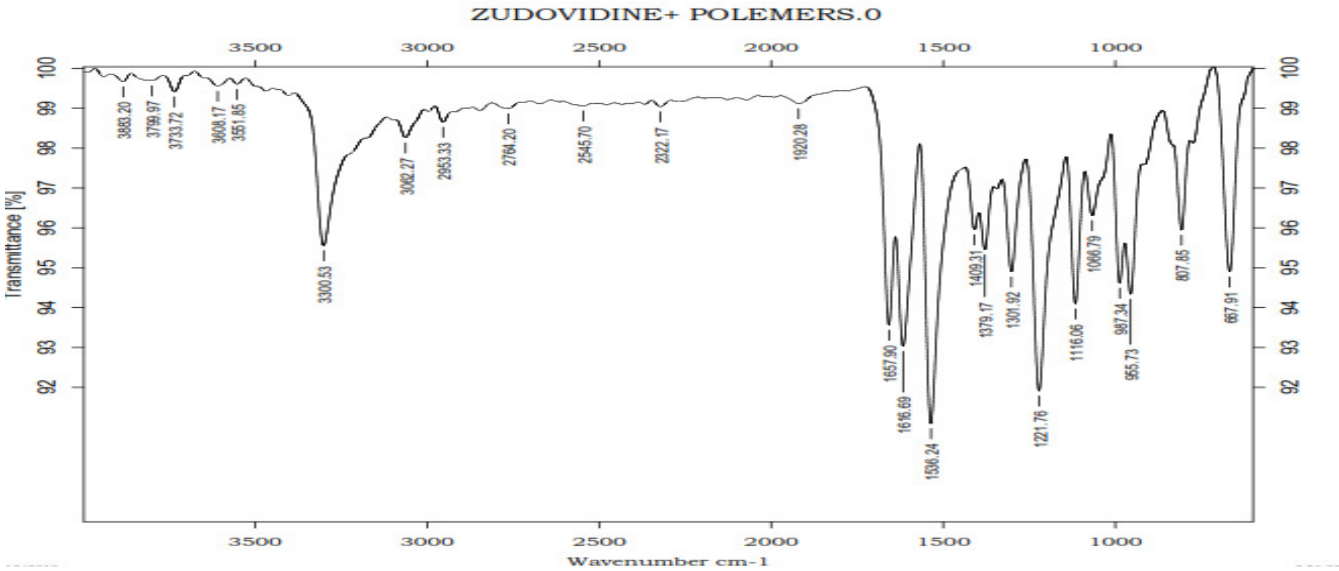

Figure-3
FT-IR graph of Zidovudine with its polymers.

Scanning electron microscopy (SEM): SEM analysis was performed to identify themorphology of a dried super porous hydrogel. The samples were coated with gold using Hummer sputter coater (Techniques, Ltd.), then carried using a Jeol JSM-840 scanning electron microscope (Jeol USA, Inc., Peabody, MA), and captured the images using a digital capture cardand Digital Scan Generator 1 (Jeol).

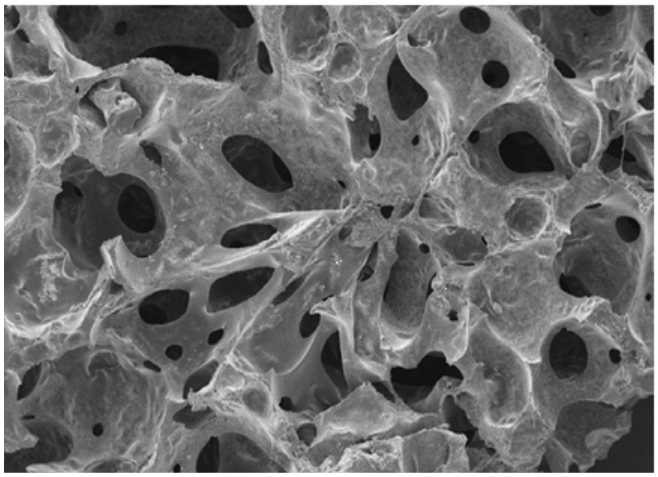

Figure-4
Scanning electron microscope image of F6

This picture clearly indicates the formations of pores in its structure. These pores are mainly responsible for swelling of superporous hydrogel composite[12].

Table-2
Calibration curve data of zidovudine

S.No	Concentration (µg/ml)	Absorbance measured at 267.8nm
1)	0	0
2)	2	0.098
3)	4	0.190
4)	6	0.273
5)	8	0.357
6)	10	0.440

Table-3
HPLC data

S.NO	Concentration (µg/ml)	Peak area
1)	30	1624.23
2)	45	2309.754
3)	60	2937.165
4)	75	3851.43
5)	90	4677.192

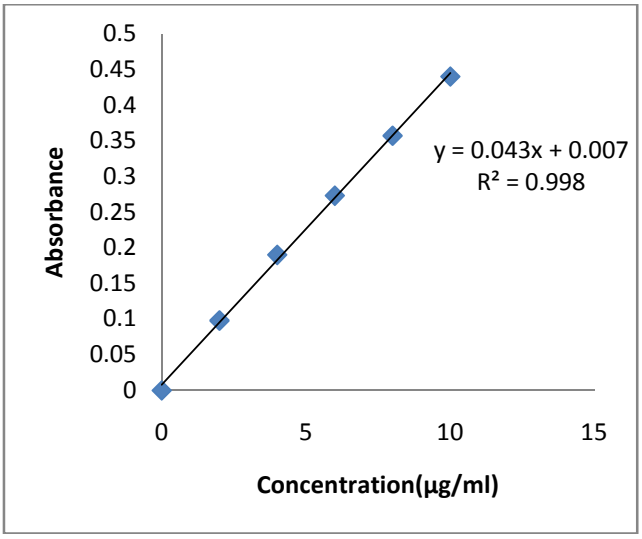

Figure-5
Calibration curve of zidovudine.

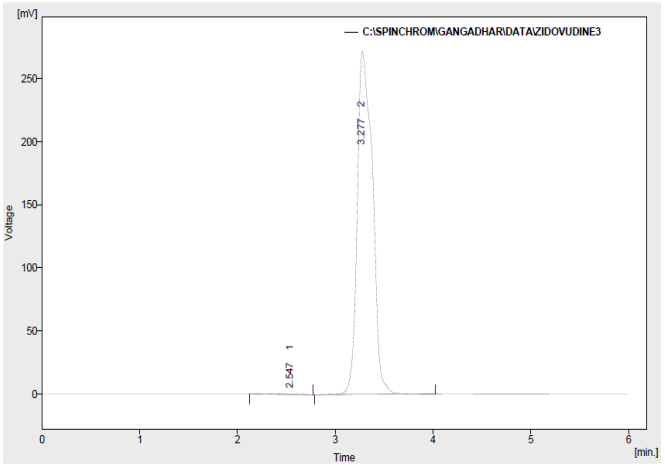

Figure-6
HPLC peak for zidovudine 60(µg/ml)

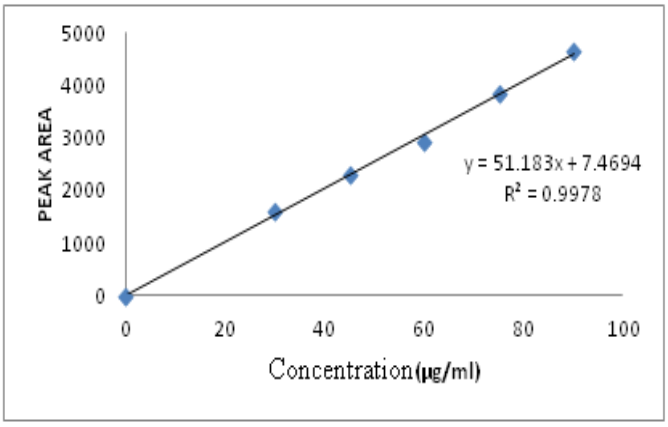

Figure-7
Calibration curve of zidovudine

Table- 4
Dissolution profiles of optimised formula (F6)

S.no	Time (mins)	Absorbance	%Drug dissolved	%Drug undissolved	Log %drug undissolved
1)	5	0.077	6.59	93.40	1.97
2)	10	0.127	10.88	89.11	1.94
3)	15	0.149	12.83	87.16	1.94
4)	20	0.164	14.05	85.94	1.93
5)	30	0.183	15.68	84.31	1.92
6)	60	0.207	17.74	82.25	1.91
7)	120	0.231	19.79	80.20	1.90
8)	180	0.264	22.62	77.37	1.88
9)	240	0.327	28.02	71.97	1.85
10)	300	0.413	35.39	64.60	1.81
11)	360	0.549	47.05	52.94	1.72
12)	420	0.611	52.36	47.63	1.67
13)	480	0.798	68.39	31.60	1.49
14)	540	0.843	72.25	27.74	1.44
15)	600	0.891	76.36	23.63	1.37
16)	660	0.943	80.82	19.17	1.28
17)	720	0.987	84.59	15.40	1.18

Table-5
Evaluation studies data

S.no	Formula	Swelling time(mins)		Swelling ratio (%)	Mechanical strength(gm)
		D.W	0.1N Hcl		
1)	F1	18	21	98	230
2)	F2	15	17	97	237
3)	F3	12	13	95	243
4)	F4	10	12	93	261
5)	F5	8	11	91	279
6)	F6	6	9	90	285

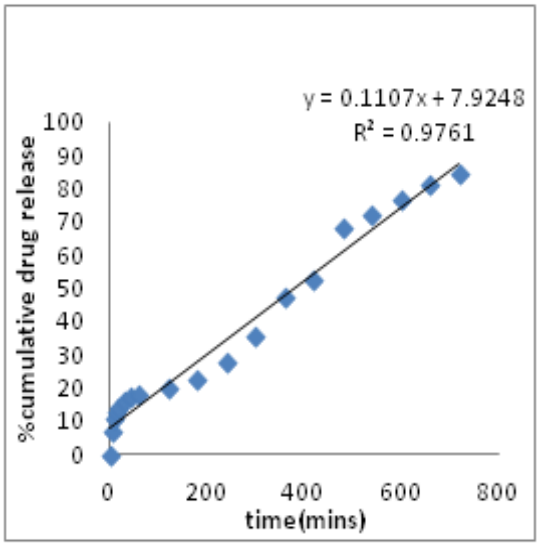

Figure-8
Zero order plot of F6

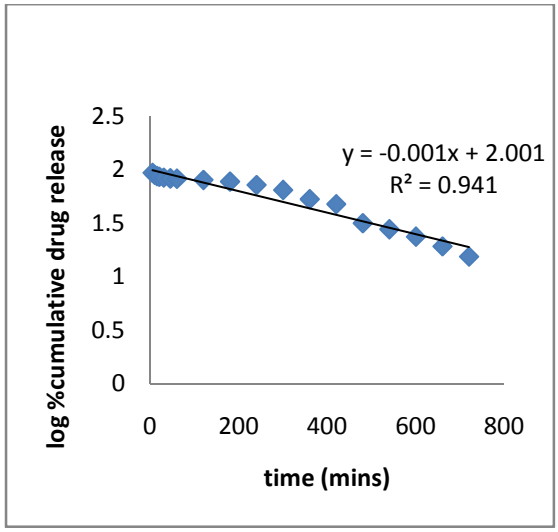

Figure-9
First order plot of F6

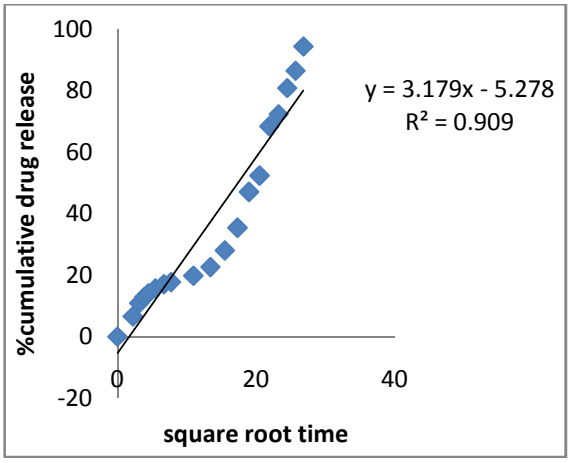

Figure-10
Higuchi model of F6

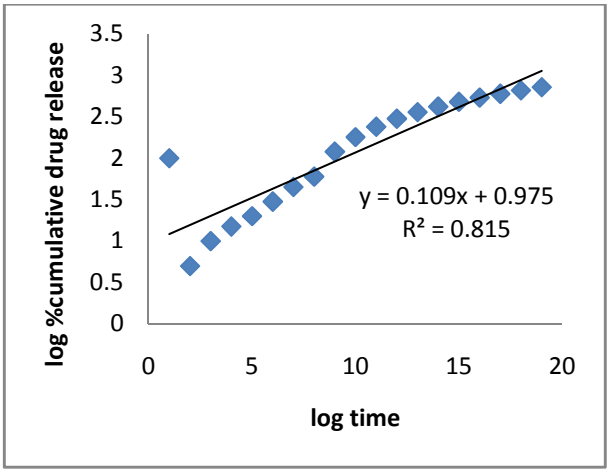

Figure-11
Korsemeyer-Peppas model of F6

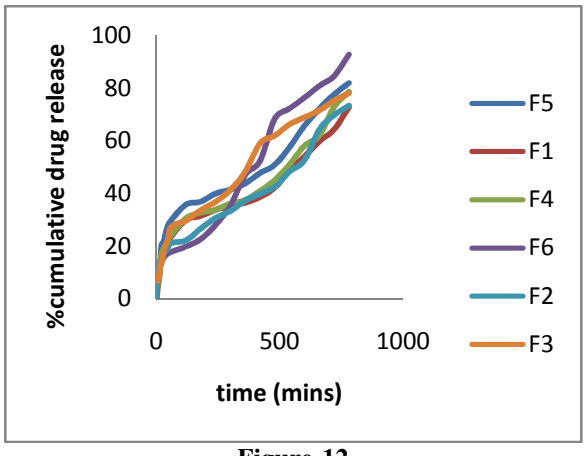

Figure-12
Comparison plot of formulae F1-F6.

Conclusion

From dissolution studies F6 releases more amount of zidovudine than other formulations was confirmed and by performing evaluation studies optimised formula shows low swelling time, swelling ratio and shows higher mechanical strength than other formulations. Finally it was concluded that prolonging the therapeutic activity of zidovudine through sph composite was successfully achieved.

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