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FORMULATION AND CHARACTERISATION OF GASTRO RETENTIVE SUPER POROUS HYDROGELS AN ANTI – RETRO VIRAL DRUG

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ABSTRACT

Gastro retentive drug delivery is an approach to prolong gastric residence time thereby targeting upper part of GIT for systemic effect. SPHs were originally developed as a novel drug delivery system to retain drugs in the gastric medium for those drugs having absorption window in stomach and upper part of the gastrointestinal tract. The main objective of this work is to prepare and characterize gastroretentive Tenofovir Disoproxil Fumarate superporous hydrogel which is an antiretroviral which are expected to maintain the therapeutic drug concentration in the blood for a prolonged period of time in the gastrointestinal tract. The aim was to increase the permeability and efficacy of the TDF by reducing its side effects. SPHs are prepared by gas blowing technique using various polymers. To characterize the prepared SPH, evaluation tests which include Swelling ratio, swelling time, SEM analysis were performed to know its swelling properties and pores of sph optimized formulation. FTIR studies were carried out to check any possible interactions between the drug and the polymer and study revealed that no interaction between the drug and the polymer. In vitro Dissolution studies were performed to know the drug release from the formulation and it was concluded that optimized formula follows Zero order diffusion and release mechanism follows Higuchi model.

KEYWORDS: Gastro retentive, Superporous hydrogels, Antiretroviral, Tenofovir Disoproxil Fumarate, polymers, Swelling ratio, FTIR – Studies.

INTRODUCTION

Hydrogel is three-dimensional network of cross linked polymers which are bonded physically (or) chemically these are used widely in drug delivery and immobilization of enzymes. These systems should instantly swell in the stomach and maintain their integrity in the harsh environment, while releasing the pharmaceutical active ingredient. They absorb large amount of water in short period of time due to porous structure. These are unique properties of SPH several other important properties are swelling capacity, swelling ratio, slipperiness, biodegradability, biocompatibility and stability after swelling SPH are made to possess mechanical strength this can be improved by adding cross linked hydrophilic polymers in to formulation SPH were used to develop gastric retention device that increases the gastric residence time of drug to get long term oral controlled drug delivery. The fast swelling property is based on water absorption through open porous structure by capillary force.

MATERIALS AND METHODS

Materials

Tenofovir Disoproxil Fumarate procured from Hetero drugs Pvt Ltd, Acrylamide from Thermo fisher scientific India Pvt Ltd. Acrylic acid, Formaldehyde were from Lobachemi Pvt Ltd, Mumbai. Ammonium per sulphate, Ac–di–sol, Sodium bicarbonate were from Qualigens fine chemicals Mumbai. Span – 80 from NR chemicals, Mumbai.

Methods

Construction of standard calibration curve for TDF

✓ **Preparation of Stock Solution**

10 mg of pure TDF was weighed and dissolved in small volume of methanol in a 10 ml 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).

✓ **Preparation of analytical concentration ranges**

From the above stock solution 1 of TDF, pipette out 0.2ml, 0.4ml, 0.6ml, 0.8 ml, 1ml, into the 10ml volumetric flasks distilled water was added up to the mark in order to prepare 20µg/ml, 40µg/ml, 60µg/ml, 80µg/ml and 100µg/ml. By using UV-Visible spectrophotometer absorbance of these solutions were measured at 305 nm.

Determination of solubility

Solubility of tenofovir disoproxil fumarate was determined by adding sufficient quantity of drug in different buffers up to its saturation point & then filtered the filtrate through whatmann filter paper. If necessary dilutions were made & measure the absorbance at 305nm by using UV-Visible double beam spectrophotometer. For this solubility studies 0.1N acidic buffer, distilled water, methanol were used.

Preparation of TDF Superporous Hydrogel

The monomers like Acrylic acid and Acrylamide are added to a test tube to that add Span 80 and Formaldehyde. All these are mixed well now TDF drug is added. Later Ac-di-sol and distilled water is added mixed well. It should be measured to pH 5 if the pH is not observed correctly then the pH is adjusted by adding 0.1N NaOH. Later Sodium bicarbonate and Ammonium persulfate is added to evolve the bubbles properly. This mixture is kept in oven for 1day at 55^0C temperature. Ethanol is added to this and the gel is removed out.

Composition of TDF SPH

This composition shows the formulation of TDF sph for this about 10 formulations were designed. Ac-di-sol, which is slightly soluble in water causes gelification of mixture leads to improper mixing of ingredients and sph doesn't forms properly.

Table no 1: Composition table of tdf loaded superporous hydrogels formulation.

S.No	INGREDIENTS	F1	F2	F3	F4
1	Acrylic acid (50%v/v)(µl)	200	200	200	200
2	Acrylamide (50%w/v))(µl)	30	300	300	300
3	Span-80(10%v/v))(µl)	50	50	50	50
4	Formaldehyde)(µl)	50	100	150	200
5	Ac-di-sol (mg)	50	75	100	150
6	Distilled water)(µl)	400	400	400	400
7	Tenofovir Disoproxil Fumarate (TDF)(mg)	300	300	300	300
8	Sodium bicarbonate (mg)	200	200	200	200
9	Ammonium persulphate (20%))(µl)	45	45	45	45

Evaluation studies

Evaluation parameter of TDF Super porous hydrogel

✓ **Estimation of Drug Content**

The amount of T0DF present in sph was estimated by taking some amount of TDF sph which was equivalent to 10mg of TDF. Then it was taken in 50ml volumetric flask. To the TDF sph

0.1N HCL was added up to the mark. The volumetric flask was shaken and kept aside for 24hrs and then absorbance of solution was measured at 305nm.

✓ **Swelling properties of SPH**

➢ **Swelling studies**

Swelling studies were measured for F4. In this swelling ratio, swelling time was measured by adding distilled water and 0.1N HCL individually to sph. After adding solvents hydrogels were swelled, size of the hydrogels was increased. Swelling is the main property shown by all hydrogels when placed in contact with water. They undergo swelling within 20 minutes or less in stomach and escapes from premature emptying through housekeeper waves there by act as gastro retentive system by using swelling parameter equilibrium swelling and equilibrium swelling ratio were determined.

➢ **Equilibrium swelling time**

Swelling time is the time taken by the hydrogel to attain its equilibrium swelling point. After this point the swelling of hydrogel was stopped. To measure the swelling time the hydrogel was immersed in distilled water, 0.1N HCL and measure the time at which equilibrium in swelling process occurs.

➢ **Equilibrium swelling ratio**

Superporous hydrogels were taken and measured its weight and then it was allowed to hydrate in distilled water in room temperature. At various time intervals measured the swollen hydrogen weight. The Equilibrium swelling ratio was calculated by using the formula,

$$Q_S = W_S\text{-}W_d/W_d x100$$

Where, W_S is the weight of weight of the swelled hydrogel,

W_d is the weight of weight of the dried hydrogel,

Q_S is the equilibrium of swelling ratio.

In-vitro dissolution studies

0.1N HCl was used as a dissolution medium for in-vitro dissolution studies of TDF sph and studies were carried out for up to 8hrs. The rotational speed was maintained at 50rpm and the temperature at 37±0.5ºC. Aliquots of dissolution medium was withdrawn periodically and were analysed using UV-visible spectrophotometer at 305nm.

Drug release kinetics

In order to understand the kinetics & mechanism of drug release, the results of in vitro drug release study of TDF sph was fitted with various kinetic equation like zero order(cumulative % release vs. Time), first order(log % drug remaining vs time) peppas plot(log of cumulative % drug release vs log time)R^2 (Coefficient of correlation) & K (release rate constant) values were calculated for the linear curve obtained by regression analysis of the plots.

Zero order equation

$$Q_t = Q_0 + K_0 t$$

Where, Q_t = amount of drug released at time t.

Q_0= initial amount of drug in the solution(most ties Q_0=0)

K_0 = zero order release rate constant.

This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs, coated forms, osmotic systems, etc. The pharmaceutical dosage forms following this profile the same amount of drug by unit time & it is ideal method of drug release in order to achieve the pharmacological prolonged action.

First order equation

$$L_n Q_t = \ln Q_0 + k_t$$

Where Q_t =amount of drug released at time t,

Q_0 = initial amount of drug in the solution,

K_t =first order release rate constant.

Thus a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi equation

It defines a linear dependence of the active fraction released per unit of the surface(Q) on the square root of time.

$$Q_H = K_H t^{1/2}$$

Where, Q_H = Amount of drug release at time t,

K_H = Higuchi diffusion rate constant.

A plot of the fraction of the drug release against root of time will the linear if the release obeys Higuchi equation. this equation describes drug release as a diffusion process based on the flick's law square root of time dependent.

Korsemeyer Peppas equation

Korsemeyer et al developed a simple semi empirical model, relating exponentially the drug release to the elapsed time.

$$M_t/M_\infty = K\, t^n$$

Peppas used this n value in order to characterize different release mechanisms, concluding for values of n=0.5 for fick's diffusion and higher values of n, between 0.5 and 1.0, anomalous transport for mass transfer following a non fickian model, n=1. Case - Ⅱ transport, higher than 1.0 for super case- Ⅱ transport.

RESULTS AND DISCUSSION

Table no 2: Calibration data of TDF by uing UV-Visible spectroscopy.

S.No	Concentration of solution (µg/ml)	Absorbance at 305nm
1	Blank	-
2	20	0.0116
3	40	0.0227
4	60	0.0347
5	80	0.0478
6	100	0.0600

The standard curve of TDF was constructed by using 0.1 HCL buffer at 305nm by using UV-Visible spectroscopy method. The curve obtained was linear and obeyed beers law in the given concentrations. The regression coefficient was found to be 0.999 which was generated using the equation y=0.0594x-0.0069. This data was used for the calculations of drug content and dissolution data.

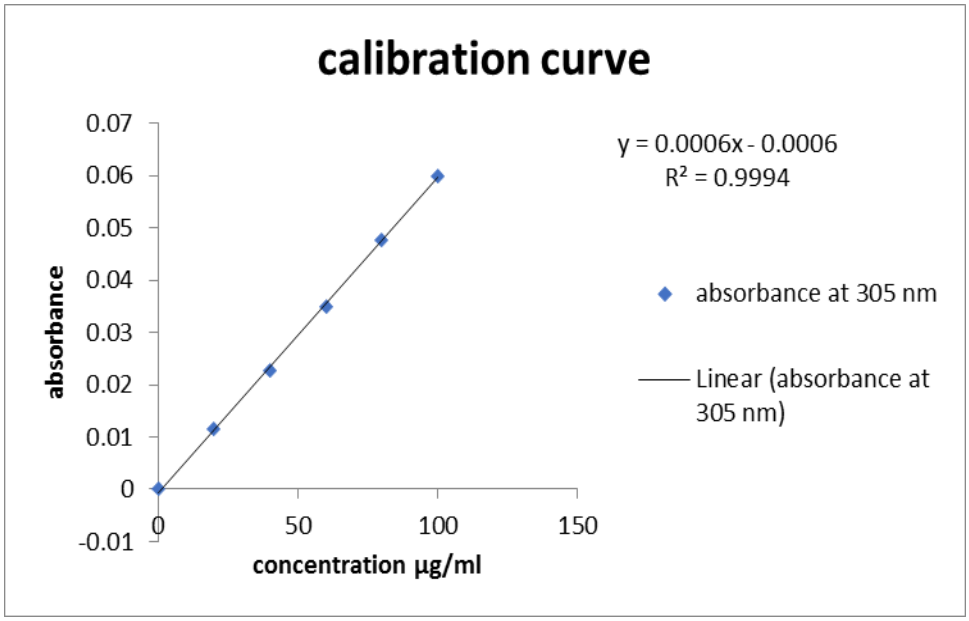

Figure no 1: Calibration data of TDF.

FT-IR Studies

The FT-IR spectrum was taken for pure TDF & also the physical mixture of polymers like acrylamide, formaldehyde, ammonium persulphate with drug. In this method 3mg of the sample & 300mg of potassium bromide was finely ground using motor & pestle. A small amount of the mixture was placed under a hydraulic press compressed 10kg/cm to form a transparent pellets, The pellet was kept in the sample holder & scanned from 4000cm to 400cm in Shimadzu FT-IR spectrophotometer.

The study of the FTIR spectra of tdf demonstrated that the characteristic absorption peaks for the carbonyl group at 1760 cm-1, N-H (amine) stretching at 3400 cm-1, C-O stretching (alcohols) at 1268cm-1 and C-H bending (alkane) at 3051cm-1. This further confirms the purity of TDF And this spectra was compared with the spectra of polymer mixture which reveals that there is no incompatibility was observed between TDF and polymers and peaks.

FT-IR Studies of pure drug

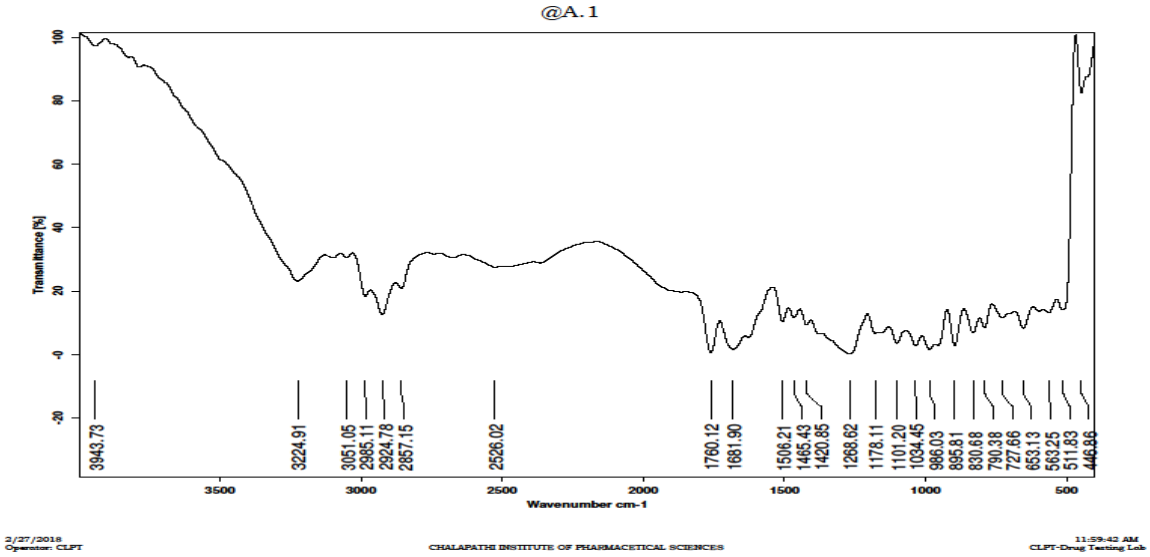

Figure no 2: FT-IR Studies of pure drug.

FT-IR Studies of pure drug and polymers

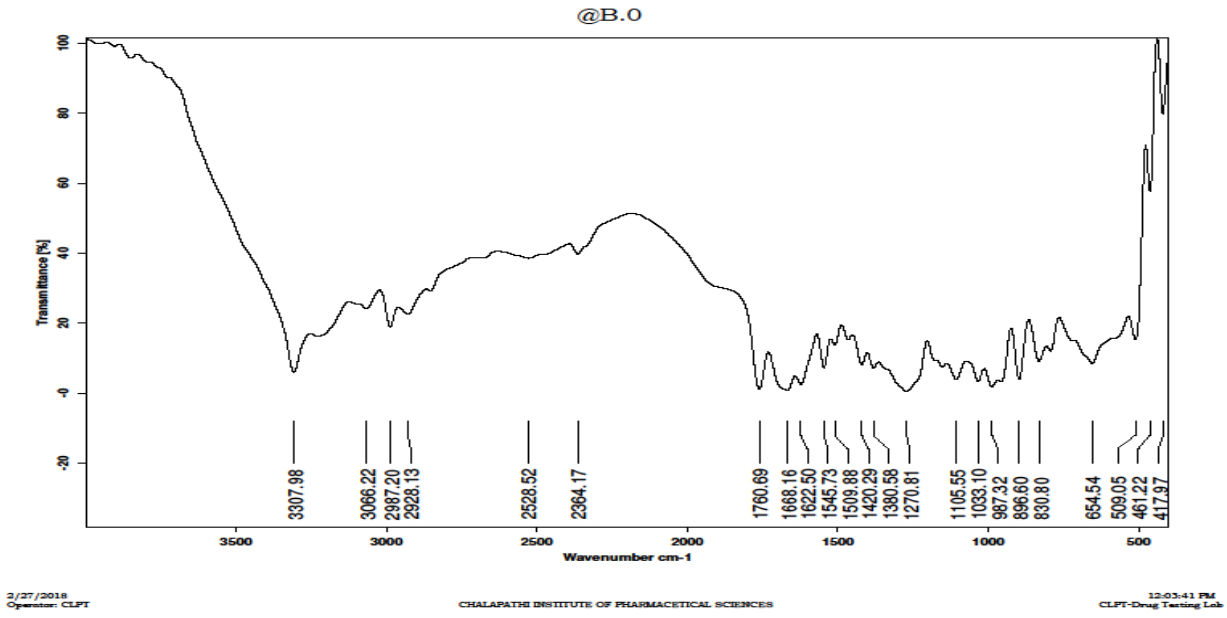

Figure no 3: FT-IR Studies of pure drug + polymers.

Scanning electron microscopy (SEM)

SEM analysis was performed to identify the morphology 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).

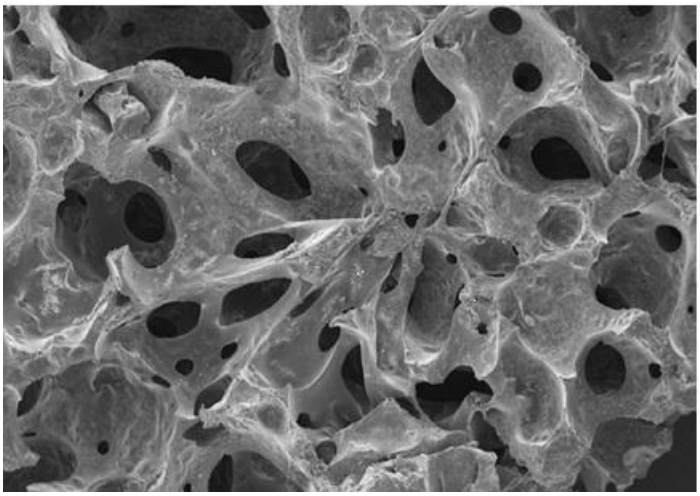

Figure no 4: SEM image of prepared tdf sph.

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

Evaluation Data of Tdf Superporous Hydrogel

Table no 5: Evaluation data of TDF sph.

S.No	Formula	Swelling time(mins) in water	Swelling time(mins) in 0.1 N HCL	Swelling ratio (%)	Mechanical strength (gm)	Porosity (%)
1	F1	15	17	97	237	71
2	F2	12	13	95	243	78
3	F3	8	11	91	279	84
4	F4	6	9	90	285	87

Swelling images of TDF sph

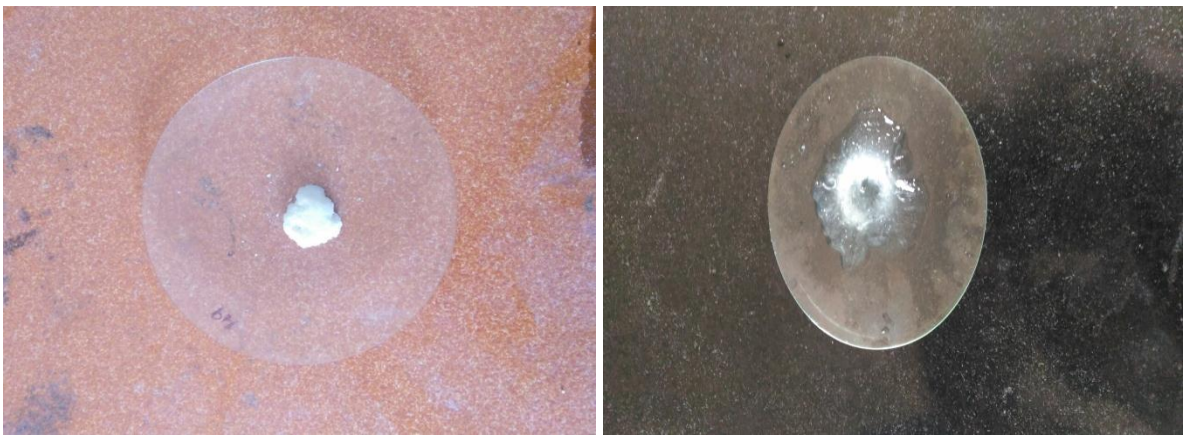

Fig no 5: Sph in dried form and in swelled.

Dissolution Data of Tdf Sph Formulation

Table no 6: Dissolution data of prepared tdf super porous hydrogels.

S.no	Time (mins)	Absorbance	%Drug dissolved	%Drugundissolved	Log %drug undissolved
1)	5	0.077	7.01	92.99	1.973
2)	10	0.127	10.87	89.13	1.949
3)	15	0.149	12.68	87.32	1.940
4)	20	0.164	14.56	85.44	1.92
5)	30	0.183	15.68	84.32	1.91
6)	60	0.207	19.79	80.21	1.88
7)	75	0.231	20.52	79.48	1.86
8)	90	0.264	21.63	78.37	1.85
9)	105	0.327	29.06	70.94	1.81
10)	120	0.413	35.39	64.61	1.79
11)	180	0.549	65.54	34.46	1.67
12)	210	0.611	68.39	31.61	1.59
13)	240	0.798	72.25	27.75	1.49
14)	270	0.843	76.36	23.64	1.44
15)	300	0.891	80.69	19.31	1.37
16)	360	0.943	84.82	15.18	1.18
17)	480	0.987	93.56.	6.44	0.85

% Drug release of F4 formulation of sph TDF

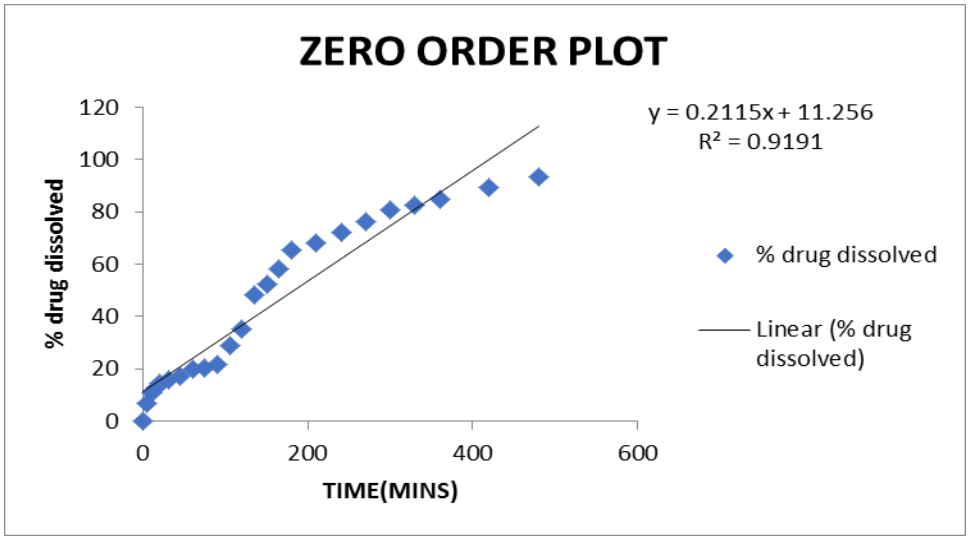

Figure no 5: % Drug release of F4 formulation of sph TDF.

Log % undissolved of F4 formulation of sph TDF

Figure no 6: Log % undissolved of f4 formulation of sph TDF.

Cummulative % drug release of F4 formulation of sph TDF

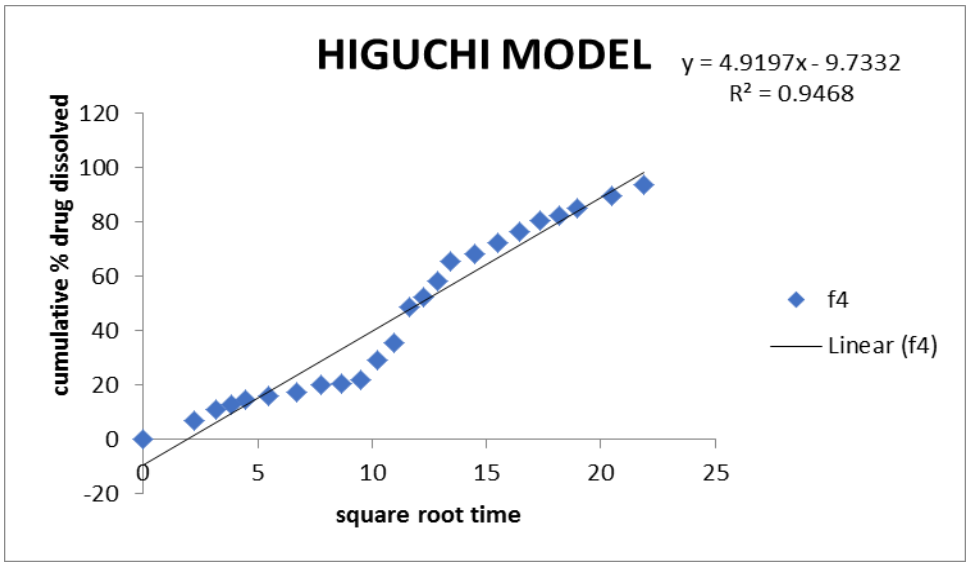

Figure no 7: cummulative % drug release of F4 formulation of sph TDF.

Log cumulative % undissolved of F4 formulation of sph TDF

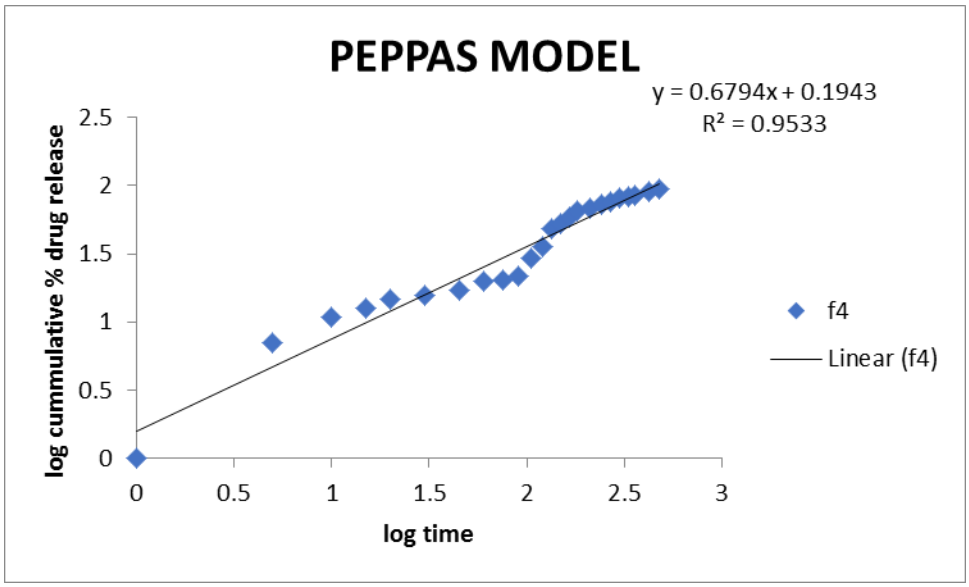

Figure no 8: Log cummulative % undissolved of F4 formulation of sph TDF.

Comaparitive % drug dissolved of F1-F4 formulation of TDF sph.

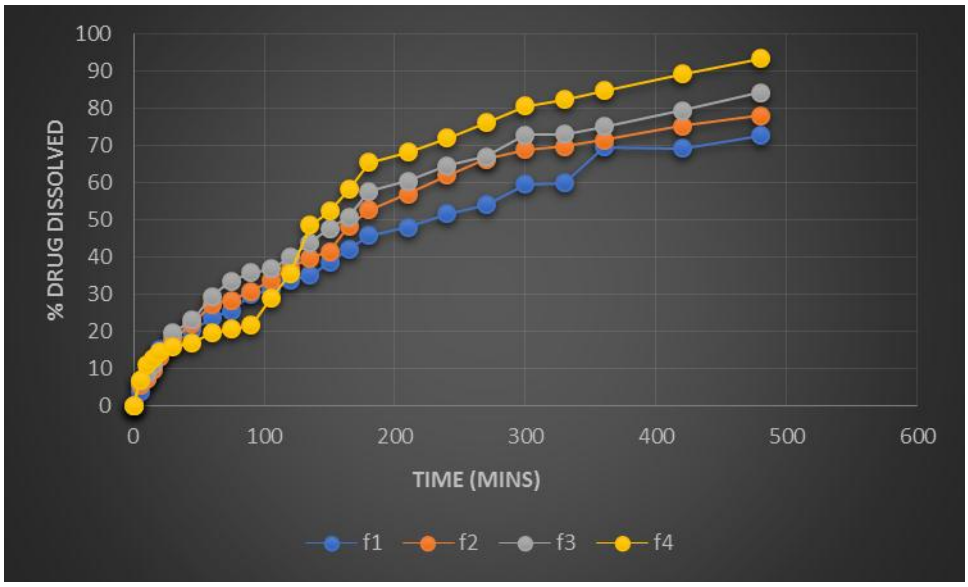

Figure no 9: Comaparitive cummulative % drug dissolved of F1-F4 formulation of tdf sph.

CONCLUSION

From dissolution studies, F4 releases more amount of TDF than other formulations and it was confirmed by performing evaluation studies for the optimised formula. It also showed less swelling time, swelling ratio and shows higher mechanical strength than other formulations. Finally it was concluded that prolonging the therapeutic activity of TDF through sph was successfully achieved. On performing invitro dissolution studies it was observed that F4

releases more amount of drug than remaining formulations due to having required mechanical strength. F1-F3 formulations due to lack of mechanical strength they are easily broked into small pieces and eliminated from the body without showing required therapeutic action. On gradual increase in concentration of composite material porosity, mechanical strength, of sph was increased. By applying drug release kinetics equations to these TDF sph, it was observed that F4 gives regression coefficient values for zero order, first order Higuchi model, Peppas model and these values stated that finalized formulation F4 follows the zero order with Higuchi model drug release.

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