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DEVELOPMENT AND EVALUATION OF TENOFOVIR DISOPROXIL FUMARATE BASED MICROSPONGES LOADED GEL

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Abstract:

Tenofovir disoproxil fumarate (TDF) is a bioavailable prodrug of tenofovir, a potent nucleotide analogue reverse-transcriptase inhibitor with activity against human immunodeficiency virus (HIV) and hepatitis B virus. Microsponges loaded with TDF were prepared by using quasi emulsion solvent diffusion with seven different proportions of polymer Eudragit RS100 and Ethyl cellulose. The developed microsponges were analysed for particle size, production yield, and entrapment efficiency. Scanning electron microscopic images of microsponges revealed that they are spherical in shape and contain pores which reveal that particle size decreases as increase in drug and polymer ratio and entrapment efficiency, production yield are directly proportional to increase in drug and polymer ratio.

Microsponges were then incorporated in to carbopol gel and evaluated for pH, viscosity spreadability and in vitro diffusion study, different kinetic model were also demonstrated. Finally concluded that the F8 was optimised formulation on the basis of pH, viscosity, spreadability and in-vitro diffusion release of drug was found to be 90.22% in 15hrs. In-vitro drug release reflected highest regression value for zero order release model. Thus the formulated microsponges based gel of TDF would be a promising alternative to conventional therapy.

Key words: Microsponges, Microspheres, control release, target release, topical, enhance stability.

Introduction:

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and

modify drug release favourably. Microsponges technology has many favourable characteristics, which make it a versatile drug delivery vehicle. Microsponges Systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as a gel, cream, liquid or powder. MDS can provide increased efficacy for topically active agents with enhanced safety, extended product stability and improved aesthetic properties in an efficient manner[1,2].

Microsponges do not pass through the skin (capable of holding four times their weight in skin secretions). Rather, they collect in the tiny nooks and crannies of skin and slowly release the entrapped drug, as the skin needs it. The microsponges system can prevent excessive accumulation of ingredients within the epidermis and the dermis.

These products are typically presented to the consumer in conventional forms like creams, gels or lotions and they contain relatively high concentration of active ingredients.

The microsponges behave like a reservoir of the active ingredients. These can potentially be used for the controlled delivery of a large variety of substances such as fragrances, emollients, sunscreens, anti-inflammatory, antifungal, antimicrobial agents A microsponge system offers the potential to hold active ingredients in a protected environment and provide controlled delivery onto the skin over a time as well as oral medication to the lower gastrointestinal (GI) tract, where it will be released upon exposure to specific enzymes in the colon [3-5].

In recent years, there has been considerable emphasis given to the development of novel microsponges base drug delivery systems, in order to modify and control the release behaviour of the drugs. By incorporation into a carrier system, it is possible to alter the therapeutic index and duration of the activity of drugs[6].

TDF is a bioavailable prodrug of tenofovir, a potent nucleotide analogue reverse-transcriptase inhibitor with activity against human immunodeficiency virus (HIV) and hepatitis B virus. It was approved for the treatment of HIV infection on the basis of data from clinical trials demonstrating activity in treatment-experienced patients, and it was subsequently shown to be effective when used as a component of initial therapy[7].

Tenofovir disoproxil is a prodrug that is quickly absorbed from the gut and cleaved to release tenofovir. Inside cells, tenofovir is phosphorylated to tenofovir diphosphate (which is analogous to

a *tri*phosphate, as tenofovir itself already has one phosphonate residue), the active compound that inhibits reverse transcriptase via chain termination. It is an inhibitor of cytochrome P450 1A2[8, 9]. It was approved for the treatment of HIV infection on the basis of data from clinical trials demonstrating activity in treatment-experienced patients, and it was subsequently shown to be effective when used as a component of initial therapy. As the bioavailability of TDF is 39%.

The present research work was taken up to develop a topical formulation and improve the therapeutic effect and their bioavailability which results in releasing the drug in controlled manner and avoid first pass metabolism and also to reduces the side effect associated with the topical drug delivery and improve product efficiency with aid of microsponges.

In the present research work, Microsponges loaded with TDF were prepared by using quasi emulsion solvent diffusion with seven different proportions of polymer Eudragit RS100 and Ethyl cellulose. The developed microsponges were analysed for particle size, production yield, and entrapment efficiency.

Experimental:

Materials and Method:

TDF was obtained as a gift sample from Medicamen biotech limited, Haridwar, Uttarakhand, India. Carbopol 940 was provided as a gift sample by QualiKem Fine chemicals, Vadodara. Eudragit Rs.100 was provided as a gift sample by Aan Pharma Pvt Ltd, Gujarat. Acetone, Poly vinyl alcohol, Ethanol, Triethanolamine, Ethyl cellulose, and Dimethyl sulfoxide (DMSO) were purchased from SD Fine Chemicals, Mumbai, India. The remaining other materials used were of analytical grade.

Methodology:

Preparation of microsponges by Quasi Emulsion Solvent Diffusion Method[10-11]:

It contain internal phase which was drug and polymer and external phase was poly vinyl alcohol and water solution. The polymer was prepared by adding given amount of methanol and sonicated after it gets clear solution.

The solution was poured slowly and accurately in external phase which was pVa and water solution under stirred at 1000 rpm. After 2hrs of stirring the product were filtered with whatmann filter paper and dried in dessicator for 12 hrs. Then powdered form microsponges were prepared.

Method of Preparation of TDF Microsponges Gel[12]

Carbopol 934 + soak in water (for 24 hours)

Moderate agitation on magnetic stirrer at 800rpm

Get smooth dispersion & stand for 20-30 minutes

Aqueous solution of triethanolamine was slowly added to above dispersion with agitation

Prepared nanoparticles were added with the help of penetration enhancer

(Dimethyl sulfoxide in ethanol).

Preparation of Trial Batches of Drug Using Different Excipients:

The trials batches of TDF microsponges loaded gel with using different concentration of different excipients or polymers such as eudragit, ethyl cellulose, carbopol, Pva (w/w), and Water.

The composition of TDF with using different concentration of different excipients or polymers such as Ethyl cellulose, Eudragit RS 100 Carbopol, triethanolamine, DMSO, etc.

With the help of using these excipients TDF were converted into firstly microsponges by using Quasi emulsion diffusion method and finally these Microsponges were converted into gel by using carbopol-934 as gelling agent and also using penetration enhancer i.e DMSO.

Drug and excipients compatibility study:

FTIR studies: The successful formulation of a suitable and effective solid dosage form depends upon the careful selection of the excipients. Excipients are added to facilitate administration, promote the consistent release and bioavailability of drug. It's necessary to study the compatibility of excipients with drug. Here, IR spectroscopy was used to investigate and predict any physicochemical interaction between components in a formulation and to the selection of suitable compatible Excipients. FTIR studies were conducted and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing a sample, drug alone and mixture of drug and polymers in KBr and compressing into discs by applying a

pressure of 7 tons for 5 min in a KBr pellets. The pellet was placed in the light path and the spectrum was obtained.

Evaluation of TDF **Gel** [13-16]

Particle size: Particle size of microsponges was determine by optical microscopy by using calibration ocular and stage micrometer under regular polarised light. A minute quantity of microsponges was spread on clean glass slide and their average particle size was calculated by measuring 100 particles of each batch.

SEM: To study morphology and topography of the surface, a microsponge which is prepared were to be coated with gold- palladium under argon at room temperature then surface morphology of microsponges can be studied. Fractured microsponges can also be used to study ultra-structure by SEM.

Production yield: Production of yield of microsponges can be studied by calculating the initial weight of microsponges and initial weight of raw material (drug and polymer).

Production yield = practical mass of microsponge / theoretical mass (drug+ polymer) *100

Encapsulated Efficiency:

It is determined by taking some amount of prepared microsponges made to be dispersed into the solution (methanol) for 24 hrs and then filtered by the filter paper and 1 ml taken from the filtered product and volume make up by the solution upto 100 ml with methanol and then check the drug content under ultraviolet spectrometer at 258nm.

- Calculate actual drug content by (conc.*dilution factor*volume) /1000.
- Encapsulated efficiency is calculated by formula=(actual drug content /theoretical drug content)*100

Evaluation of Microsponge Loaded Gel[17]:

Visual investigation: Visual inspection of microsponges loaded gel was done on the bases of colour, texture and appearance.

pH measurement: pH of the gel was calculated by using digital pH meter. One gram of gel was dissolved in 100 ml of distilled water and stored for 1hr. The measurement of pH was done.

Drug content: For the estimation of the drug in gel, TDF was extracted from 1 gm of gel formulation with 50 ml of phosphate buffer 6.8 and mixture was filtered through whatman filter paper. From this, 2 ml was pipette out and made upto 10 ml. The absorbance of the sample was determined spectrophotometrically at 258 nm. The concentration of TDF was estimated from the calibration curve.

Spreadability:

Spreadability is determined by apparatus suggested by Spreadability test apparatus. It consists of wooden block, which is provided by a pulley at one end. By this method, Spreadability is measured on the basis of "Slip" and "Drag". A ground glass slide is fixed on this block. A sample of 0.1 g of gel under study is placed on this ground slide.

The gel is fixed on the formula was pressed between two slides and a 1 kg weight is placed on the top of two slides and left for about 5 min to expel air and to provide a uniform film of the gel between two slides. Excess of the gel is scrapped from edges. The top plate is then subjected to pull the weight. With help of string attaches to the hook and the time required by top slide to cover the distance is noted.

Spreadability was calculated by using the formula,

$$S=M.L/T,$$

Where,

S = Spreadability,

L = Length of glass slide,

M = weight tied to upper slide,

T = Time taken to separate the slides.

Extrudability: It is a usual empirical test to measure the force required to extrude the material from tube. The method adopted for evaluating gel formulation for Extrudability is based upon the quantity in percentage of gel and gel extruded from lacquered aluminium collapsible tube on application of weight in grams required at least 0.5cm ribbon of gel in 10 sec. The measurement of Extrudability of each formulation shows the triplicate and averages value is presented.

Extrudability = Applied weight to extrude the gel from tube (in gm)/ Area (in cm^2).

In-vitro drug release: The in-vitro drug release studies were carried out using Franz diffusion cell. The formulation was applied on dialysis membrane which was placed between the donor and receptor compartment of the Franz diffusion cell. The temperature of the cell was maintained at 37˚C by circulation jacket. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. A similar blank set was run simultaneously as a control. Sample 5 ml was withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media. Samples were analysed

spectrophotometrically at 258 nm and % drug release and control was used as the actual reading in each case. % drug release

Kinetic study: To study the release of drug pattern from microsponge loaded gel was done by using in-vitro data and treated by conventional mathematical equation model. (Zero order first order higuchi model korsmeyer peppas model. The values of r which is correlation coefficient, k is release constant and n diffusion exponent obtain from the curve fitting of release data were determine suitable release data were estimated a release model for the formulation.

Zero order models: Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be presented by the following equation:

$$Q = K_0 t$$

Where, Q is the amount of drug released at time t,

K_0 is the zero order rate constant expressed in units of concentration/time.

and t-is the time in hours.

The pharmaceutical dosage forms following this profile, release the same amount of drug by a unit of time. This model represents an ideal release profile in order to achieve the prolonged pharmacological action[18].

First order model: The release of drug follow first order model of kinetics can be determine by equation.

$\text{Log } C = \log C_0 - Kt/2.303.$

Where, k is the first order rate constant and t is time.

and C_0 is the initial concentration of drug.

The graph was plotted between log cumulative% of the drug remain and time, a straight line was obtain with a slope of –K/2.303. This model is used to determine absorption or elimination of the drug. This drug model is used in pharmaceutic to determine the dissolution of drug in dosage form for the drug which are water soluble.

Higuchi model: The equation which is to study this model is

ft = Q= KH X t1/2

Where, KH is the higuchi dissolution constant the graph was plotted between cumulative % drug release and square root of time.

Korsmmeyer-peppes model: This model is determined by following equation.

Mt/M= Ktn

Where, Mt/M is the release of drug at time.

t and k is release rate constant and n is the release exponent.

The value of n is used to characterize different release for cylindrical shape matrix. The data was plotted between log cumulative% drug release and time (log).

Results and Discussion:

Drug excipients compatibility studies FTIR:

The drug of TDF and other excipients were taken in ratio 1:1 and well mixed that by using of poly bags. Then after mixture of drug and excipients was transferred from poly bag to glass vials & sample was put in to the stability chamber at 40^0C for 21days.

Through Fourier transform Infrared Spectroscopy: The compatibility study of drug excipients was done by FTIR analysis.

Possible interactions between drug and polymer were investigated by FTIR. FT-IR of pure TDF shown characteristic stretching absorption bands of N-H bending group at 1626 cm^{-1}, C=O stretching (amide) absorption bands at 1678 cm^{-1}, C=O stretching (alcohol) absorption bands at 1309 cm^{-1}, S=O stretching shows stretching at 1281 cm^{-1} and Also exhibited C-N vibration at 1037 cm^{-1}.

From the Fig.1, it can be concluded that the IR spectra of TDF and different excipients clearly indicates that overall there was no alteration in peaks of TDF pure drug and different excipients in the formulation, suggesting that there was no interaction between drug & excipients.

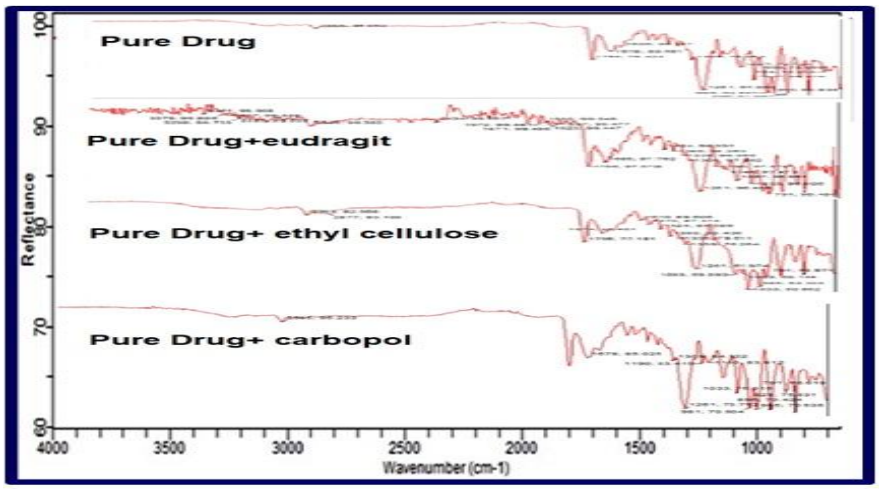

Fig 1: FTIR of pure drug TDF, Drug + eudragit, Drug + ethyl cellulose, Drug + carbopol.

Evaluation results of microsponges:

Particle size: Particle size was evaluated by the help of optical microscopy of different formulation shows that as ratio of drug and polymer increases particle size decreases.

SEM (Scanning Electron Microscopy): It was observed that the optimised Microsponge (F1 and F8) are having smooth surface, porous and spherical in shape they were studied under 100 and 800x respectively.

The production yield of the microsponges was determined by calculating accurately the initial weight of the raw materials and the final weight of the microsponges obtained. In all the prepared microsponges shows good production yield. The production yield wre calculated by using the below formula.

Production yield = practical mass of microsponge / theoretical mass (drug+ polymer) X 100

Table-1: Composition of trial batches of TDF microsponges with combination of different concentration of polymers.

FC	Microspong	EU	EC	PVA	Water	Stringger
FCN_1	200 mg	300 mg	-	80	40	1000
FCN_2	200 mg	500 mg	-	80	40	1000
FCN_3	200 mg	700mg	-	80	40	1000
FCN_4	200 mg	900 mg	-	80	40	1000
FCN_5	200 mg	300 mg	300 mg	80	40	1000
FCN_6	200 mg	500 mg	500 mg	80	40	1000
FCN_7	200 mg	700 mg	700 mg	80	40	1000
FCN_8	200 mg	900 mg	900 mg	80	40	1000
FCN_9	200 mg	--	300 mg	80	40	1000
FCN_{10}	200 mg	--	500 mg	80	40	1000
FCN_{11}	200 mg	--	700 mg	80	40	1000
FCN_{12}	200 mg	--	900 mg	80	40	1000

**FC= Formulation Code, FCM=Formulations containing microsponges, EU = Eudragit RS 100, EC= Ethyl Cellulose, DM= Dichloromethane, PVA= Poly Vinyl Alcohol*

Table-2: Composition of TDF Microsponges loaded gels.

FC	TDF	Microsponges	carbopol	DMSO (ml)	Triethanolamine	Ethanol	Water	Stirrer
F1	200 mg	200 mg	350 mg	2	2	3	q.s to 50	1000
F2	200 mg	200 mg	350 mg	2	2	3	q.s to 50	1000
F3	200 mg	200 mg	350 mg	2	2	3	q.s to50	1000
F4	200 mg	200 mg	350 mg	2	2	3	q.s to 50	1000
F5	200 mg	200 mg	350 mg	2	2	3	q.s to 50	1000
F6	200 mg	200 mg	350 mg	2	2	3	q.s to50	1000
F7	200 mg	200 mg	350 mg	2	2	3	q.s to 50	1000
F8	200 mg	200 mg	350 mg	2	2	3	q.s to 50	1000
F9	200 mg	200 mg	350 mg	2	2	3	q.s to50	1000
F10	200 mg	200 mg	350 mg	2	2	3	q.s to 50	1000
F11	200 mg	200 mg	350 mg	2	2	3	q.s to 50	1000
F12	200 mg	200 mg	350 mg	2	2	3	q.s to50	1000

Evaluation Results of Microsponges Loaded Gel:

Evaluation of Visual Appearance, pH and Drug Content of Gel: All the developed formulation of gels of parameter detected by such as measurement of visual appearance, pH and drug content. Visual Appearance, pH and Drug Content results were shown in table 3.

Table-3: Evaluation of visual appearance, pH, drug content, Spreadability and Extrudability of Microsponges Loaded Gel.

FC	Visual appearance	pH	Drug content (%)	Entrapped Efficiency (%)	Spreadability (in cm^2)	Extrudability
F1	Clear	6.69	98.95%	49.47%	113.04	+++
F2	Creamish yellow	6.76	92.45%	46.22%	98.47	++
F3	Creamish light yellow	6.79	98.36%	49.18%	116.84	+++
F4	Brown	6.82	93.02%	46.51%	120.57	++

F5	Yellowish brown	6.64	96.94%	48.32%	132.66	+++
F6	Orange brown	6.78	97.31%	48.65%	109.27	+++
F7	Creamish	6.69	95.52%	47.76%	95.57	+++
F8	Creamish yellow	6.90	99.77%	49.97%	111.22	+++
F9	Creamish light yellow	6.66	96.34%	48.17%	110.34	++
F10	Brown	6.72	98.21%	49.10%	102.55	+++
F11	Yellowish brown	6.88	93.11%	46.55%	97.32	+++
F12	Orange brown	6.79	96.03%	48.01%	130.55	+++

**Fc= Formulation Code*

The pH value of all prepared formulations was found to be in the range of 6.6 to 6.9, which was considered to be acceptable to avoid the risk of irritation upon application to the skin. Drug content studies for microsponges gel formulations were carried out. Drug content of all formulations are shown in table 3. The drug content of the formulations showed that the drug was uniformly distributed in the gels. From above result, microsponges gel (F8) has higher drug content. Use of the higher amounts of PVA and polymer while preparing microsponges at a higher drug: polymer ratios caused slightly an increased viscosity of the dispersed phase. When solvents in inner phase were diffused out, nearly all of the dispersed phase was converted to the form of solid microsponges and separated particles appeared. The highest drug loading efficiency (results were shown in Table 3) of these formulations could be explained through the fact that the amount of polymer to per unit drug was greater than that in other formulations.

The values of spreadability indicated that the gel was easily spreadable by a small amount of shear. Spreadability of microsponges gel (F8) was found to be 7.5g. Cm/sec; indicating that spreadability of drug loaded microsponges gel was good. Spreadability results are shown in table 3.

All the microsponges gel loaded formulations were tested for Extrudability. All most all the formulations show excellent Extrudability. Few formulations showed good Extrudability. It was observed that as the polymer concentration is increased the Extrudability gets decreased. Extrudability results are shown in table 3. The in-vitro drug release studies were carried out using Franz diffusion cell. The formulation was applied on dialysis membrane which was placed between the donor and receptor compartment of the franz diffusion cell. The temperature of the cell was maintained at 37˚C by circulation jacket using phosphate buffer pH 7.4.

The prepared TDF microsponges loaded gel formulations drug release was carried out up to 15 hours. From the in-vitro release data it was noticed that the drug release was ranges from 68.14 – 90.22%. The variation of drug release may be due to D/P ratios. It was observed that the formulation F8 showed a higher amount of drug diffused at the end of 15 h. The drug release was found to be 90.22%. The in-vitro drug release studies results were shown in Fig 2-4. The in-vitro release profiles of TDF from its various microsponges gel formulations in table 4.

Table-4: % drug release of different TDF microsponges loaded gel formulation.

Time	Percentage drug relase of different formulation											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
1	6.048	6.36	7.04	4.48	6.86	7.12	7.14	7.68	6.09	5.33	4.89	4.26
2	11.35	11.78	12.88	12.88	14.8	12.67	13.87	14.26	13.78	14.67	14.78	14.66
3	18.9	18.98	19.9	18.76	21.33	22.78	23.78	26.24	20.89	21.66	25.66	22.43
4	29.02	30.77	32.92	29.84	31.21	28.78	31.78	33.46	33.66	34.77	28.66	27.62
5	37.36	38.78	41.84	38.78	42.47	35.33	38.66	40.12	39.09	38.09	34.88	33.74
6	45.68	48.8	49.85	45.56	49.44	42.42	46.78	48.24	45.66	49.8	48.09	46.28
7	47.21	49.67	51.66	47.55	51.76	50.66	50.78	53.78	52.89	55.78	53.09	50.26
8	49.55	50.55	54.23	52.67	55.65	52.88	52.33	58.84	50.66	57.6	53.59	52.89
9	55.57	52.88	56.77	53.12	56.88	53.89	56.77	61.26	54.21	59.26	57.89	56.68
10	60.22	59.67	58.11	56.32	58.23	54.9	62.9	65.22	63.09	64.22	63.97	60.32
11	64.46	62.11	60.44	57.66	60.34	56.88	64	70.22	65.09	67.46	64.09	62.21
12	72.24	69.55	61.09	61.45	63.9	66.89	72.89	75.64	70.9	69.22	64.9	64.12
13	75.22	71.66	64.11	62.23	66.02	67.27	74.9	80.22	73.78	70.12	66.09	66.9
14	80.24	74.32	66.05	65.09	65.08	68.92	77.89	84.84	75.87	71.46	68.09	67.09
15	87.26	77.9	70.01	68.14	68.25	72.54	80.6	90.22	77.09	73.14	71.42	69.12

It was observed that the formulation F8 showed a higher amount of drug diffused 90.22% at the end of 15 h. while other Formulation showed the lower amount of drug diffused at the end of 15 h.

The model fitting analysis like zero order, first order and higuchi plot were done by comparing the coefficient of regression (R2) values for F8 formulations shown in table 5. The value on ‘N’ from the korsmeyer and peppas plot determines the mechanism of release.

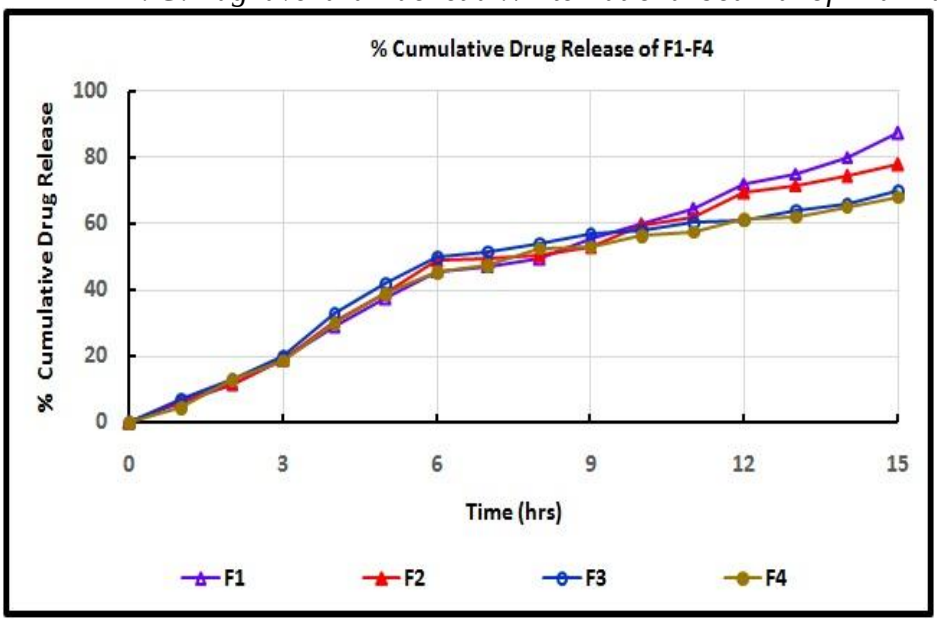

Fig 2: In-vitro drug release from TDF microsponges gel formulation F1- F4.

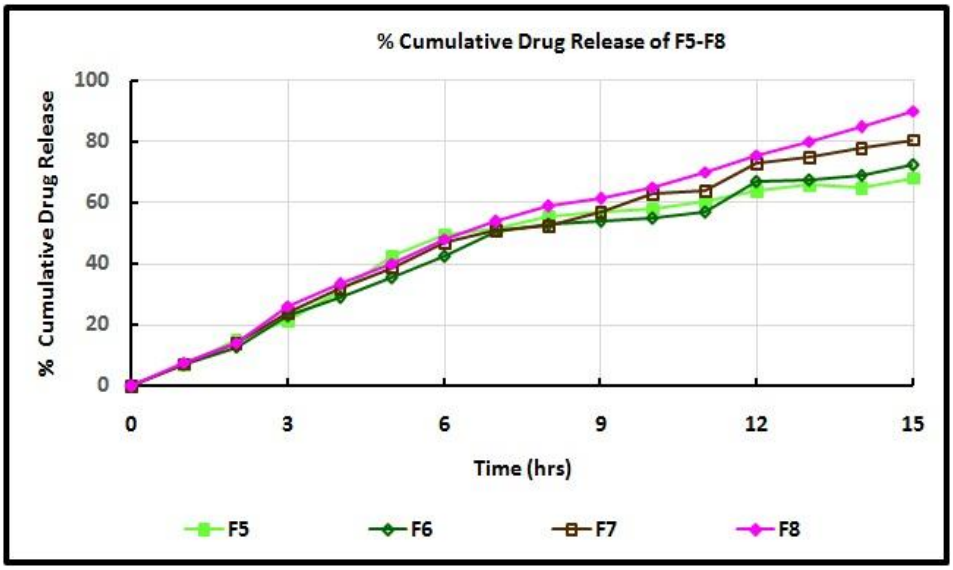

Fig 3: In-vitro drug release from TDF microsponges gel formulation F5- F8.

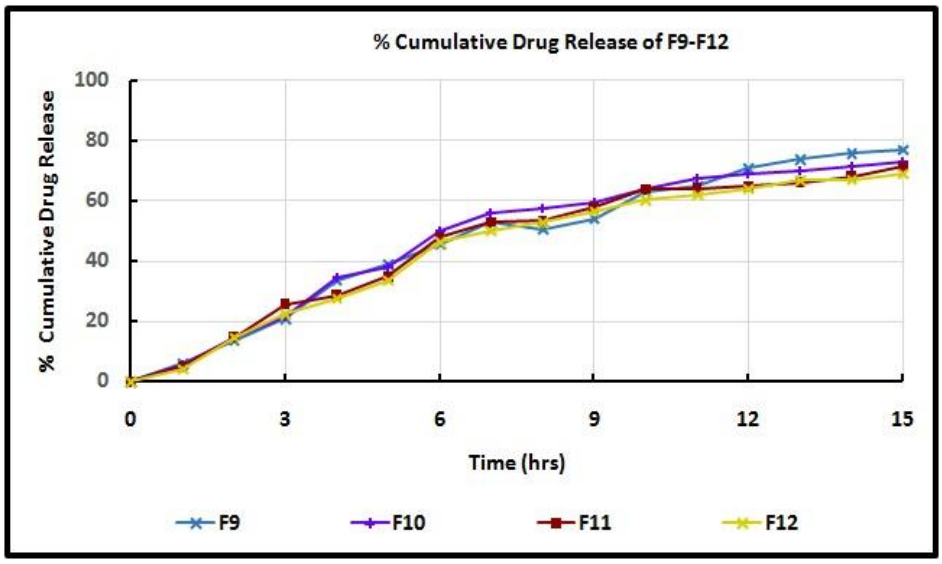

Fig 4: In-vitro drug release from TDF microsponges gel formulation F9- F12.

Table-5: Drug release kinetic with model fitting of F8.

Model Fitting	**R^2**	**Parameters for Korsmeyer-Peppas Equation**	
Zero order	0.9672	**N**	0.8785
1st order	0.9877	**K**	2.5101
Higuchi matrix	0.9297		Hixon Crowell
Peppas	0.9797	**Best fit model**	
Hix.crow	0.9923	Anomalous Transport	
Mechanism of release			

Conclusions:

In the present research work, it was concluded that Developed and evaluated TDF microsponges loaded gels by reducing first pass metabolism and increasing the bioavailability. It is a nucleoside reverse transcriptase inhibitors (NRTIs) used to treat HIV infections.

The microsponges were prepared by quasi emulsion diffusion method using two different polymers in different ratios Eudrait and Ethyl cellulose. All formulation of gels was prepared by using carbopol and DMSO showed the better homogenecity, Spreadability, Extrudability and uniformity. pH ranges of all formulations were under the standard limits.

Finally concluded that the F8 was optimised formulation on the basis of pH, viscosity, spreadability and in-vitro diffusion release of drug was found to be 90.22% in 15hrs. In-vitro drug release reflected highest regression value for zero order release model. Thus the formulated microsponges based gel of TDF would be a promising alternative to conventional therapy.

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