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Formulation and evaluation of triclabendazole nanoparticles

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Abstract

The aim of the study is the formulation and evaluation of triclabendazole nanoparticles. There is a need to develop alternative novel drug delivery formulations of Triclabendazole to improve its intestinal absorption and also reduce its side effects during regular therapy. The Triclabendazole nanoparticles were prepared by hot homogenization method under high magnetic stirring using stearic acid as lipid, and poloxamer 188 was used as a surfactant. Initial pre-formulation studies using FTIR spectroscopy reveal no interactions between Triclabendazole and other excipients; hence, they can be used for the preparation of nanoparticles. The entrapment efficiencies varied from a minimum of 44.63 ± 0.94 to 83.15 ± 0.62%, and it can be concluded that higher amount of lipid is necessary for obtaining a good entrapment efficiency. The drug content of Triclabendazolenanoparticles for all formulations ranges from 65.9 % to 98.4%. Triclabendazole, being a hydrophobic drug, has moderate entrapment efficiency. A spherical shape was observed for the particles, and the particles had a smooth morphology when examined under SEM. In vitro release studies of the formulations carried out in pH 7.4 PBS showed that the total amount of drug is released for 9hrs with sustained effect. The formulations showed a drastic increase in size when stored at room temperature, where particles increased from an initial to 346.8 ±8.8 nm at the end of 1 month to 899.8 ± 5.9 nm at the end of 2 months. The entrapment efficiency of the formulation was determined at each interval to ensure that the drug molecules didn't undergo any degradation during storage.

Keywords: Triclabendazole; Nanoparticles; Particle size; Entrapment efficiency.

1. Introduction

Targeted delivery of a drug molecule to specific organ sites is one of the most challenging research areas in pharmaceutical sciences. By developing colloidal delivery systems such as liposomes, micelles, and nanoparticles, new frontiers have opened for improving drug delivery [1]. Nanoparticles, with their unique characteristics of small particle size, large surface area, and the capability of changing their surface properties, have numerous advantages compared with other delivery systems. Nanoparticles are solid colloidal particles ranging from 10 to 1000 nm (1.0 µm), in which the active principles (drug or biologically active material) are dissolved, entrapped, and to which the functional code is adsorbed or attached [1]. In recent years, significant effort has been devoted to developing nanotechnology for drug delivery since it offers a suitable means of delivering small molecular weight drugs, as well as macromolecules such as proteins, peptides, or genes to cells and tissues and prevents them against enzymatic degradation [2]. The advantages of nanoparticles as drug delivery systems are that they are biodegradable, non-toxic, and can be stored for extended periods as they are more stable [2]. Nanoparticle is aqueous colloid-al dispersions, the matrix comprising solid biodegradable lipids. Nanoparticles combine the advantages and avoid the drawbacks of several colloidal carriers of its class, such as physical stability, protection of incorporated labile drugs from degradation, controlled release, and excellent tolerability [3]. Improving the bioavailability of Triclabendazole may result in better outcomes of treatment [4].

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Our study focused on enhancing Triclabendazole absorption by improving lipid and water solubility and avoiding intestinal metabolic breakdown [3].

2. Materials and Methods

2.1. Formulation of Triclabendazole Nanoparticles

Nanoparticles of Triclabendazole were prepared by hot homogenization method under high-speed magnetic stirring using stearic acid as lipid, Bees wax act as Wax, and poloxamer 188 as surfactant. Overall, eight formulations were prepared by changing the different ratios of lipids &Wax. The percentage of surfactant used ranged from 0.5, 0.75, 1.0 & 1.25%).

2.2. Formulation Design

2.2.1. Formulation Development of Triclabendazole Nanoparticles

The Nanoparticles of Triclabendazole were prepared by the hot homogenization method under high-speed magnetic stirring with slight modifications. An accurately weighed quantity of lipid & Wax was heated carefully in a water bath at 80 °C to form a melted phase of the lipid & Wax [4]. Triclabendazole was added and heated to this melted lipid until a clear homogeneous phase was formed. Simultaneously, a weighed quantity of the surfactant was added to the water to start an aqueous phase which is also heated to 80°C. The hot lipid phase was dispersed in the surfactant solution and stirred on a magnetic stirrer for 30 minutes continuously to form solid lipid nanoparticles of Triclabendazole [6].

Table 1 Composition of Triclabendazole Nanoparticles formulations

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Triclabendazole (mg)	30	30	30	30	30	30	30	30
Stearic acid (mg)	160	160	160	160	160	160	120	120
Bees Wax (mg)	110	110	130	130	160	160	140	140
Polaxamer (mg)	210	210	210	210	210	210	210	210
Span 80 (ml)	1.5	0.85	2.0	1.35	1.5	0.85	2.0	1.35
Ethanol (ml)	20	20	110	20	20	20	20	20

2.3. Compatibility Studies

2.3.1. FT-IR Studies

The purity of the drug was determined by subjecting Triclabendazole to I.R. analysis using Fourier Transform Infrared Spectroscopy (FT/IR 8400S (C.E.) Shimadzu spectrophotometer). The samples were prepared as the KBr pellet method. Drug and potassium bromide are mixed in a ratio of 1:100, and a pellet is formed by compressing at 8 tons/mm^2 pressure [7]. The Shimadzu FT-IR spectrophotometer selected the wavelength range from 400 - 2000 cm-1. Similarly an I.R. peak is obtained for the physical mixture of Triclabendazole, Stearic acid, Beeswax, Polaxamer 188, and combinations.

2.4. Surface Morphological Studies

2.4.1. Scanning Electron Microscopy

The prepared Nanoparticle formulation was examined for surface morphology and shape using a scanning electron microscope. The scanning electron microscopy was performed on Hitachi high technologies corporation-S4800 type II, Japan. The samples were dried thoroughly in vacuum desiccators before mounting them on brass specimen studies [8].

2.5. Characterization Studies [9-12]

2.5.1. Determination of Particle Size by zeta sizer

The average mean diameters and size distribution of Tacrine HCl loaded nanoparticles were found by photon correlation spectroscopy using a Zeta sizer (nano ZS90, Malvern Instruments) at 25°C. The samples were kept in a polystyrene cuvette, and the readings were noted at a 90° fixed angle.

2.5.2. Determination of Zeta Potential by zeta sizer

The electrophoretic mobility (zeta potential) measurements of drug-loaded nanoparticles were made using a Zeta sizer (Nano ZS90, Malvern Instruments). The samples were placed in a polystyrene cuvette (at 25°C), and a Zeta dip cell was used to determine the potential.

2.5.3. Determination of Entrapment Efficiency (%)

Using the Eppendorf centrifuge, 2ml of the formulation was taken and ultra-centrifuged at 13, 000 rpm at 4°C for 90 minutes. The supernatant was recovered using a micropipette and analyzed using the U.V. method for free drug content.

$$\text{Encapsulation efficiency: } \frac{\text{Amount of drug added} - \text{amount of free drug in the supernatant}}{\text{Amount of drug added}} \text{ x } 100$$

2.5.4. Drug content determination

50mg of Triclabendazole nanoparticles was crushed and suspended in water to extract the drug from the nanoparticles. After 24 h, the filtrate was assayed spectrophotometrically at 306 nm for drug content against water as blank.

2.6. *In Vitro* Release Studies

The *in vitro* release studies were carried out using pH 7.4 phosphate buffer by dialysis bag method with a molecular weight cut off of 12,000- 14,000 Da. Precisely 2 ml of the formulation was placed in the dialysis bag by sealing both ends with the help of clips. The dialysis bag is dipped in a 50 ml dissolution medium maintained at 37 ± °C and stirred at 100 rpm using a magnetic stirrer [13]. 2 ml of the buffer solution is removed at an interval of 1, 2, 3, 4, 6, 7, 8 and 10 hrs and is replaced by an equal amount of fresh buffer to maintain sink conditions. The drug content in the samples was determined by ultra-visible spectroscopy at $\lambda_{max}$of 306 nm [14].

2.7. Stability Studies as per ICH guidelines

The stability of formulations during storage includes preserving initial particle size and preventing degradation reactions. Stability studies were carried out for the freeze-dried method. The samples were stored at room temperature (25 to 30 °C) and in the refrigerator (3 to 5 °C) over two months. Samples were evaluated at 0, 1, and 2 months for their particle size, entrapment efficiency, and changes in their physical appearance [15].

3. Results and Discussion

3.1. Drug excipients compatibility studies

Table 2 F.T. IR Interpretation Data for Triclabendazole

Frequency (cm^{-1})		**Bond**	**Functional group**
Observed	obtained		
850–550	742.87	C–Cl stretch	alkyl halides
1250–1020	1069.93	C–N stretch	aliphatic amines
1250–1020	1247.59	C–N stretch	aliphatic amines
1740–1720	1731.94	C=O stretch	aldehydes, saturated aliphatic
3500–3200	3463.35	O–H stretch, H–bonded	alcohols, phenols

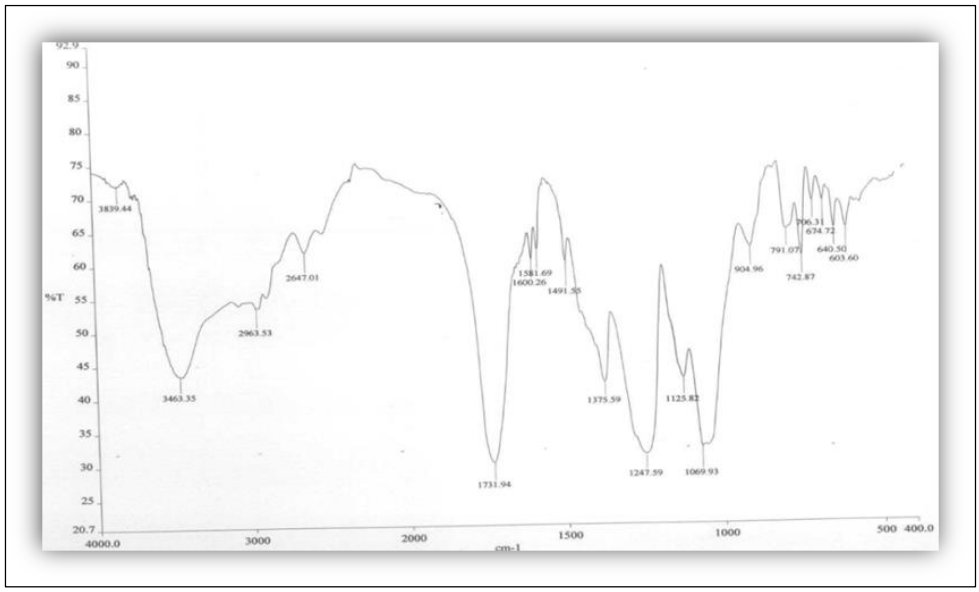

Figure 1 FT IR Spectra of Triclabendazole

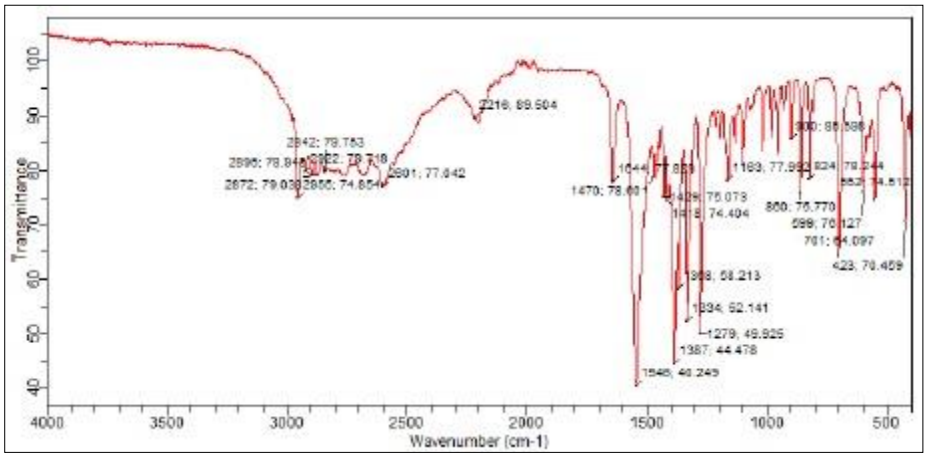

Figure 2 FTIR spectra of Stearic acid

Table 3 Interpretation data of FTIR spectra of Stearic acid

I.R. Absorption bands (cm^{-1})		**Bond**	**Functional groups**
Observed peak	**Characteristic peak**		
2955,2895 2922,2872	3000-2850 3400-3250 3100-3000	C-H Stretch N-H Stretch C-H Stretch	Alkenes 1^0,2^0 amines, amides aromatics
1644 1546	1650-1580 1600-1585	C-H Bend C-C Stretch(in ring)	Ten amines Aromatics
1429 1470	1550-1475 1500-1400	N-O Asymmetric Stretch C-C Stretch (in a ring)	Nitro compounds Aromatics
1368,1387 1334,1279	1335-1250 1360-1290	C-N stretch	Aromatic amines Nitro compounds

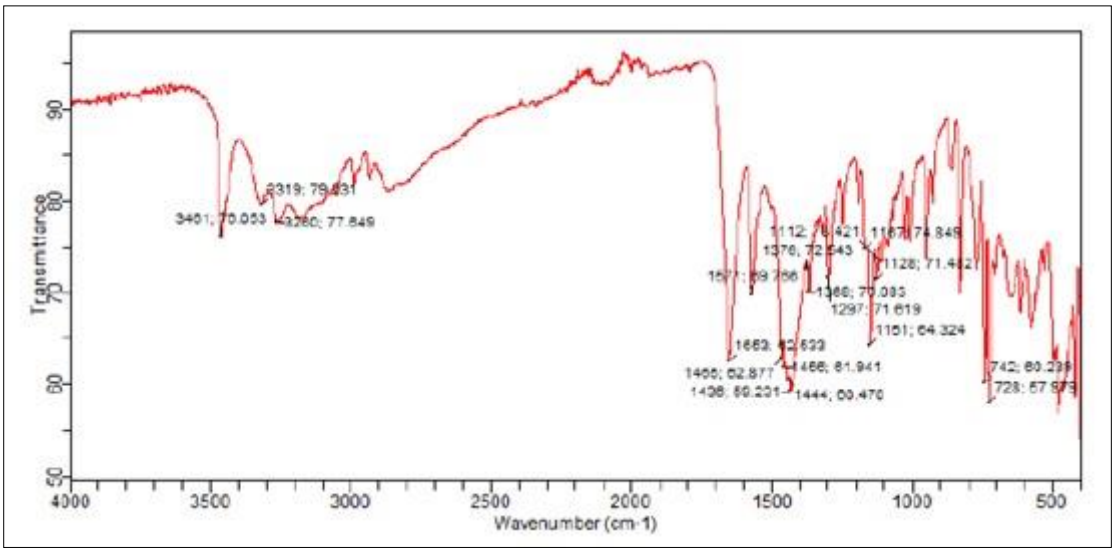

Figure 3 FTIR spectra of Beeswax

Table 4 Interpretation data for FTIR spectra of Beeswax

Frequency (cm^{-1})		**Bond**	**Functional groups**
Observed peak	**Characteristic peak**		
690-515(m)	**641.88**	**C-Br Stretch**	**Alkyl halides**
950-910(m)	633.87	O-H Bend	Carboxylic acids
1320-1000(m)	1297.71 1151.64	C-O Stretch	Alcohols, Carboxylic acids, Esters, and others
1470-1450(m)	1465.62 1456.61	C-H Bend	Alkenes

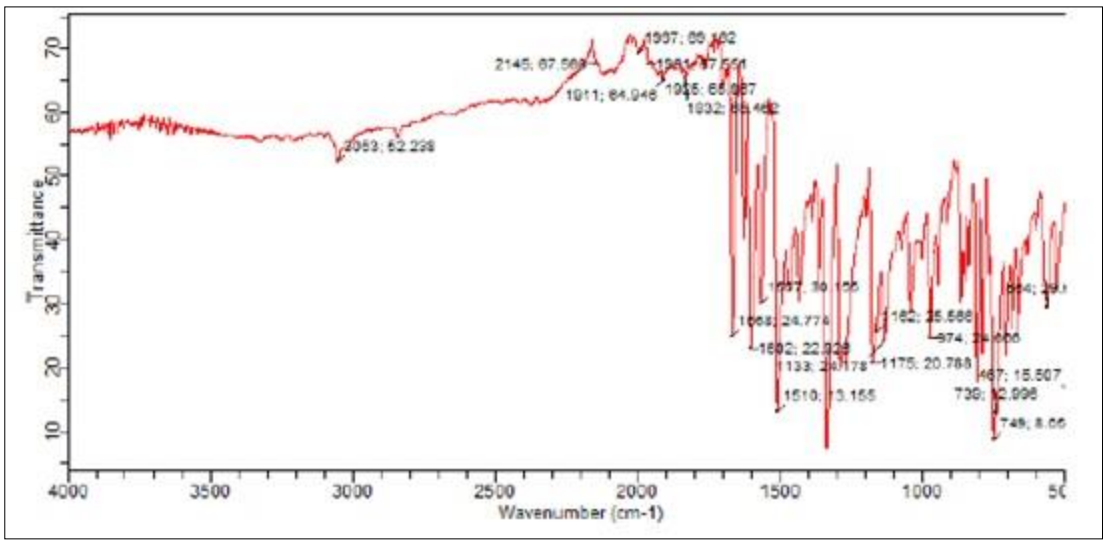

Figure 4 FTIR spectra of Poloxamer 188

Table 5 Interpretation data for Poloxamer 188

Frequency (cm^{-1})		Bond	Functional groups
Observed peak	**Characteristic peak**		
1320–1000	1175	C–O stretch	Alcohols, carboxylic acids
1300–1150	1133	C–H wag (–C.H. $_2$X)	Alkyl halides
1500–1400	1423	C–C stretch (in–ring)	Aromatics
1650–1580	1602	N–H bend	1° amines

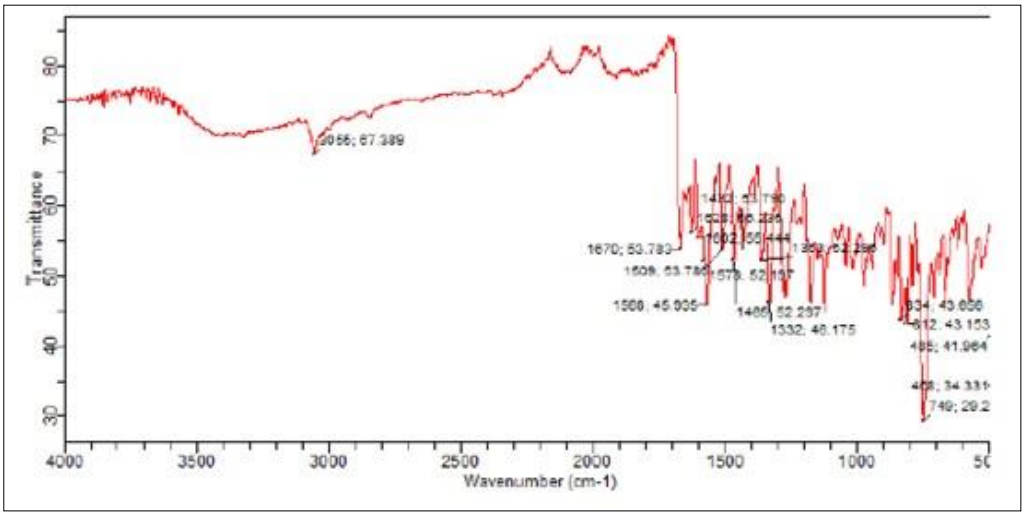

Figure 5 FTIR spectra of drug and polymer mixture

Table 6 Interpretation data for Triclabendazole + polymer mixture

Frequency (cm^{-1})		Bond	Functional groups
Observed peak	**Characteristic peak**		
3055,2955 2922,2895 2872	3300-2500 3400-3250	O-H stretch N-H Stretch	Carboxylic acids 1^0,2^0 amines, amides
1128 1167	1320-1000	C-O Stretch	Alcohols, Carboxylic acids, esters & others
1628 1578	1650-1580 1600-1585	N-H Bend C-H Stretch (in-ring)	Ten amines Aromatics
1509 1432	1550-1475 1500-1400	N-O Asymmetric Stretch C-C Stretch(in-ring)	Nitro compounds Aromatics

3.2. Formulation of Triclabendazole Nanoparticles

Nanoparticles of Triclabendazole were prepared by hot homogenization method under high-speed magnetic stirring using stearic acid as lipid, Bees wax act as Wax, and poloxamer 188 as surfactant. Overall, eight formulations were prepared by changing the different ratios of lipids &Wax. The surfactant percentage ranged from 0.5, 0.75, 1.0 & 1.25%).

3.3. Determination of Particle Shape and Surface Morphology

3.3.1. By Using Scanning Electron Microscopy

Scanning electron microscopy images revealed the particles' smooth texture and spherical morphology.

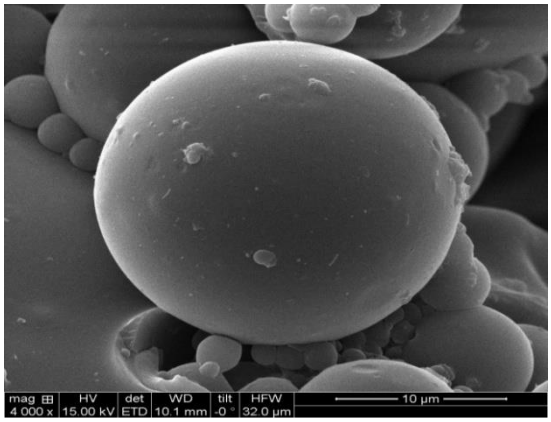

Figure 6 Scanning Electron Microscope image of the Nanoparticles

3.4. Determination of particle size by photon correlation spectroscopy

The Zeta average diameters of the formulations are mentioned in Table 11. The values show that the size of the nanoparticles for all formulations ranges from 110.6 ±1.5 nm to 400.9 ± 2.4nm. The effect of various concentrations of lipids and surfactants on the size of the particles was studied. The Zeta size of the formulation is shown below.

Table 7 Zeta average diameter and zeta potential of the particles

Formulation code	Zeta Average Size (nm)	Polydispersive index (PDI)	Zeta potential (mV)
TNF1	112.7 ± 1.6	0.216 ±0.23	-4.72 ±1.4
TNF2	212 ±1.24	0.305±0.4	-1.17 ±1.8
TNF3	228 ± 2.4	0.356 ±0.12	-4.28 ±1.8
TNF4	368.4 ±0.98	0.522 ±1.3	-0.05 ±1.7
TNF5	333 ± 1.42	0.408 ±1.9	-9.16 ±1.2
TNF6	250 ± 0.58	0.216±1.4	-0.262 ±1.3
TNF7	401.8 ±2.5	0.03 ±1.2	-4.33 ±2.4
TNF8	109.7 ±0.95	0.660 ±1.9	-6.85 ±0.99

3.5. Determination of zeta potential

The Zeta potential of all the formulations varied between -4.72 ±1.4mV and -0.262 ±1.3 mV and is mentioned in Table 11. Poloxamer, a non-ionic surfactant, could not induce potential on the surface of the nanoparticles. The partial negative observed was due to the charge caused by the lipid and drug.

3.6. Determination of entrapment efficiency

The encapsulation efficiencies mentioned in Table 12 reveal that the drug is moderately encapsulated in all the formulations, and the values varied between a minimum of 44.63 ±0.93 to 83.15 ± 0.62%. Triclabendazole being a hydrophobic drug, has shown moderate entrapment in the stearic acid

Table 8 Entrapment efficiency of the formulations

Formulation code	Entrapment Efficiency(%)
TNF1	44.63 ±0.94
TNF2	55.61 ±1.4
TNF3	48.93 ±1.3
TNF4	57.35 ±0.55
TNF5	46.75 ±0.71
TNF6	83.15 ±0.62
TNF7	49.04 ±1.5
TNF8	65.8 ± 1.4

3.7. Percentage drug content Determination

The Drug content mentioned in Table 13 reveals that the in all the formulations, the drug is moderately encapsulated, and the values varied between a minimum of 65.9 % to 98.4% for formulation.

Table 9 Percentage Drug Content Determinations of Triclabendazole Nanoparticles

Sl.no	Formulation codes	Percentage drug content determination (%)
1	TNF1	65.9
2	TNF2	69.6
3	TNF3	90.4
3	TNF4	87.4
4	TNF5	78.8
5	**TNF6**	**98.4**
6	TNF7	88.6
7	TNF8	77.3

3.8. *In Vitro* drug release studies

In this section, the *in vitro* drug release studies have been carried out in pH 7.4 buffer (simulated intestinal pH) using a Dialysis bag which allows only the drug released from the nanoparticles to pass across the membrane. The drug solution was placed in the Dialysis bag in the buffer, and samples were withdrawn at regular intervals to measure drug concentration. All the formulations have shown release till 10hrs, extending the therapeutic activity in the disease site. The release followed a biphasic pattern where 30-40% of the drug was released in the first 1 hr, and the remaining got released till 9 hrs. This is due to U.N. entrapped drug present on the particle surface releasing quickly, followed by the release of entrapped ones.

Table 10 *In Vitro* Release Release Studies of Triclabendazole Nanoparticles

Sl.no	Time (Hrs)		% of Drug release						
		TNF1	TNF2	TNF3	TNF4	TNF5	TNF6	TNF7	TNF8
1	1 Hrs	6.56	5.08	5.99	14.16	13.58	5.25	15.66	8.70
2	2 Hrs	21.64	18.98	18.26	17.98	17.44	19.08	30.34	13.38
3	3 Hrs	29.98	26.48	25.07	24.18	21.34	25.82	34.18	25.66
4	4 Hrs	40.70	33.60	34.66	34.96	25.18	40.66	38.74	40.35
5	5 Hrs	43.60	47.44	49.34	47.33	40.08	48.40	48.88	43.20
6	6 Hrs	57.44	59.08	52.93	59.66	47.08	52.24	53.50	57.40
7	7 Hrs	69.08	66.08	76.83	61.98	61.44	76.14	66.63	69.67
8	8 Hrs	73.03	74.50	83.12	72.13	64.66	83.88	79.65	75.22
9	9 Hrs	90.69	82.24	89.14	77.58	72.28	96.94	88.30	90.88

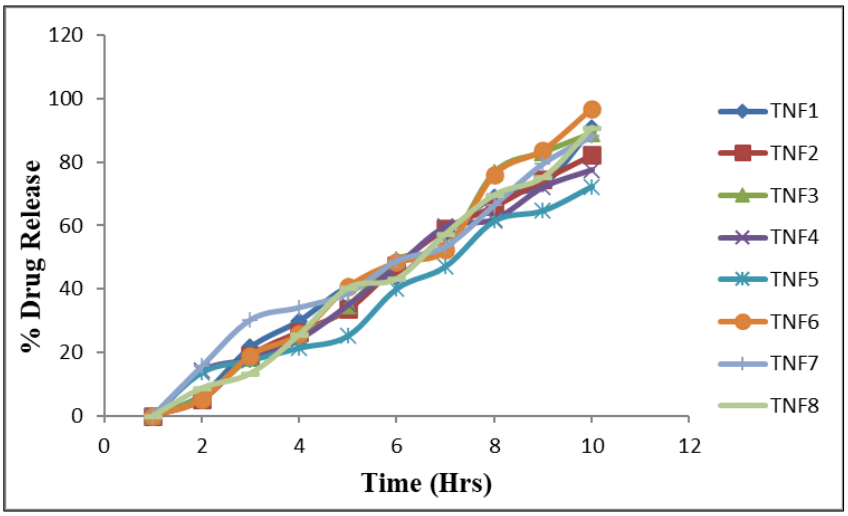

Figure 7 *In Vitro* Release Release Studies of Triclabendazole Nanoparticles

3.9. Release Order Kinetics of Triclabendazole Nanoparticles:

Table 11 Release order kinetics of zero order kinetics of TNF 6

Sl.no	Time	% cumulative drug release
1	1 Hrs	15435
2	2 Hrs	15445
3	3 Hrs	27060
4	4 Hrs	35810
5	5 Hrs	38660
6	6 Hrs	46385
7	7 Hrs	50230
8	8 Hrs	54220
9	9 Hrs	89930

Table 12 Release order kinetics of first-order kinetics of TNF 6

Sl.no	Time	Log cumulative % drug release
1	1 Hrs	4.190
2	2 Hrs	4.195
3	3 Hrs	4.435
4	4 Hrs	4.545
5	5 Hrs	4.590
6	6 Hrs	4.675
7	7 Hrs	4.735
8	8 Hrs	4.740
9	9 Hrs	4.950

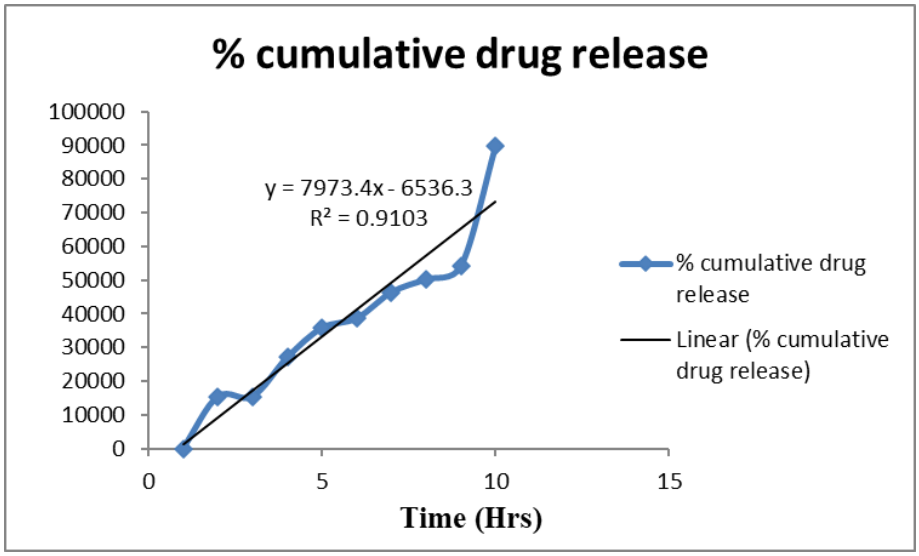

Figure 8 I*n vitro* release studies of TNF 6 (Zero order Kinetics)

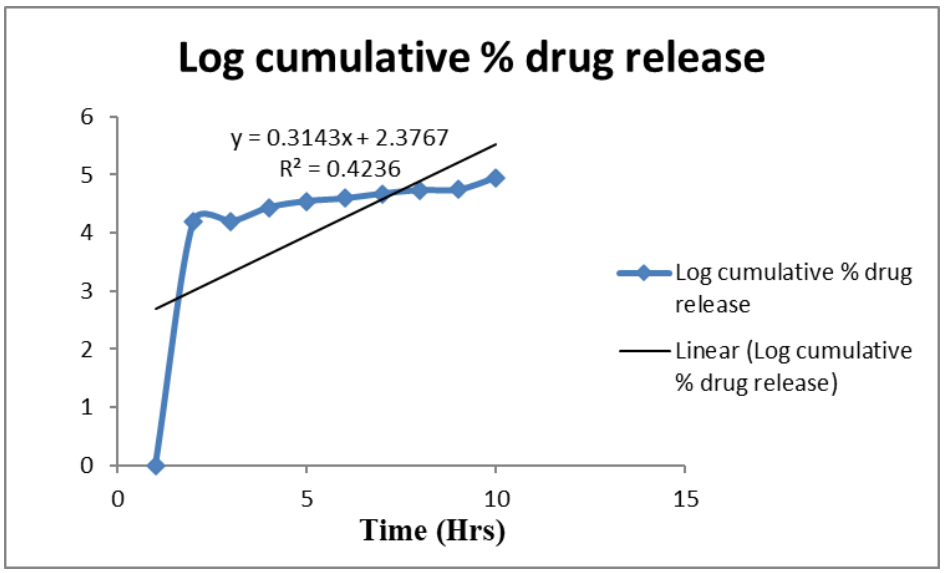

Figure 9 I*n vitro* release of TNF 6 (First order kinetics)

Table 13 Release order kinetics of korsmeyerpeppas of TNF 6

Sl.no	Time	Log cumulative % drug release
1	5	4.122
2	10	4.435
3	15	4.545
4	20	4.589
5	25	4.670
6	30	4.730
7	35	4.735
8	40	4.950
9	45	4.952

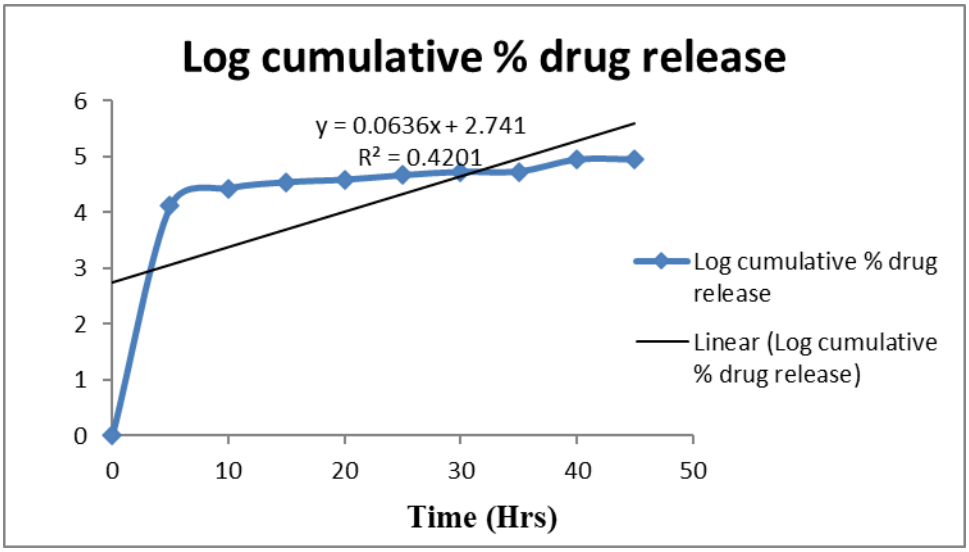

Figure 10 I*n vitro* release of TNF 6 (Korsmeyer Pappas)

Table 14 Release order kinetics of Higuchi of TNF 6

Sl.no	The square root of time	% cumulative drug release
1	2.23	15430
2	3.16	27265
3	3.87	34890
4	4.47	38745
5	5.0	46485
6	5.47	52225
7	5.91	54225
8	6.32	64327
9	6.34	89024

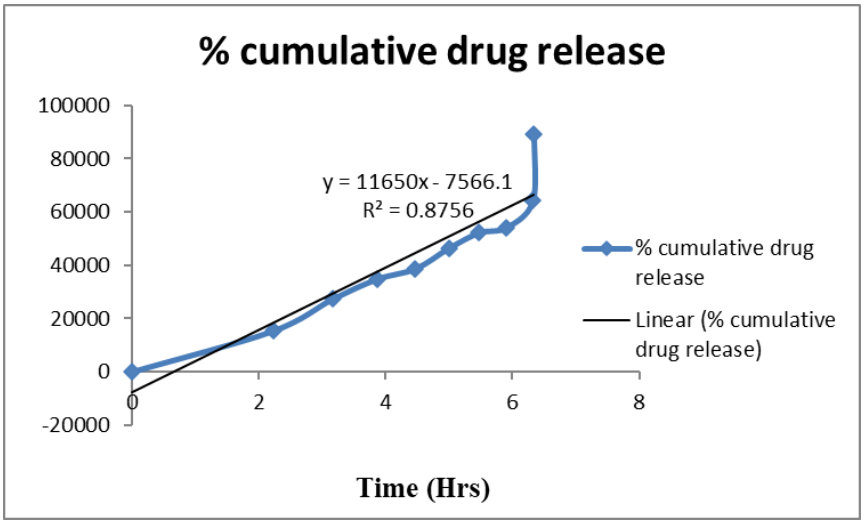

Figure 12 *In vitro* release of TNF 6 (Higuchi)

Table 15 Release kinetics of Triclabendazole Nanoparticles TNF1 TO TNF5

Model	**TNF 1**		**TNF 2**		**TNF 3**		**TNF 4**		**TNF 5**	
	R^2	m	R^2	m	R^2	m	R^2	m	R^2	m
Zero-order	0.655	69.4	0.939	1123	0.007	15.93	0.917	15.49	0.928	1414
First order	0.494	0.061	0.540	0.067	0.257	0.038	0.481	0.052	0.438	0.062
Higuchi's Matrix	0.516	4508	0.767	7420	0.023	212.0	0.798	1057	0.803	9618
Korsmeyer -Peppar	0.835	2.354	0.884	2.545	0.572	1.709	0.835	2.032	0.806	2.517

Table 16 Release kinetics of Triclabendazole Nanoparticles TNF6 TO TNF8

Model	**TNF 6**		**TNF 7**		**TNF 8**	
	R^2	**m**	R^2	m	R^2	m
Zero-order	**0.910**	**72.88**	0.949	154.4	0.937	1593
First order	**0.423**	**0.045**	0.465	0.051	0.399	0.061
Higuchi's Matrix	**0.875**	**515.5**	0.848	1067	0.899	11409
Korsmeyer-Peppas	**0.420**	**1.813**	0.827	2.033	0.785	2.560

Table 17 Release Kinetics of Triclabendazole Nanoparticles for Best TNF6

Formulation Code	**Zero-order**		**First order**		**Higuchi Matrix**		**Korsmeyer Peppas**		**Best fit Model**
	R2	m	R2	m	R2	m	R2	m	
TNF 6	0.910	72.88	0.423	0.045	0.875	515.5	0.420	1.813	Zero-order

3.10. Stability Studies

Smaller particles tend to aggregate faster during transport, storage, and dispersion. Stability studies were conducted on freeze-dried at room temperature (20 - 25°C) and refrigerator (3 to 5 °C) over two months. Particle size, formulation appearance, drug release, and FT-IR were evaluated to confirm the stability of the formulation.

3.11. The appearance of the formulation:

When stored at room temperature, the formulations showed instability by forming larger floccules, and when dispersed in water, the solution turned into heavier particles. At the same time, when stored in refrigerated condition, the formulation was stable with no visible floccules formation. Hence, it is concluded that the formulations should be stored in refrigerated conditions.

3.12. Particle size

The particle size of the formulation is evaluated by photon correlation spectroscopy, and the particle size is mentioned in Table 22. From the table, it is clear that the formulations showed a drastic increase in size when stored at room temperature, where the size of particles increased from an initial to 346.8 ±8.8 nm at the end of 1 month to 899.8 ± 5.9 nm at the end of 2 months. This indicates that the formulations are unstable when stored at room temperature.

Table 18 Particle Size of The Formulations During Stability Studies

Stability Condition	**The average Particle size of DS15 (nm)**		
	0 days	One month	Two months
Room temperature (25°C)	250 ± 0.60	346.8 ±8.8	899.8 ± 5.9
Refrigerated temperature (3 to 5 °C)	250 ± 0.60	256 ± 0.20	282 ± 0.40

3.13. Entrapment efficiency

The entrapment efficiency of the formulation was determined at each interval to ensure that the drug molecules didn't undergo any degradation during storage. The formulation didn't change during the 60 days of storage in refrigerated and room temperatures. The entrapment efficiency is mentioned in Table 23.

Table 19 Entrapment efficiency of formulation on storage condition

Storage condition	**Day 30**	**Day 60**
Room temperature	74.1 ±0.59%	73.30 ±3.3%
Refrigerated temperature	75.1 ±0.59%	77.54±3.7%

4. Conclusion

Triclabendazolenano particles were prepared by hot homogenization method under high magnetic stirring using stearic acid as lipid, and poloxamer 188 was used as a surfactant. Eight batches of formulations were prepared by varying the amount of lipids and surfactants. They were evaluated for parameters like particle size, shape, morphology, physical state, entrapment efficiency, Drug content, and *in vitro* drug release. Particle size was measured using a Malvern Zeta sizer, and the size range of the particles was found to be in the field of -4.72 ±1.4 nm to -6.85 ± 0.99 nm. Considering the particle size, entrapment efficiency, and in vitro release, F6 was the best formulation with a particle size of 250 ± 0.58 nm and entrapment efficiency of 83.15 ±0.62%. The drug content was released from 98.4%. Further, F6 is one among the few formulations which showed a drug release up to 9hrs, performed with release order kinetics like zero order, first order, Higuchi matrix, and Korsmeyerpeppas it must best fit the model was zero order kinetics.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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