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Formulation and evaluation of thiabendazole-loaded nanoparticles

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Abstract

Therefore, there is a need to develop alternative novel drug delivery formulations of Thiabendazole to improve its intestinal absorption and reduce its side effects during regular therapy. The Thiabendazole 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 that there are no interactions between Thiabendazole and other excipients; hence, they can be used to prepare nanoparticles. The entrapment efficiencies varied from a minimum of 43.62±0.93 to a maximum of 82.14 ± 0.61%, and it can be concluded that a higher amount of lipid is necessary for obtaining a good entrapment efficiency. The drug content of Thiabendazole nanoparticles for all formulations ranges from 66.8 % to 99.3%. 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 9 hours with sustained effect. The formulations showed a drastic increase in size when stored at room temperature, where particles increased from an initial to 345.9 ±8.9 nm at the end of 1 month to 899.7 ± 5.8 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: Thiabendazole; 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, 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/or to which the functional code is adsorbed or attached. 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. 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

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class, such as physical stability, protection of incorporated labile drugs from degradation, controlled release, and excellent tolerability [3].

2. Material and methods

2.1. Formulation of ThiabendazoleNanoparticles

Nanoparticles of Thiabendazole 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. On the whole, eight formulations were prepared by changing the different ratios of lipids and resin. The surfactant percentage ranged from 0.5, 0.75, 1.0 & 1.25%).

2.1.1. Formulation Design

Table 1 Composition of Thiabendazole Nanoparticles formulations

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Thiabendazole (mg)	25	25	25	25	25	25	25	25
Stearic acid (mg)	155	155	105	105	155	155	115	115
Bees Wax (mg)	105	105	125	125	155	155	135	135
Polaxamer (mg)	205	205	205	205	205	205	205	205
Span 80 (ml)	1.0	0.80	1.5	1.30	1.0	0.80	1.5	1.30
Ethanol (ml)	15	15	105	15	15	15	15	15

2.2. Compatibility Studies

2.2.1. FT-IR Studies

The purity of the drug was determined by subjecting Thiabendazole to I.R. analysis using Fourier Transform Infrared Spectroscopy (FT/IR 8400S (C.E.) Shimadzu spectrophotometer). The samples were prepared using 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 ton/mm^2 pressure. The Shimadzu FT-IR spectrophotometer selected the wavelength range from 400 - 2000 cm-1. Similarly, an I.R. peak is obtained for a physical mixture of Thiabendazole, Stearic acid, Beeswax, Poloxamer 188, and mixtures [4].

2.3. Surface Morphological Studies

2.3.1. Scanning Electron Microscopy

A scanning electron microscope examined The prepared Nanoparticle formulation for surface morphology and shape. 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 on brass specimen studies [5].

2.4. Characterization Studies [6-10]

2.4.1. Determination of Particle Size by Zetasizer

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.

2.4.2. Determination of Zeta Potential by Zetasizer

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.

2.4.3. Determination of Entrapment Efficiency (%)

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

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

2.5. Drug content determination

50mg of Thiabendazole nanoparticles was crushed and suspended in water to extract the drug from the nanoparticles. After 24 h, the filtrate was assayed spectrophotometrically at 298 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 [11]. The dialysis bag is dipped in a 50 ml dissolution medium maintained at 37 ± °C and stirred at 100 rpm using a magnetic stirrer. 2 ml of the buffer solution is removed at an interval of 1, 2, 3, 4, 6, 7, 8 and 10 hrs. It 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 298 nm [12].

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 [13].

3. Results and discussion

3.1. Drug excipients compatibility studies

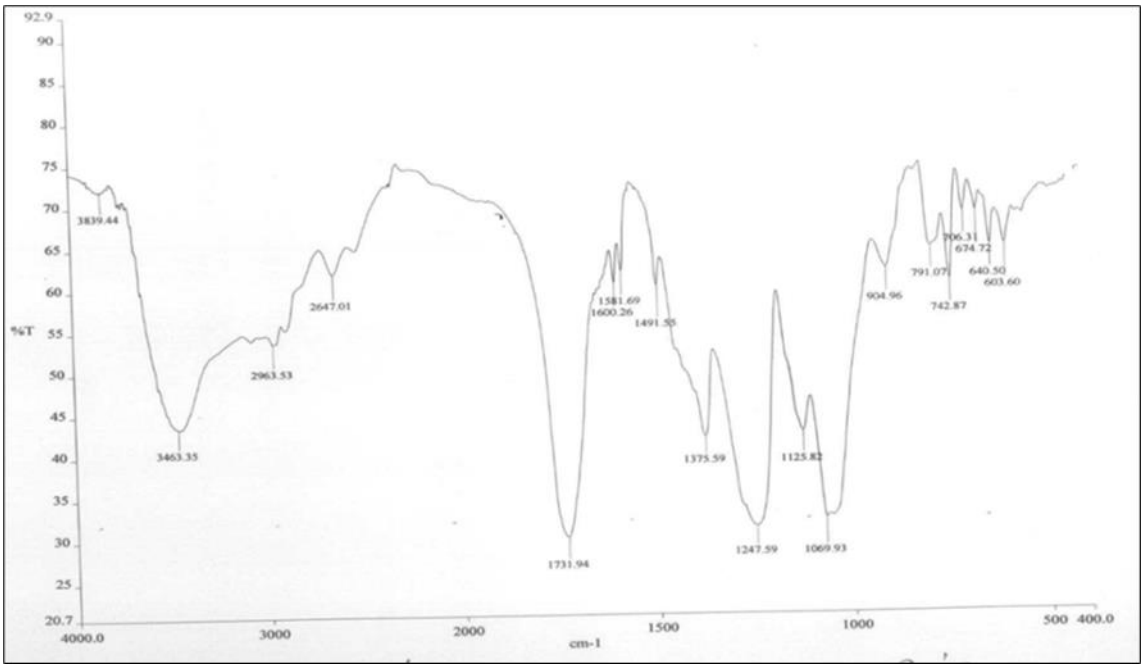

Figure 1 FT IR Spectra of Thiabendazole

Table 2 F.T. IR Interpretation Data for Thiabendazole

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

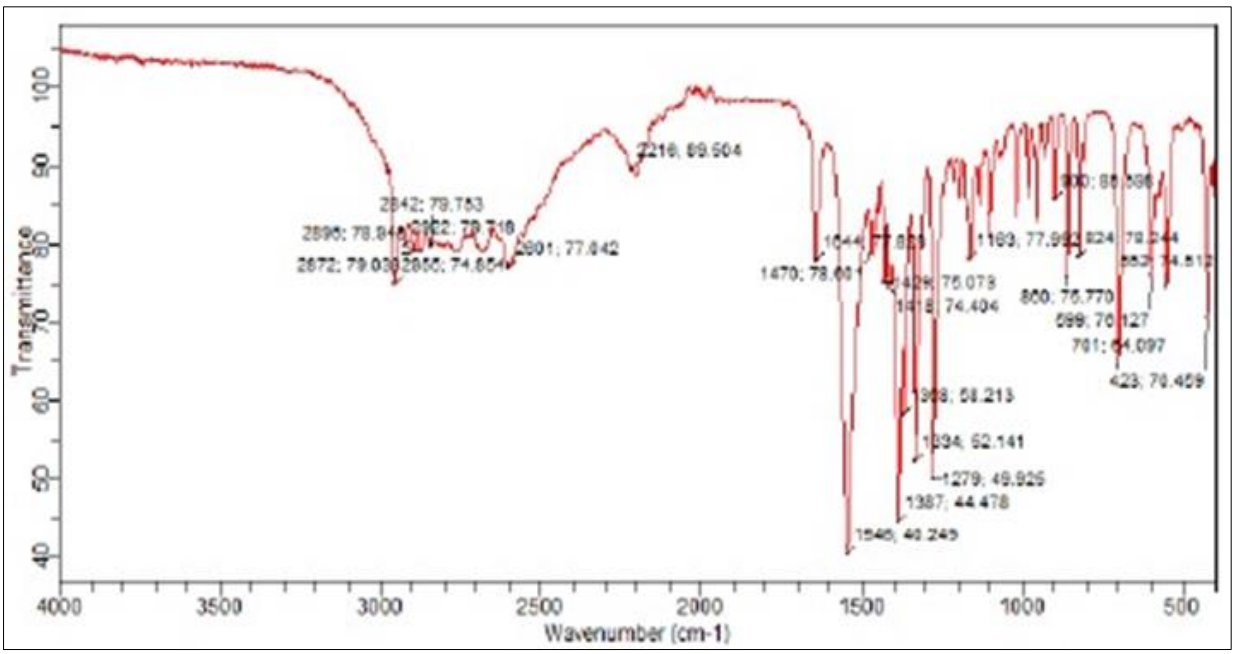

Figure 2 FTIR spectra of Stearic acid

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	3000-2850	C-H Stretch	Alkenes
2922,2872	3400-3250	N-H Stretch	1^0,2^0 amines, amides aromatics
	3100-3000	C-H Stretch	
1644	1650-1580	C-H Bend	Ten amines Aromatics
1546	1600-1585	C-C Stretch (in the ring)	
1429	1550-1475	N-O Asymmetric Stretch	Nitro compounds Aromatics
1470	1500-1400	C-C Stretch (in the ring)	
1368,1387	1335-1250	C-N stretch	Aromatic amines
1334,1279	1360-1290		Nitro compounds

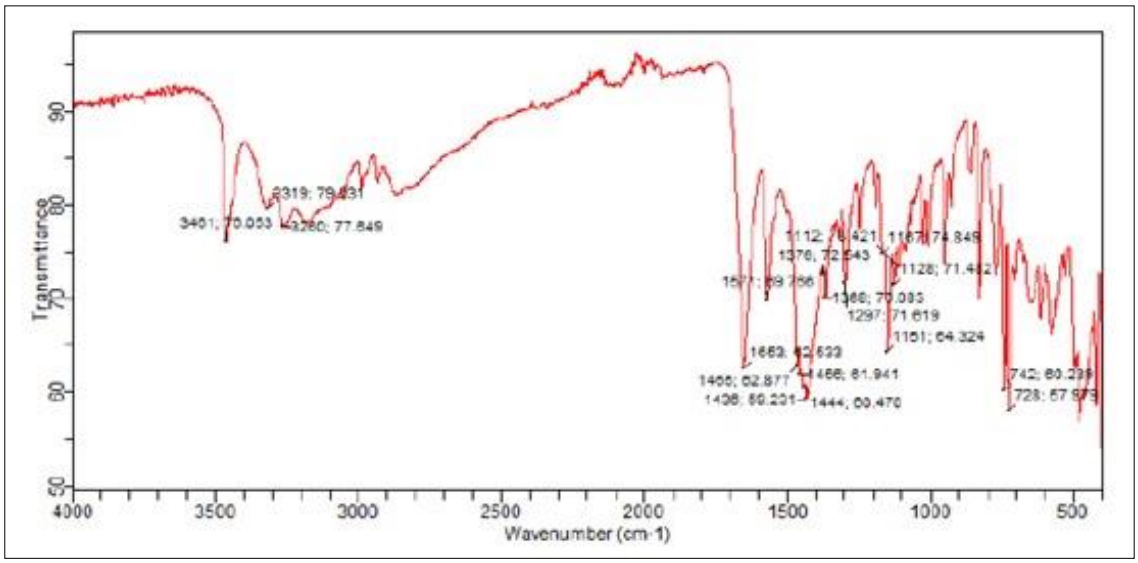

Figure 3 FTIR spectra of Beeswax

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	C-O Stretch	Alcohols, Carboxylic acids, Esters, and others
	1151.64		
1470-1450(m)	1465.62	C-H Bend	Alkenes
	1456.61		

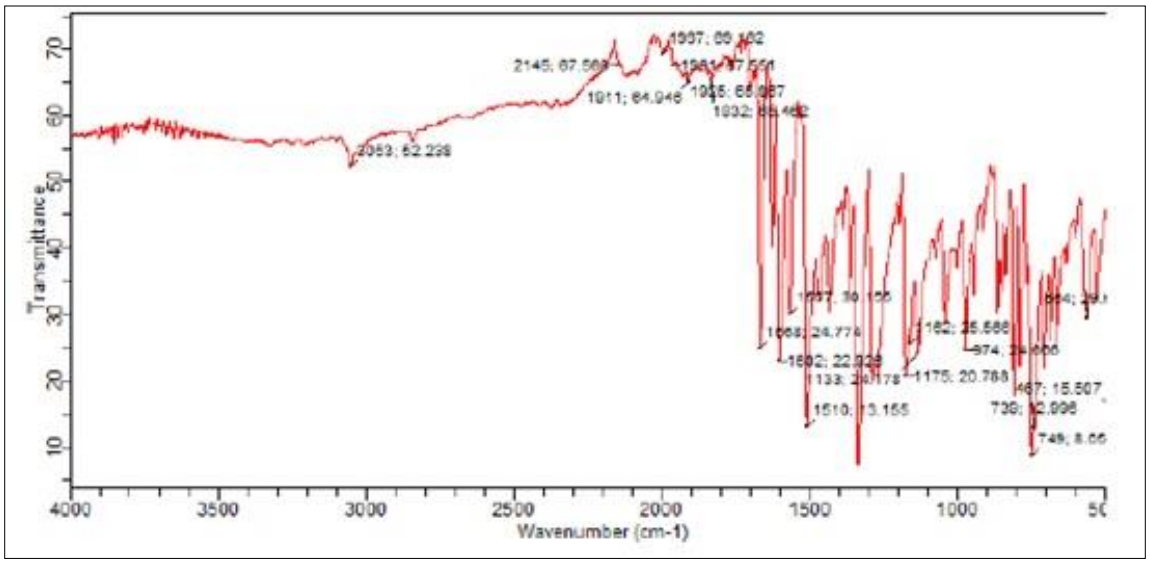

Figure 4 FTIR spectra of Poloxamer 188

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

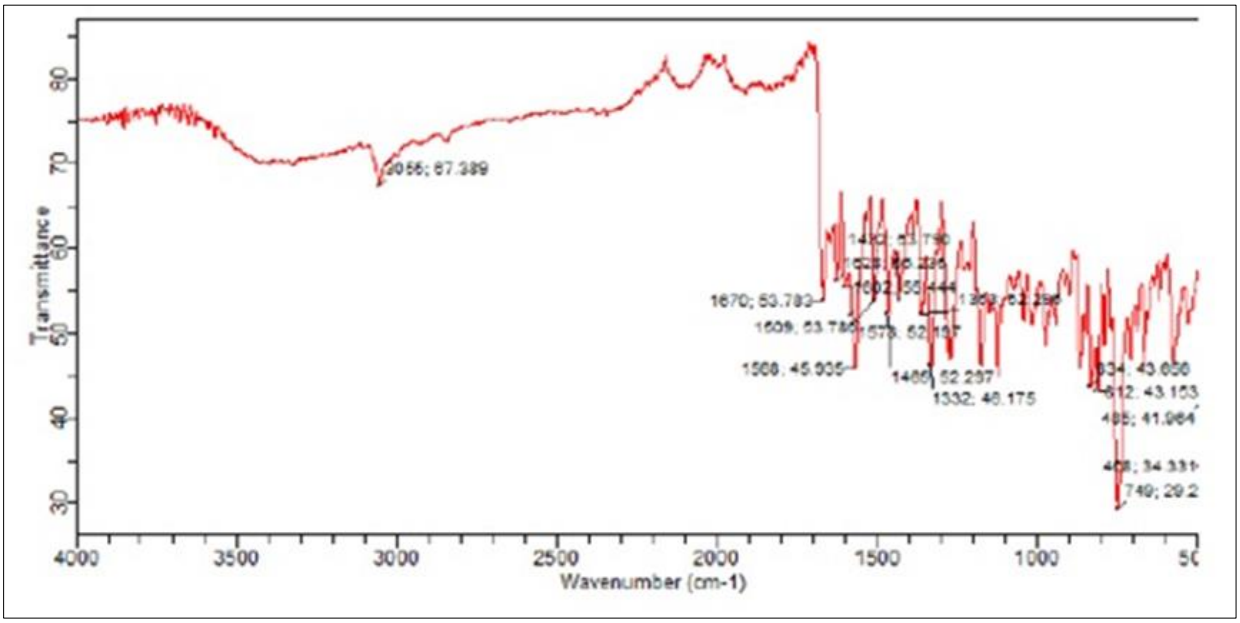

Figure 5 FTIR spectra of drug and polymer mixture

Table 6 Interpretation data for Thiabendazole + polymer mixture

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

3.2. Determination of Particle Shape and Surface Morphology

3.2.1. By Using Scanning Electron Microscopy

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

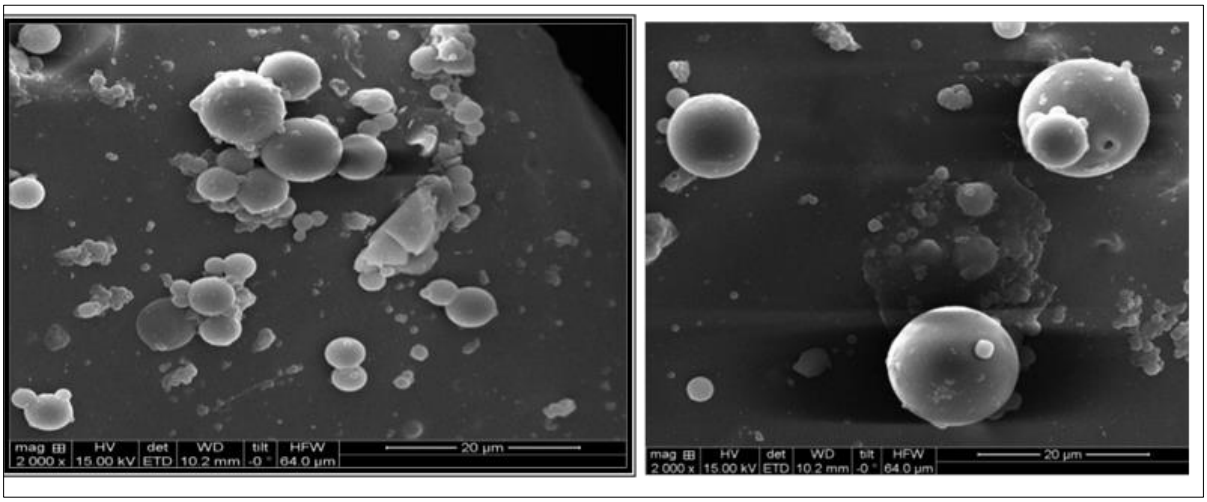

Figure 6 Scanning Electron Microscope image of the Nanoparticles

3.2.2. 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)
ANF1	110.6 ± 1.5	0.215 ±0.23	-4.71±1.3
ANF2	211 ±1.23	0.304±0.4	-1.16 ±1.7
ANF3	227 ± 2.3	0.355 ±0.12	-4.29 ±1.9
ANF4	249 ± 0.59	0.215±1.4	-0.261 ±1.2
ANF5	332 ± 1.41	0.407 ±1.9	-9.15 ±1.1
ANF6	367.3 ±0.99	0.521 ±1.3	-0.04 ±1.6
ANF7	400.9 ±2.4	0.02 ±1.1	-4.32 ±2.3
ANF8	108.6 ±0.94	0.656 ±1.8	-7.83 ±0.98

3.2.3. Determination of zeta potential

The Zeta potential of all the formulations varied between -4.71 ±1.3mV and -0.261 ±1.2 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.

3.2.4. Determination of entrapment efficiency

The encapsulation efficiencies reveal that the drug is moderately encapsulated in all the formulations, and the values varied between a minimum of 43.62±0.93 to 82.14 ± 0.61%. Thiabendazole, a hydrophobic drug, has shown moderate entrapment in the stearic acid.

Table 8 Entrapment efficiency of the formulations

Formulation code	Entrapment Efficiency (%)
ANF1	43.62±0.93
ANF2	54.60 ±1.3
ANF3	47.92 ±1.2
ANF4	82.14 ±0.61
ANF5	45.74 ±0.70
ANF6	56.34 ±0.54
ANF7	48.03 ±1.4
ANF8	64.9 ± 1.3

3.2.5. Percentage drug content Determination

The Drug content mentioned in Table 13 reveals that the drug is moderately encapsulated in all the formulations, and the values varied between a minimum of 66.8 % to 99.3% for formulation.

Table 9 Percentage Drug Content Determinations of Thiabendazole Nanoparticles

Sl.no	Formulation codes	Percentage drug content determination (%)
1	ANF1	66.8
2	ANF2	68.5
3	ANF3	91.2
4	ANF4	99.3
5	ANF5	76.7
6	ANF6	86.2
7	ANF7	89.5
8	ANF8	79.2

3.3. *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 the U.N. entrapped drug present on the particle surface releases quickly, followed by the release of entrapped one.

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

Sl.no	Time (Hrs)	% of Drug release							
		ANF1	ANF2	ANF3	ANF4	ANF5	ANF6	ANF7	ANF8
1	1 Hrs	6.55	4.07	5.98	5.24	12.59	14.15	14.65	7.69
2	2 Hrs	20.63	17.97	17.25	18.07	16.43	17.97	29.33	12.37
3	3 Hrs	28.97	25.47	24.06	24.81	20.33	24.17	33.17	24.65
4	4 Hrs	39.69	32.59	33.65	39.65	24.17	34.95	37.73	39.33
5	5 Hrs	42.59	46.43	48.33	47.39	39.07	47.32	47.87	43.17
6	6 Hrs	56.43	58.07	51.92	51.23	48.09	59.65	52.49	55.35
7	7 Hrs	68.07	65.09	75.82	75.13	60.43	61.99	65.62	68.65
8	8 Hrs	72.02	73.49	82.11	82.87	63.65	72.12	78.64	74.2
9	9 Hrs	89.68	81.23	88.13	95.93	71.27	77.57	87.29	89.87

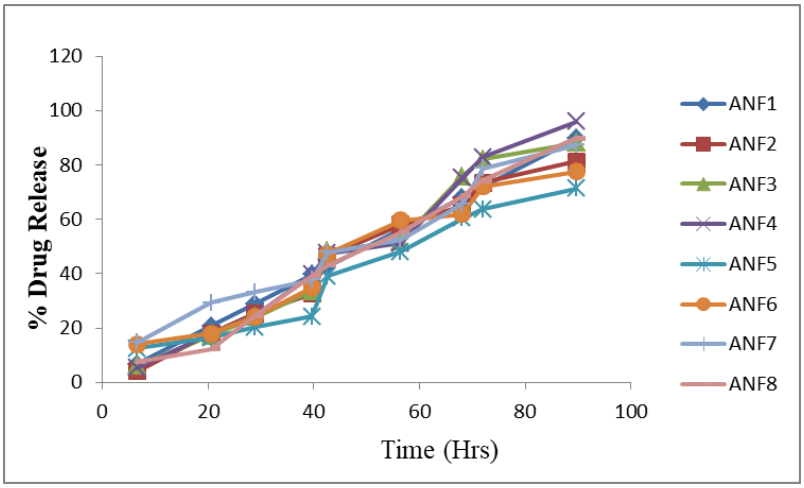

Figure 7 *In Vitro* Release Release Studies of Thiabendazole Nanoparticles

3.4. Release Order Kinetics of Thiabendazole Nanoparticles

Table 11 Release order kinetics of zero order kinetics of ANF 4

Sl.no	Time	% cumulative drug release
1	1 Hrs	15430
2	2 Hrs	15440
3	3 Hrs	27055
4	4 Hrs	35805
5	5 Hrs	38655
6	6 Hrs	46382
7	7 Hrs	50225
8	8 Hrs	54215
9	9 Hrs	89925

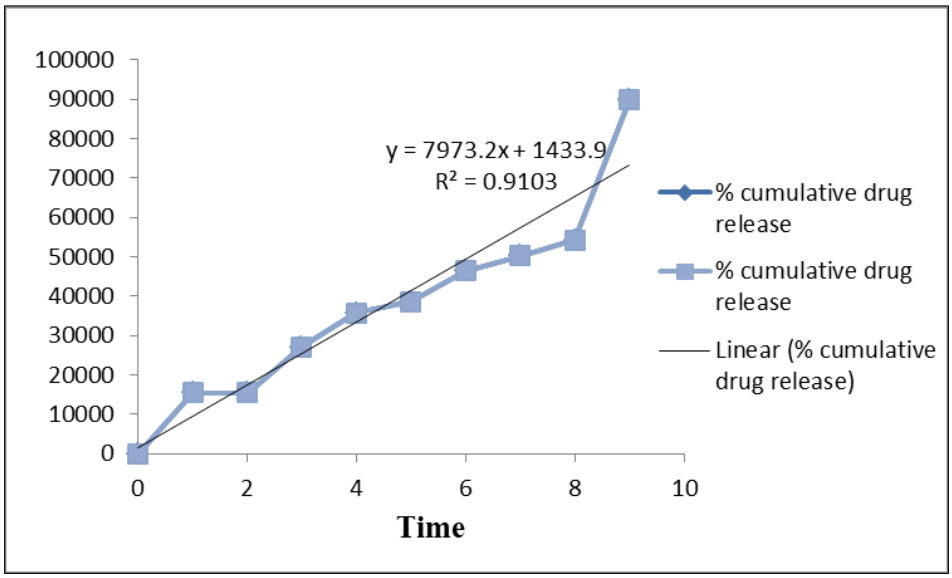

Figure 8 *In vitro* release studies of ANF 4 (Zero order Kinetics)

Table 12 Release order kinetics of first-order kinetics of ANF 4

Sl.no	Time	Log cumulative % drug release
1	1 Hrs	4.188
2	2 Hrs	4.190
3	3 Hrs	4.433
4	4 Hrs	4.542
5	5 Hrs	4.588
6	6 Hrs	4.670
7	7 Hrs	4.732
8	8 Hrs	4.735
9	9 Hrs	4.949

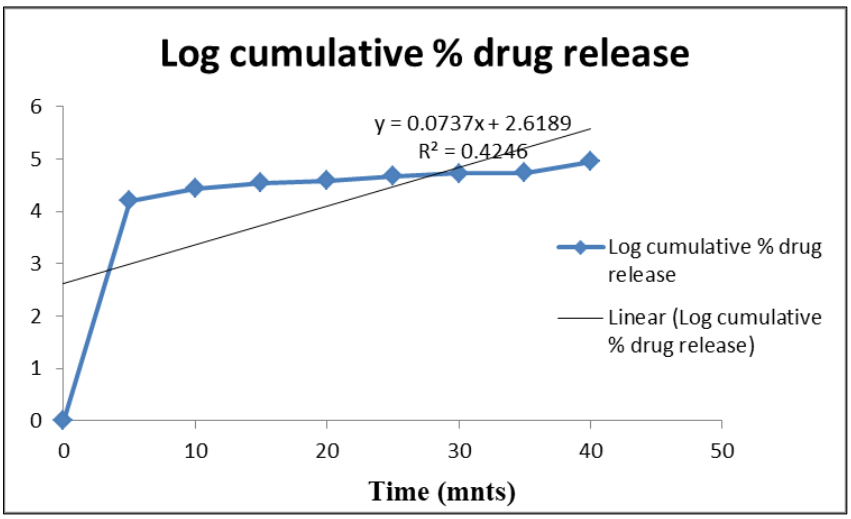

Figure 9 In *vitro* release of ANF 4 (First-order kinetics)

Table 13 Release order kinetics of Korsmeyer Peppas of ANF 4

Sl.no	Time	Log cumulative % drug release
1	5	4.198
2	10	4.434
3	15	4.542
4	20	4.588
5	25	4.668
6	30	4.728
7	35	4.734
8	40	4.949
9	45	4.951

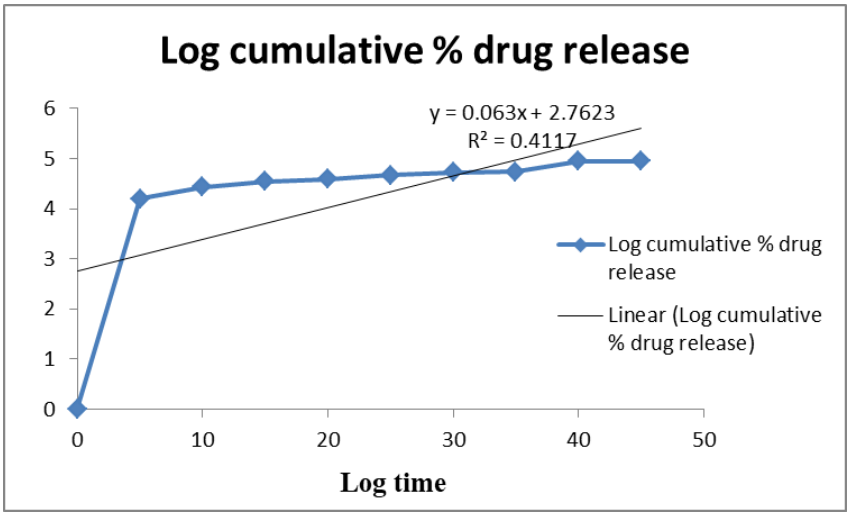

Figure 10 In *vitro* release of ANF 4 (Korsmeyer Pappas)

Table 14 Release order kinetics of Higuchi of ANF 4

Sl.no	The square root of time	% cumulative drug release
1	2.23	15428
2	3.16	27264
3	3.87	34889
4	4.47	38743
5	5.0	46482
6	5.47	52221
7	5.91	54224
8	6.32	64324
9	6.34	89023

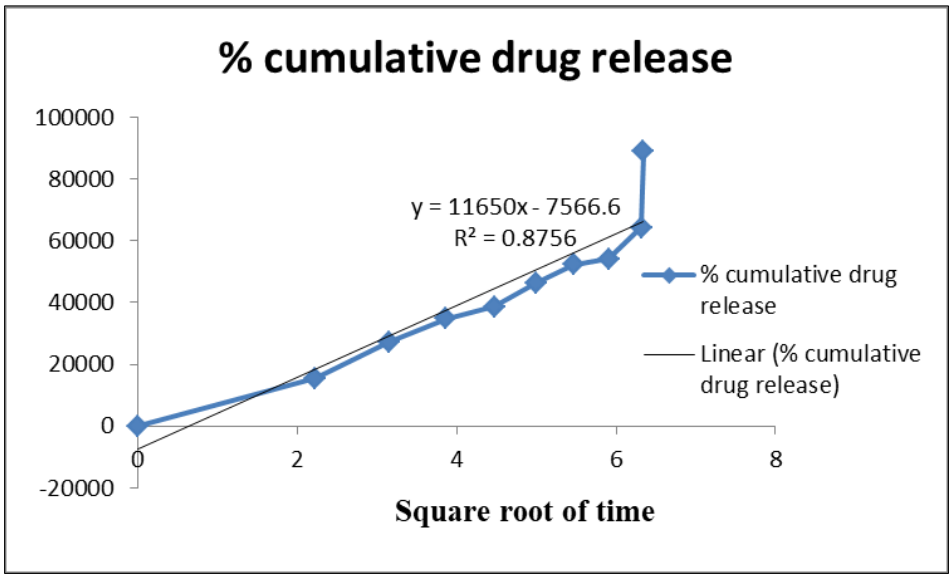

Figure 11 *In vitro* release of ANF 4 (Higuchi)

Table 15 Release kinetics of Thiabendazole Nanoparticles ANF1 TO ANF5

Model	ANF1		ANF2		ANF3		ANF4		ANF5	
	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	0.910	72.88	0.928	1414
First order	0.494	0.061	0.540	0.067	0.257	0.038	0.424	0.044	0.438	0.062
Higuchi's Matrix	0.516	4508	0.767	7420	0.023	212.0	0.875	515.5	0.803	9618
Korsmeyer-Peppar	0.835	2.354	0.884	2.545	0.572	1.709	0.411	1.813	0.806	2.517

Table 16 Release kinetics of Thiabendazole Nanoparticles ANF6 TO ANF8

Model	ANF6		ANF7		ANF8	
	R^2	m	R^2	m	R^2	m
Zero-order	0.917	15.49	0.949	154.4	0.937	1593
First order	0.481	0.052	0.465	0.051	0.399	0.061
Higuchi's Matrix	0.798	1057	0.848	1067	0.899	11409
Korsmeyer-Peppas	0.835	2.032	0.827	2.033	0.785	2.560

Table 17 Release kinetics of Thiabendazole Nanoparticles for Best ANF4

Formulation Code	Zero-order		First order		Higuchi Matrix		Korsmeyer Peppas		Best fit Model
	R2	m	R2	m	R2	m	R2	m	
ANF 4	0.910	72.88	0.424	0.044	0.875	515.5	0.411	1.813	Zero-order

3.5. 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, Appearance of the formulation, drug release, and FT-IR were evaluated to confirm the stability of the formulation.

3.5.1. 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. Whereas the formulation was stable when stored in refrigerated condition with no visible floccular formation. Hence, it is concluded that the formulations should be stored in refrigerated conditions.

3.5.2. 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 345.9 ±8.9 nm at the end of 1 month to 899.7 ± 5.8 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	**Average Particle Size of DS15 (nm)**		
	0 days	**One month**	**Two months**
Room temperature (25°C)	249 ± 0.60	345.9 ±8.9	899.7± 5.8
Refrigerated temperature (3 to 5 °C)	249 ± 0.60	255 ± 0.19	280 ± 0.39

3.5.3. 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	73.1 ±0.58%	72.29 ±3.2%
Refrigerated temperature	75.1 ±0.58%	76.53±3.6%

4. Conclusion

Thiabendazole nanoparticles 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 lipid and surfactant and 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. Considering the particle size, entrapment efficiency, and in vitro release, F4 was the best formulation with a particle size of 249 ± 0.60 nm and entrapment efficiency of 75.1 ±0.58%. The drug content was released from 98.1%. Further, F4 is among the few formulations that showed a drug release of up to 9, 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

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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