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Formulation and *in-vitro* Evaluation of Nanosponge Loaded Extended Release Tablets of Trimethoprim

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Abstract

Trimethoprim is an antibiotic primarily used in the treatment of bladder infections and urinary tract infections. Its low aqueous solubility leads to the poor oral bioavailability. In order to enhance its solubility, we prepared Trimethoprim Nanosponges loaded extended release tablets to delay the drug release at urinary tract. Nanosponges are tiny sponges with an average diameter below 1 µm and consist of cavities filled with drug molecules. Initially eight formulations of trimethoprim nanosponges were prepared by using ethyl cellulose as entrapping agent, dichloromethane as cross linking agent in various proportions and evaluated for powder flow properties, % yield, entrapment efficiency, morphology, zeta potential, particle size and *in-vitro* drug release characteristics. Based on the evaluation results, formulation F4 was selected to prepare six extended release tablet formulations by using HPMC K100M and HPMC K15M as extended release polymers. All six formulations were evaluated for thickness, hardness, friability, % drug content and *in-vitro* drug release. From the results, it was found that all the evaluation results are within IP limits and all formulations showed maximum drug release of 98.43 ± 0.1% at the end of 10 h. From this study, we concluded that nanosponge loaded extended release tablets of trimethoprim showed delayed drug release upto 10 h with enhanced solubility and dissolution. Hence, nanosponge technique will be a challenging approach for enhancing the solubility of poorly soluble drugs.

Key words: Dichloromethane, HPMC, Nanosponges, Solubility, Trimethoprim.

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1. Introduction

Nanosponges are nanoparticle sized system for the delivery of drugs that have reduced side effects with providing flexibility in formulation and stability improvement. Owing to their small size and porous nature, they can bind poorly soluble drugs within the matrix and improve their bioavailability by modifying the pharmacokinetic parameters of actives [1]. Nanosponges are obtained by suitable cross linking process and also by different organic and inorganic substances. These can encapsulate different molecules upon forming complexes such as inclusion and non inclusion complexes [2]. These are non-mutagenic, non-irritating, non-toxic in nature and can extend the drug release up to 12 h. Nanosponges are stable at pH range upto 1 to 11 and temperature up to 130°C. The disadvantages associated with microsponges and microspheres can be overcome by formulating them into nanosponges [3].

Trimethoprim is an antibiotic used mainly in the treatment of bladder infections and having low solubility and bioavailability. For improving solubility and bioavailability, it is incorporated into nanosponges. There are various methods available for the formulation of nanosponges such as emulsion solvent evaporation method, solvent method, ultrasound assisted synthesis and by using hyper crosslinked cyclodextrins. Among them emulsion solvent evaporation is most widely used, easiest and laboratory method [4]. The main components used in the formulation of nanosponges are polymers ethyl cellulose and polyvinyl alcohol for entrapment of drug because the drug is water insoluble and the polymer is also water insoluble in nature. Dichloromethane acts as crosslinker for EC. No literature reported that trimethoprim formulated as nanosponge loaded extended release tablets. Hence, we have taken the step to formulate the trimethoprim as nanosponge loaded extended release tablets.

2. Experimental

2.1. Materials

Trimethoprim was obtained as gift sample from KP Labs, Hyderabad, India. Ethyl cellulose, Polyvinyl alcohol, Dichloromethane, HPMC K15M, HPMC K100M, Magnesium stearate, Talc and MCC pH 102 was procured from SD Fine Chemicals, Mumbai, India.

2.2. Methods

2.2.1. *Drug-excipient compatibility studies*

It was performed by using FTIR in-order to determine the incompatibility between used excipients and pure drug. KBr pellet press technique was used to prepare the sample pellets (2 mg sample in 200 mg KBr). The obtained pellets were scanned from 4000 cm^{-1} to 400 cm^{-1} at the resolution of 1 cm^{-1}. The obtained IR spectra of drug with excipients were compared with the IR spectrum of pure drug for any incompatibilities [5].

2.2.2. Formulation of Nanosponges

Eight formulations of nanosponges were prepared by emulsion solvent evaporation method and composition of each formulation was showed in table 1. Ethyl cellulose acts as water insoluble polymer and Polyvinyl alcohol and Dichoromethane acts as cross linkers. Ethyl cellulose, drug and dichloromethane mixture acts as dispersed phase and polyvinyl alcohol and water acts as aqueous phase. Dispersed phase was prepared by dissolving ethyl cellulose and drug in dichloromethane and this mixture was added to the aqueous phase. Both are stirred well at 1000 rpm for 2 h by using Magnetic stirrer. Obtained nanosponges were dried at 40°C and stored in desiccators for the removal of solvents [6].

Table 1. Formulation of Trimethoprim nanosponges.

Formulation	Drug (mg)	Ethyl cellulose (mg)	Polyvinyl alcohol (gm)	Dichloro-methane (ml)	Distilled water (q.s) (ml)
F1	100	100	2	20	100
F2	100	200	2	20	100
F3	100	300	2	20	100
F4	100	400	2	20	100
F5	100	100	3	20	100
F6	100	200	3	20	100
F7	100	300	3	20	100
F8	100	400	3	20	100

2.3. Evaluation of Nanosponges

2.3.1. *Micrometric properties*

Angle of repose, Bulk density, Tapped density, Hausner's ratio and Carr's index were determined to assess the flow ability of the prepared nanosponges powder [7].

2.3.2. *Determination of percentage yield*

It was calculated accurately by using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for preparation of nanosponges [8].

2.3.3. *Determination of Entrapment efficiency*

Nanosponge equivalent to 100 mg of the drug were taken and then crushed into powder followed by transferred into a 100 ml volumetric flask consist of 10 ml of methanol and the volume was made up with simulated gastric fluid of pH 1.2. After 24 h, the solution was filtered through Whatmann filter paper and the absorbance was measured spectrophotometrically (Lab India 1700 UV-Visible spectrophotometer, India) after suitable dilutions [9].

2.3.4. *Morphology and Surface Topography*

Morphology and surface topography of the optimized nanosponge formulation was done by scanning electron microscopy method (JEOL JSM-5200). Before dissolution study only, gold-palladium coated nanosponges were subjected to SEM study [10].

2.3.5. *Particle size and Zeta Potential determination*

The zeta potential and particle size of sample was determined using zetasizer (Malvern Instrument Ltd, UK) [11].

2.4. *In-vitro dissolution studies*

900 ml of 0.1 N HCl was placed in vessel and the USP apparatus type II (Paddle Method) was assembled. The medium was allowed to equilibrate to temperature of 37°C $\pm$ 0.5°C. Trimethoprim nanosponge powder was placed in the vessel and operated for 2 h in 0.1 N HCl and then the medium was replaced with pH 6.8 phosphate buffer and the process was continued up to 8 h at 50 rpm. At definite time intervals, 5 ml of the receptor fluid were withdrawn, filtered, diluted and analyzed spectrophotometrically [12].

2.5. Formulation of Nanosponge loaded extended release tablets

From the results of evaluation studies of nanosponges, the formulation F4 was selected and optimized for preparation of nanosponge extended release tablets by direct compression method.

Compositions of different formulations were given in table 2. The total weight of the tablet was taken as 500 mg. Here, HPMC K15M and HPMC K100M were used as polymers, talc as lubricant and magnesium stearate acts as glidant and microcrystalline cellulose was used as a directly compressible binder [13]. Six formulations with varying concentrations of HPMC K15M and HPMC K100M were used to prepare extended release tablets by direct compression method. Trimethoprim nanosponges and all other ingredients were individually passed through sieve number #60 and all the ingredients were mixed thoroughly by triturating up to 15 min followed by lubricated with talc. Finally the lubricated mixture was subjected to direct compression by using RIMEK rotary tablet punching machine.

Table 2. Formulation of nanosponge loaded extended release tablets of Trimethoprim.

Formulation	Trimethoprim Nanosponges (mg)	HPMC K100M (mg)	HPMC K15M (mg)	Magnesium Stearate (mg)	Talc (mg)	MCC pH 102 (mg)
F1	340	50	-	3	3	104
F2	340	75	-	3	3	79
F3	340	100	-	3	3	54
F4	340	-	50	3	3	104
F5	340	-	75	3	3	79
F6	340	-	100	3	3	54

2.6. Evaluation of tablets

2.6.1. *Pre compression studies*

Angle of repose, bulk and tapped density, hausner's ratio and carr's index were determined to assess the flow ability of the prepared nanosponges tablet powder [14].

2.6.2. *Post compression studies*

The manufactured nanosponge loaded tablets were subjected to weight variation, hardness (Pfizer hardness tester), thickness (vernier Calipers) and friability (Roche) studies according to the standard procedures [15].

2.6.3. *Drug content*

Ten tablets were weighed, finely powdered and triturate equivalent to 10 mg of the drug was accurately weighed, dissolved in pH 1.2 buffer and volume was made upto 100 ml with the same buffer. Further dilutions were done to get concentration of 10µg/ml and absorbance was read at 236 nm against blank by UV Visible spectrophotometer [15].

2.6.4. *In-vitro drug release studies of tablets*

900ml of 0.1N HCl was placed in vessel and the USP apparatus-II (Paddle Method) was assembled. The medium was allowed to equilibrate to temperature of 37°C $\pm$ 0.5°C. Nanosponge loaded tablet was placed in the vessel and operated for 2 h at 50 rpm. Then the medium was replaced with pH 6.8 phosphate buffer and continued upto 10 h at 50 rpm. At definite time intervals, 5 ml of the receptor fluid was withdrawn and same volume was replaced with fresh medium. The withdrawn fluid was filtered, suitably diluted and analyzed using UV-spectrophotometer [16].

3. Results and discussion

The present study was aimed for developing Trimethoprim nanosponge loaded extended release tablets using various polymers and excipients. FTIR studies confirmed that there are no chemical interactions between the drug and excipients used for formulation development (Figure 1-3). All the

prepared formulations were evaluated for physicochemical properties and *in-vitro* drug release studies. Initially eight formulations of Trimethoprim nanosponges were prepared by emulsion solvent evaporation method and were evaluated for flow properties. All the formulations showed values within the ranges [17] and it confirms good flowability of nanosponge powder (Table 3).

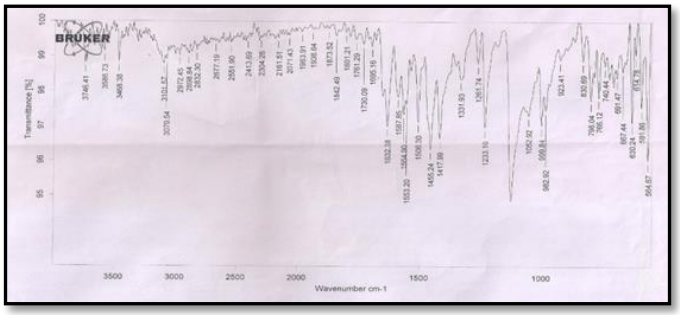

Figure 2. IR spectrum of Trimethoprim with Ethyl cellulose.

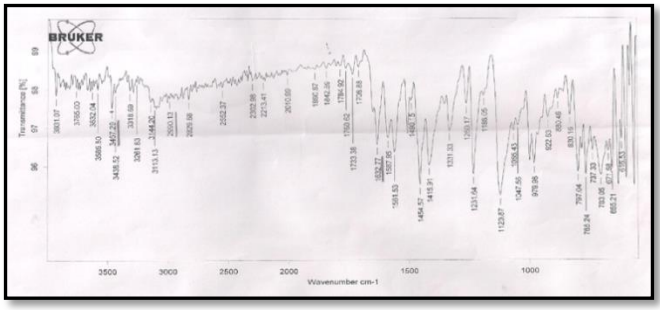

Figure 1. IR spectrum of Trimethoprim pure drug.

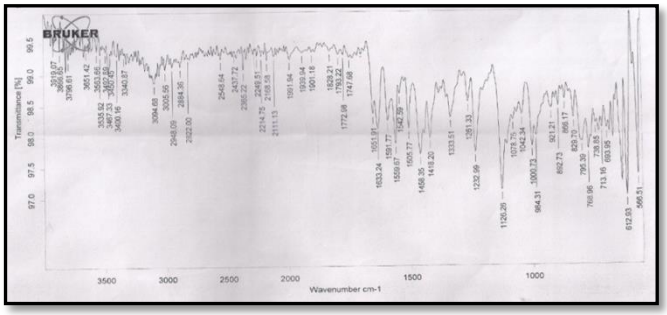

Figure 3. IR spectrum of Trimethoprim with Polyvinyl Alcohol.

Table 3. Preformulation parameters of trimethoprim nanosponges.

Formulation	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index	Hausner's Ratio	Angle of repose (θ)
F1	0.43±0.04	0.54±0.04	16.21±0.06	0.86±0.06	$25^{o}.11^{1}$±0.05
F2	0.52±0.09	0.52±0.04	16.87±0.05	0.98±0.05	$25^{o}.67^{1}$±0.02
F3	0.50±0.03	0.58±0.05	17.11±0.01	0.64±0.03	$25^{o}.54^{1}$±0.04
F4	0.51±0.06	0.54±0.07	17.67±0.08	1.12±0.04	$25^{o}.43^{1}$±0.02
F5	0.52±0.03	0.57±0.03	16.92±0.04	0.68±0.08	$27^{o}.34^{1}$±0.02
F6	0.53±0.04	0.56±0.06	17.73±0.09	1.06±0.09	$28^{o}.54^{1}$±0.03
F7	0.50±0.04	0.53±0.04	16.24±0.06	0.84±0.06	$27^{o}.11^{1}$±0.07
F8	0.51±0.09	0.54±0.04	16.67±0.05	0.87±0.05	$26^{o}.67^{1}$±0.01

Results expressed in mean (n=3) ± SD (Standard Deviation).

Percentage yield value of nanosponges was found to be the best for F4 and the % yields were ranged from 75.41±0.4 to 91.24±0.5. It was observed that as the polymer ratio in the formulation increases, the percentage yield also increases (upto optimum concentration). Further increase in the concentration of polymer (beyond the optimum level), the % yield was found to be decreased due to the sticky nature of the product which cannot be filtered. The low percentage yield in some formulations may be due to wastage of the drug-polymer solution.

The % drug entrapment efficiency of the nanosponges was found to be best for the formulation F4 and it was ranged from 68.86±0.10 to 88.66±0.5 and the results indicated that the ethyl cellulose concentration is directly proportional to the entrapment efficiency but polyvinyl alcohol concentration is indirectly proportional to the entrapment efficiency which is due

to the low solubility of polymer in aqueous phase (Table 4).

Table 4. Percentage yield and entrapment efficiency of nanosponge formulations.

Formulation	Percentage yield (%)	% Drug entrapment efficiency
F1	87.12±0.1	82.66±0.3
F2	76.36±0.2	84.4±0.2
F3	87.34±0.4	84.66±0.4
F4	91.24±0.5	88.66±0.5
F5	84.26±0.8	53.2±0.8
F6	87.51±0.1	68.86±0.10
F7	89.62±0.2	76.66±0.4
F8	75.41±0.4	85±0.9

The morphology and surface topography were investigated by Scanning electron microscopy for formulation F4 (containing 2 grams of polyvinyl alcohol) and F8 (containing 3 grams of polyvinyl alcohol). It was observed that the nanosponges were uniformly spherical in shape, spongy and porous in nature (Figure 4). The mean particle size of nanosponge was increased with increase in polymer concentration which was due to a significant increase in the viscosity, thus leading to an increased droplet size and finally a higher nanosponges size was obtained.

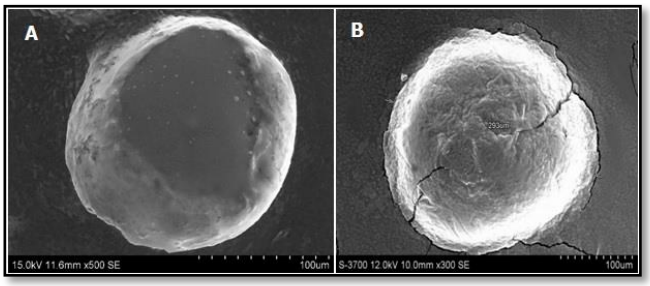

Figure 4. SEM studies, A. Formulation F4, B. Formulation F8.

The Particle size distribution of nanosponge formulation (F4) was checked by PDI (polydispersibility index) and it was found to be 0.204. This value is <1 which indicates narrow size distribution of nanosponges and the surface charge of nanosponges was determined by zeta potential and it was found to be -39.4mv (±30mv) (Figure 5-6).

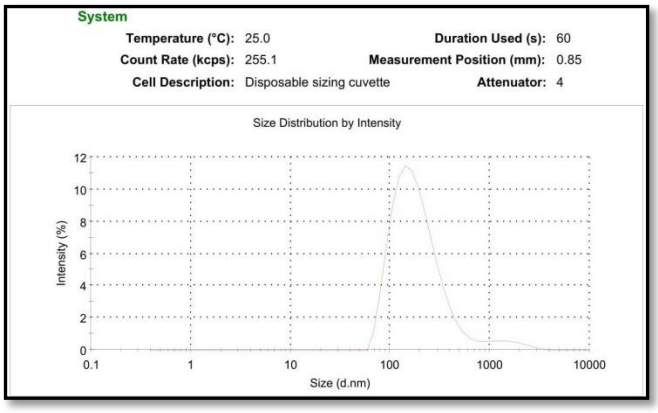

Figure 5. Size distribution image of nanosponge formulation F4.

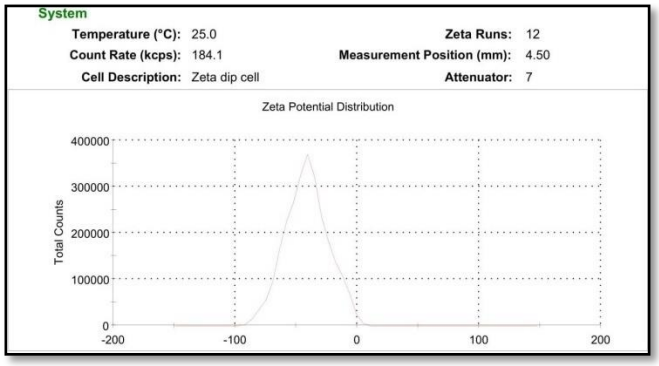

Figure 6. Zeta potential graph of nanosponge formulation F4.

The *in-vitro* drug release studies of Trimethoprim nanosponges were performed for all the 8 formulations by using USP Type-II i.e. paddle. All the formulations showed drug release for a period of 8 h (Table 5).

Table 5. *In-vitro* drug release profiles of Trimethoprim nanosponge formulations.

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	15.50±0.5	20.54±0.6	29.02±0.3	22.09±0.4	7.04±0.3	6.18±0.1	7.65±0.6	9.09±0.6
2	35.43±0.3	45.78±0.4	35.7±0.1	33.03±0.5	20.31±0.4	12.36±0.5	15.27±0.3	17.98±0.1
3	46.18±0.1	61.6±0.3	46.25±0.3	47.15±0.5	38.15±0.3	28.96±0.3	26.3±0.3	35.54±0.5
4	55.89±0.6	67.63±0.1	60.92±0.1	58.38±0.1	51.07±0.6	41.27±0.6	40.03±0.3	53.47±0.5
5	64.53±0.6	75.76±0.6	70.44±0.1	73.38±0.1	63.03±0.4	53.79±0.4	55.62±0.1	68.98±0.3
6	73.44±0.5	81.6±0.1	81.9±0.3	85.44±0.1	73.39±0.1	65.24±0.5	68.38±0.6	81.34±0.4
7	79.98±0.6	83.82±0.3	89.56±0.4	91.56±0.5	77.89±0.6	78.12±0.3	79.87±0.4	88.93±0.3
8	83.98±0.6	86.88±0.5	92.33±0.6	93.47±0.4	81.78±0.6	85.67±0.6	86.84±0.1	92.67±0.1

Results expressed in mean (n=3) ± SD (Standard Deviation).

Among the formulations from F1 to F4, the F4 is having the highest percentage of drug release, this is because of the polymer concentration is directly proportional to the drug release. Similarly, drug release was increased from the formulation F5 to F8 but with increase in Polyvinyl alcohol concentration causes decrease in drug release because of its low entrapment efficiency. So, among all the formulations F4 is showing highest percentage of drug release i.e., 93.47± 0.4 at the end of 8 h. From the results of evaluation parameters, formulation F4 showed acceptable results and hence, F4 was selected for further studies. Six formulations were developed by taking F4 using HPMC K100M and HPMC K15M. the powder blend was subjected to precompression studies and obtained results were complied with the pharmacopoeial limits (Table 6). The manufactured tablets were evaluated for post compression parameters which were showed acceptable results (Table 7).

Table 6. Results of Precompression parameters of extended release formulations.

Formulation	Bulk Density	Tapped Density	Carr's Index (%)	Hausner's ratio	Angle Of Repose(Θ)
F1	0.45±0.02	0.55±0.04	18.18±0.6	1.22±0.7	$27^{o}.91^{1}$±0.9
F2	0.47±0.04	0.55±0.02	14.54±0.4	1.17±0.6	$28^{o}.23^{1}$±0.7
F3	0.50±0.04	0.58±0.06	13.79±0.2	1.16±0.4	$29^{o}.34^{1}$±0.6
F4	0.46±0.06	0.55±0.02	16.36±0.7	1.19±0.2	$26^{o}.71^{1}$±0.4
F5	0.50±0.07	0.58±0.04	13.79±0.2	1.16±0.4	$29^{o}.34^{1}$±0.2
F6	0.47±0.09	0.55±0.06	14.54±0.4	1.17±0.2	$28^{o}.23^{1}$±0.9

Results expressed in mean (n=3) ± SD (Standard Deviation).

Table 7. Results of post compression parameters of extended release tablets.

Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F1	505±0.5	4.5±0.4	3.59±0.9	0.43±0.9	97.23±0.6
F2	504±0.4	4.6±0.5	3.64±0.4	0.34±0.4	98.55±0.8
F3	501±0.6	4.5±0.8	3.59±0.5	0.49±0.6	98.16±0.9
F4	506±0.8	4.6±0.6	3.58±0.9	0.47±0.5	99.25±0.4
F5	499.4±0.4	4.3±0.5	3.59±0.6	0.49±0.5	98.16±0.5
F6	502±0.9	4.7±0.4	3.64±0.5	0.34±0.6	98.55±0.5

Results expressed in mean (n=3) ± SD (Standard Deviation).

The *in-vitro* drug dissolution studies of nanosponge loaded extended release tablets were performed by taking USP dissolution apparatus-2 using 500ml of 0.1 N HCl (for first 2 h) and pH 6.8 phosphate buffers (3rd h to 10th h). Most of the formulations showed linear drug release pattern for the period of 10 h. At the end of 10 h, the cumulative percentage drug release found to be 91.56±0.8, 93.84±0.3, 98.43±0.1**,** 79.95±0.1, 78.83±0.1, 85.01±0.2 for the formulations F1-F6 respectively (Table 9 & 10). All the formulations from F1 to F6 were prolonged the drug release up to 10 h. But in comparison of both the polymers, the HPMC K100M prolonged the drug release with maximum drug release concentration of 98.43±0.1 (F3) at the end of 10th h and this is because of its high viscosity when compared to the HPMC K15M. Hence, from the dissolution studies, it was found that the formulation F3 was the best formulation among the nanosponge loaded extended release formulations (Table 8).

Table 8. Dissolution profiles of nanosponge loaded extended release formulations.

Time (h)	Pure drug solution	SF1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
1	2.65±0.3	19.42±0.3	16.18±0.2	15.02±0.1	11.52±0.9	16.56±0.2	16.14±0.9
2	6.54±0.9	23.05±0.8	38.27±0.9	22.55±0.2	29.36±0.3	29.92±0.3	27.35±0.2
3	15.28±0.3	34.17±0.6	44.96±0.1	40.89±0.2	35.2±0.9	36.52±0.8	30.73±0.2
4	28.32±0.2	42.25±0.1	51.2±0.2	58.48±0.6	49.65±0.1	42.85±0.2	45.24±0.3
5	42.64±0.1	54.33±0.2	68.63±0.3	69.62±0.2	61.1±0.2	57.21±0.1	58.37±0.8
6	53.82±0.3	62.24±0.6	75.85±0.3	75.87±0.2	68.99±0.3	60.05±0.2	62.83±0.2
7	68.91±0.8	76.45±0.9	81.89±0.2	84.35±0.8	72.58±0.8	69.16±0.9	69.19±0.2
8	70.95±0.9	86.48±0.2	86.18±0.1	90.54±0.2	76.56±0.6	72.61±0.2	75.02±0.8
9	-	89.45±0.3	90.28±0.2	92.99±0.1	79.95±0.1	78.83±0.1	85.01±0.2
10	-	91.56±0.8	93.84±0.3	98.43±0.1	83.25±0.2	82.21±0.2	90.58±0.2

Results expressed in mean (n=3) ± SD (Standard Deviation).

4. Conclusion

From this study, it was concluded that nanosponge loaded extended release tablets of Trimethoprim showed extended drug release for about 10 h with enhanced solubility and dissolution. Hence, nanosponge technique will be a challenging approach for enhancing the solubility of poorly soluble drugs and there is lot of scope for future *in-vivo* studies.

5. Conflict of Interest

The author(s) report no conflict(s) of interest(s). The author along are responsible for content and writing of the paper.

6. Acknowledgment

NA

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