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Sustained-Release Matrix Tablets of Nitrofurantoin: Formulation and Evaluation

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Abstract : Urinary Tract Infection is a serious health problem affecting millions of people each year. Infection of the urinary tract is the second most common type of infections in the body. Nitrofurantoin is a drug of choice for UTIs. Sustained release drug delivery system offer advantages of attenuation of adverse effects, fewer fluctuations in plasma drug concentration, improved patient compliance, reduction in dosing frequency, etc. Therefore, present study attempt has been made to develop, optimize and evaluate sustained release tablets of Nitrofurantoin using polymer such as HPMC K-100 LV Premium and different exipients by wet granulation technique. The prepared tablets were evaluated for hardness, friability, thickness, weight variation, drug content and *in vitro* dissolution studies. All formulated tablets showed acceptable pharmacotechnical properties and complied with pharmacopoeial specifications but batch F_{10} shows better results and release than other formulated tablets. The *in-vitro* release data was plotted for Formulation F_{10} which indicates that drug release was governed by nearly zero-order kinetics. Formulation F_{10} showed no change in physical appearance, drug content after storage 40 ^{o}C ± 2 ^{o}C / 75% RH ± 5% for 3 months. Further, in vivo and continuation of stability studies are recommended.
Keywords: Sustained release, Tablets, Nitrofurantoin, HPMC K-100 LV Premium.

Introduction

Nitrofurantoin is a nitrofuran derivative that is used in the treatment of urinary tract infections including prophylaxis or long-term supressive therapy in recurrent urinary tract infection[1-5].

Urinary tract infection is one of the commonest problems faced by the clinicians. Urinary tract infection is serious health problem affecting millions of people each year. Infection of the urinary tract is the second most common type of infections in the body. Urinary tract infections (UTIs) account for about 8.3 million doctor visits each year. Women are especially prone to UTIs; one woman in five develops a UTI during her lifetime. UTIs in men are less as in women but can be very serious when they occur. Sulfonamides, Tetracycline, Nitrofurantoin, Cotrimoxazole, Ampicillin, Amino glycosides, Fluoroquinolones and Cephalosporin, etc. are the drugs which are chiefly used in urinary tract infections[6-8].

The oral route is the most important method for administration of drugs, especially solid oral dosages forms. During the past few years there has been much work devoted to the development of systems which promote the release of pharmaceutical ingredients over a prolonged period of time. Sustained release systems have been widely used in oral medication, since early 1950s. The advantage of administering orally active drugs in a sustained release formulation is numerous. Administration of SR medication once a day instead of numerous times a day eliminates a major source of inconvenience for the patient as well as providing for a more even

distribution of drug concentration in blood and sustained release dosages form also not effect the potency of the drug. Other oral dosages forms releases drug quickly in the stomach it can cause stomach upset. The acid environment of stomach may adversely affect the potency of the drug [9-12].

With the view to all the above information, an attempt had been made to devlop a sustained release tablet of Nitrofurantoin, which is used in the urinary tract infection to produce sustained effect, attenuation of adverse effect, and improved patient compliance.

Materials And Methods

Materials

Nitrofurantoin (monohydrate) was procured from Panchsheel organics Ltd., Indore. HPMC K-100 LV Premium was obtained from Colorcon asia Pvt. Ltd. Goa. Granulac–200 was obtained from Meggle Pvt. Ltd. Talc, Iso propyl alcohol, and Magnesium stearate were obtained from Vijay chemicals, Merck industries, and Nitika chemicals, Ahemdabad, respectively. All other chemicals/solvents used were of analytical grade and purchased from authorized dealer.

Methods

Formulation of sustained release tablets of Nitrofurantoin

Tablets containing 107.5 mg of Nitrofurantoin each were prepared as per composition given in Table1. Mixture of drug and polymer was first passed through sieve no. 40. Iso propyl alcohol and water were used for wet granulation. After drying, granules were passed through sieve no. 20 and lubricants were passed through sieve no. 60 and mixed thoroughly with dried granules. The granules were compressed using Cadmach 16 station compression machine equipped with 9.6 mm punch size. A minimum of 500 flat, round, both side plain, uncoated tablets were prepared for each batch.

Pre compression parameters (Evaluation of granules)

Angle of Repose [13, 14]

Angle of repose was determined using funnel method. The blend was poured through funnel that can be elevated vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using the formula

$$\theta = \tan^{-1}\frac{h}{r}$$

Where, θ is the angle of repose, h is height of pile; r is the radius of the base of pile.

Bulk Density [13]

Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated measuring cylinder. The bulk volume (V_b) and weight of powder (M) were determined. The bulk density was calculated using the formula

$$\rho_b = \frac{M}{V_b}$$

Tapped Density [13]

The graduated measuring cylinder containing known mass of blend was tapped for a fixed time / or specified time. The tapping was continued until no further change in volume was noted. The minimum volume occupied in the cylinder and weight of the blend was measured. The tapped density (ρ_t) was calculated using the following formula

$$\rho_t = \frac{M}{V_b}$$

Carr's Compressibility Index [13]

The compressibility index of the granules was determined by Carr's compressibility index, which was calculated by using the following formula

$$I = \frac{Vo - Vt}{Vo} \times 100$$

Where, Vo is bulk density, Vt is tapped density.

Hausner Ratio [13, 15]

It is calculated by the following formula

$$\text{Hausner Ratio} = \frac{\rho t}{\rho d}$$

Where ρ_t is tapped density and ρ_d is bulk density. Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Drug – Excipient Interaction Studies [16, 17]

The FT-IR spectra for pure drug, polymer and mixture of drug-polymer were recorded using potassium bromide disk method. Samples were prepared in potassium bromide disk by means of a hydrostatic press. Spectral measurements were obtained by powder diffuse reflectance on a FT-IR spectrophotometer (Perkin Almer) in the wave number region 400-2000 cm^{-1} to find out drug-excipients interactions, if any.

Evaluation of Nitrofurantoin SR tablets (Post-compression parameters)

Thickness[13, 18]

Control of physical dimensions of the tablets, such as size and thickness is essential for consumer acceptance and to maintain tablet-to-tablet uniformity. The dimensional specifications were measured using digital micrometer calipers. The thickness of the tablet is mostly related to the tablet hardness and it can be used as initial control parameter.

Hardness [13]

The hardness of the tablet from each formulation was determined using Monsanto hardness tester.

Weight variation [13, 18]

Twenty tablets from each formulation were selected at random and average weight was determined, then individual tablets were weighed and individual weight was compared with average weight.

Friability [13, 18]

Weighed amount of twenty dedusted tablets was placed in drum of friability test apparatus, i.e. Roche Friabilator. The apparatus was operated for 4 minutes at a speed of 25 rpm and tablets were then dusted and reweighed. Friability was calculated by the following formula.

$F = 100[W_0 - W] / W_0$
F = Friability
Wo = Initial weight
W = Final weight

Assay [19]

Twenty tablets of Nitrofurantoin were weighed and powdered. From this, powder equivalent to 0.15 gm Nitrofurantoin was weighed accurately and poured in volumetric flask. To this, 50 ml of dimethylformamide was added, after shaking it for 5 minutes sufficient water was added to produce 1000 ml, with gentle mixing. Thereafter, 5 ml of solution was taken out and diluted upto 100 ml with a solution containing 1.8 % w/v solution of sodium acetate and 0.14 % v/v of glacial acetic acid. The absorbance of the resulting solution was measured at 367nm, using sodium acetate-acetic acid solution as a blank. The content of $C_8H_6N_4O_5$ was calculated taking 765 as the specific absorbance at 367 nm.

***In Vitro* dissolution studies** [20]

In vitro dissolution studies for all the fabricated tablets and marketed tablet of Nitrofurantoin (Nitrofur SR tablet, Wanbury) were carried out by using USP Type II apparatus at 75 rmp in 900 ml of pH 0.1 N HCl and pH 7.5 phosphate buffer maintained at $37^oC \pm 0.5^oC$. To obtain pH 7.5 buffer, 50 ml of solution (KH_2PO_4 and KOH) was added into 900 ml of pH 0.1 HCl. Aliquots of 10 ml were withdrawn at the specified time intervals, i.e., 1, 2, 4, 6, 8 hrs. An equal volume of fresh medium, which was pre- warmed at 37^0C was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. Samples were filtered through whatmann filter paper and assayed spectrophotometrically at 274nm using Shimadzu 1700 spectrophotometer. The amount of drug present in the samples was calculated with the help of standard plot/curve constructed from reference standard.

Analysis of release data: [21, 22]

The *In-Vitro* release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time), Korsmeyer-Peppas (log cumulative percentage of drug released versus log time), and Hixson-Crowell [(Percentage released) $^{1/3}$ versus time] equation models.

Statistical evaluation of dissolution (Calculation of Similarity factor): [23-25]

According to US FDA guidance for dissolution data equivalence, model independent approach is recommended. This involves use of similarity factor (f_2) which provides simple means to compare the data. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between two curves. FDA suggests that dissolution profiles may be compared using following equation, which defines a similarity factor (f_2).

$$f_2 = 50 \log_{10} \{[1 + (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$$

Where R_t and T_t are the percentage of dissolved drug data at each time point, and n is the number of paired dissolution data. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar.

Stability study [26, 27]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light, etc. In the present study, Accelerated stability testing was carried out as per ICH guidelines. For this optimized SR formulation of Nitrofurantoin (F_{10}) was suitably packed (Blister packing) and stored at 40°C ± 2°C / 75% ± 5% RH for a period of three months. Sampling was done at 0, 1, 2, 3 months and sampled tablets were evaluated for tablet properties, that is, thickness, hardness, weight variation, friability, drug content and drug release at each sampling time point.

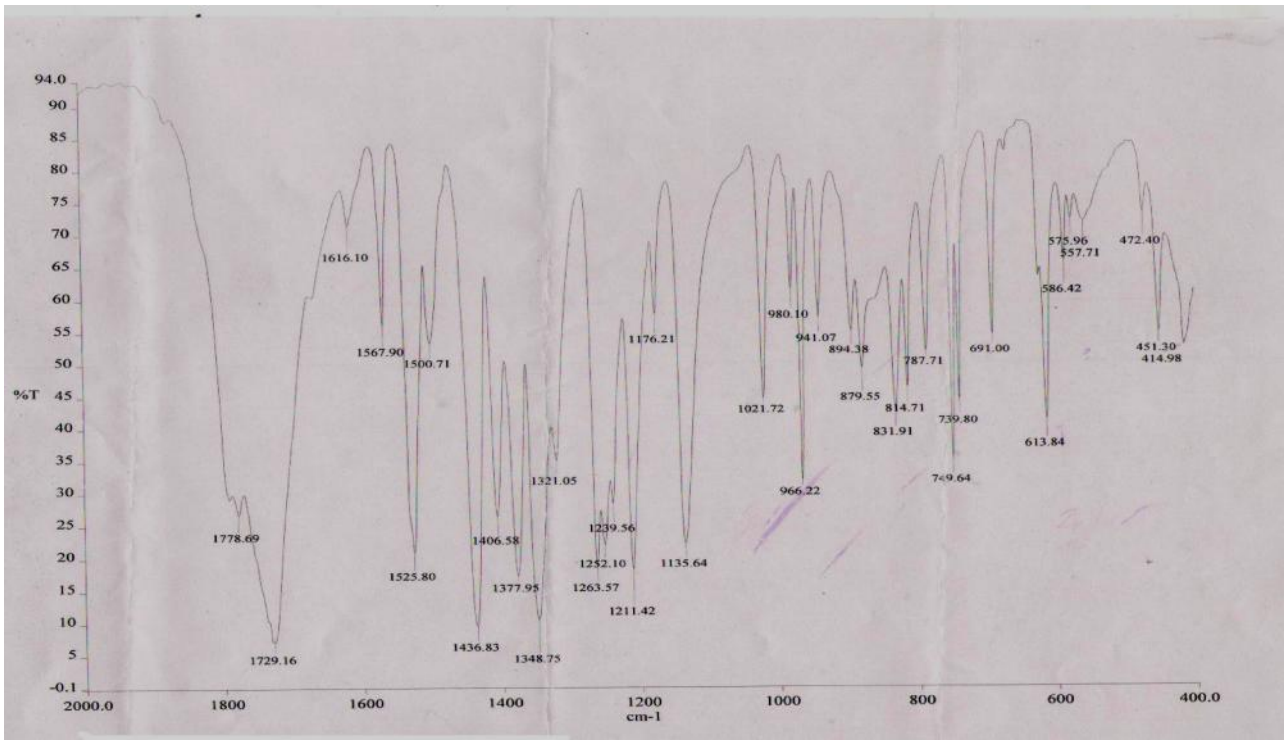

Figure 1-A: FTIR spectral of pure Nitrofurantoin

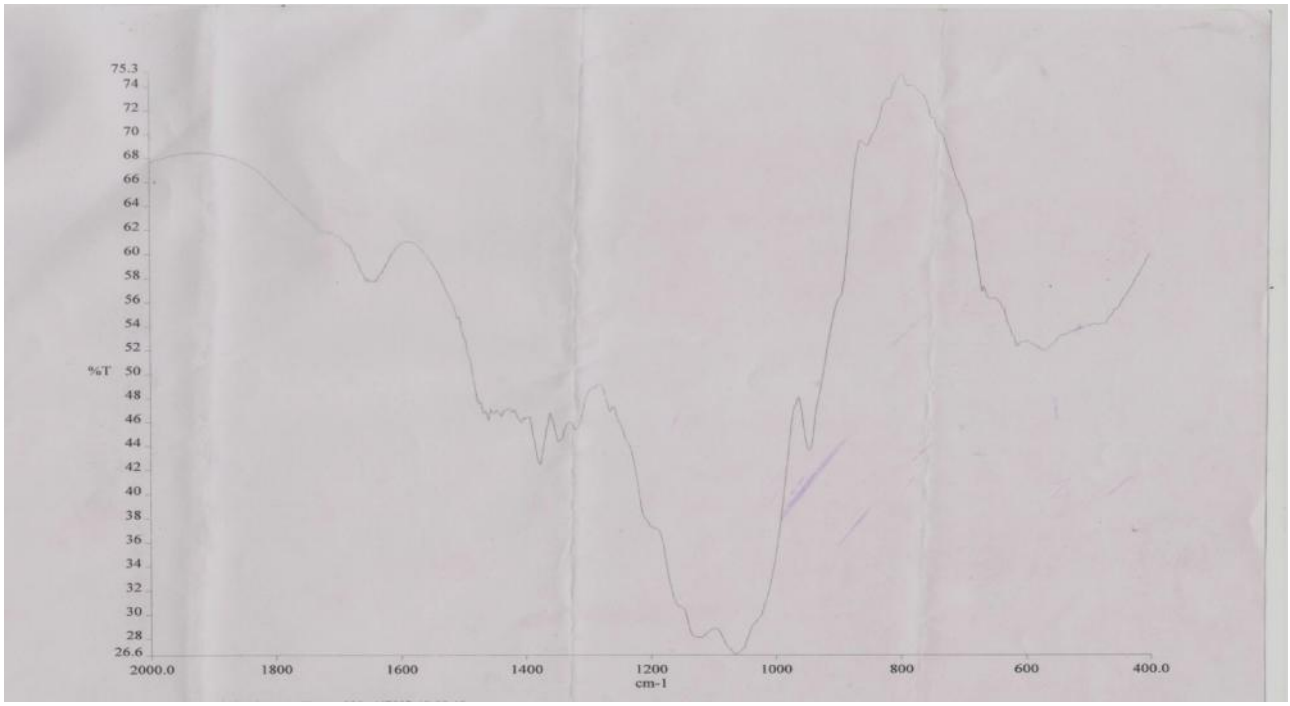

Figure 1-B: FTIR spectral of HPMC K-100

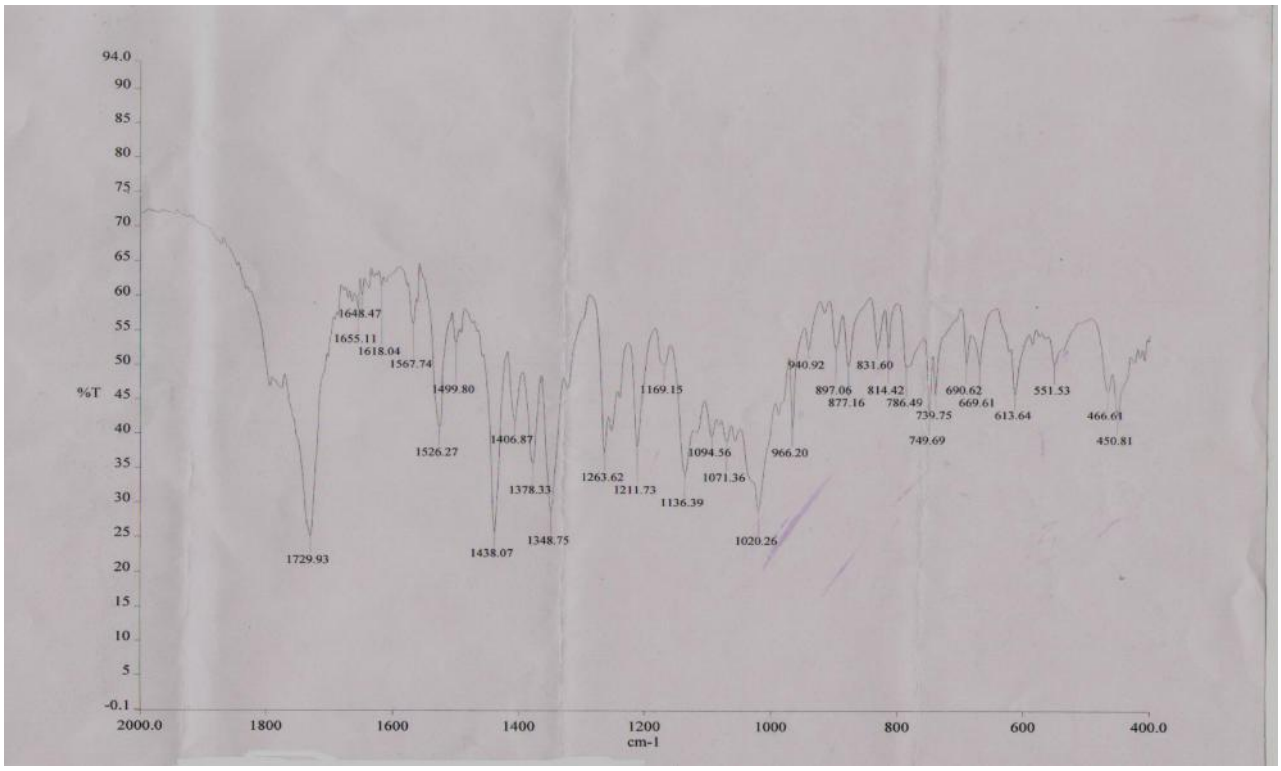

Figure 1-C: FTIR spectral of HPMC K-100

Table I: Composition of different batches of sustained release tablets of Nitrofurantoin

Ingredients (mg)	Formulations									
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
Nitrofurantoin (monohydrate)	107.6	107.6	107.6	107.6	107.6	107.6	107.6	107.6	107.6	107.6
HPMC K-100 LV Premium	47.52	40	45	47.52	45	47.52	40	15	25	30
Granulac -200	81.88	89.4	84.4	76.88	79.4	81.88	89.4	114.7	104.7	99.4
Iso propyl alcohol	100%	100%	-	50%	25%	75%	75%	75%	75%	75%
Water	-	-	100%	50%	75%	25%	25%	25%	25%	25%
Talc	10	10	10	15	15	10	10	10	10	10
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3

Table II: Evaluation of mixed blend of drug and exipients

Formulation	Angle of Repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's Ratio	Compressibility Index (%)
F_1	30.11	0.6231	0.7224	1.15	13.74
F_2	30.56	0.6346	0.7378	1.16	13.98
F_3	31.35	0.6767	0.7965	1.17	15.04
F_4	30.91	0.6723	0.7845	1.16	14.30
F_5	30.18	0.6298	0.7269	1.15	13.35
F_6	29.87	0.6321	0.7323	1.15	13.68
F_7	28.79	0.6367	0.7434	1.16	14.35
F_8	28.68	0.6432	0.7421	1.15	13.32
F_9	28.46	0.6294	0.7293	1.15	13.69
F_{10}	28.16	0.6236	0.7160	1.14	12.90

Table III: Evaluation of tablets

Formulations	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability %	Assay %	% Drug release
F1	3.06±0.12	6±0.034	247-253 (Within the IP limit of ±7.5%)	0.013	100.87±0.65	61.20
F2	3.08±0.06	6±0.038		0.016	101.46±0.39	72.11
F3	3.00±0.09	5±0.054		0.030	99.89±1.08	38.96
F4	3.10±0.10	6±0.036		0.020	99.87±0.84	78.00
F5	3.08±0.14	6±0.38		0.014	101.67±0.62	51.45
F6	3.04±0.7	6±0.036		0.014	101.23±0.44	72.59
F7	3.06±0.13	6±0.040		0.018	102.06±0.32	80.34
F8	3.04±0.4	6±0.024		0.011	101.93±0.34	106.34
F9	3.06±0.4	6±0.22		0.01	101.54±0.19	101.03
F10	3.06±0.2	6±0.018		0.01	101.73±0.24	95.19

Results and Discussion

Ten formulations of Nitrofurantoin were prepared with different concentrations of HPMC K100 LV Premium and different excipients by using wet granulation method. For each formulation, blend of drug and exipients was prepared and evaluated for various parameters/properties. Bulk density was found in the range of 0.6231-0.6767 g/cm^3 and the tapped density between 0.7160-0.7965 g/cm^3 **(**Table II). Using these two density data Hausner's ratio and compressibility index was calculated. The powder blend of all the formulations had hausner's ratio of less than 1.25 indicating good flowability. The compressibility index was found between 12.90 and 15.04 % and the compressibility-flowability correlation data indicating a fairly good flowability of the blend. The good flowability of blend was also evidenced angle of repose (value range of 28.16 - 31.35 ^{0}), which is below 40^0 indicating good flowability. Drug-excipient interaction was determined by using FTIR. IR spectrum of blend of polymer with drug exhibits characteristic peaks at 1729.16^{cm-1}, 1567.90^{cm-1}, 1406.58^{cm-1}, 1348.75^{cm-1}, 1263.57^{cm-1}, 1211.42^{cm-1}, 966.22^{cm-1}. Peaks observed for drug-polymer blend are same as observed for pure drug molecule, indicating no chemical interaction between HPMC K-100 LV Premium and Nitrofurantoin.

The prepared matrix tablets were evaluated for parameters such as thickness, hardness, friability, weight variation, assay, and *in-vitro* release. Results for these parameters are shown in Table III. Thickness of the tablets was measured by screw gauge by picking tablets randomly from all the batches. The mean thickness was (n=3) almost uniform in all the formulations and value ranged from 3 ± 0.09 mm to 3.10 ± 0.10 mm. The standard deviation values indicated that all formulations were within the range. Friability of the tablets was found below 1 % indicating a good mechanical resistance of tablets. Since the powder material was free flowing, tablets thus obtained were of uniform weight due to uniform die fill, with acceptable weight variations as per pharmaceutical specifications. The drug content was found in the range of 99.87 – 102.06 % (acceptable limit) and the hardness of the tablet between 5.0 – 6.0 kg/cm^2 (Table III). Results of *in- vitro* release profile indicated that among all the formulations, F_{10} was the most promising formulations as it showed 29.97%, 61.75%, 83.48%, 90.41% and 95.19% drug release within 1, 2, 4, 6 and 8 hrs. respectively and all physical parameters were compiled with pharmacopoeial specifications. *In-Vitro* drug release of all the formulated tablets were compared with marketed preparation (Nitrofur SR tablet) and tablet F_{10} was found to be the best one among all the formulated tablets. All studies were done in triplicate. Moreover, Similarity factor (f_2) between optimized formulation F_{10} and marketed formulation was found to be 84.302 this indicates that optimized formulation F_{10} and marketed formulation show similar dissolution profiles. The *in-vitro* release data was plotted for various kinetic models. The R^2 value for zero-order was found to be 0.9123 which indicates that optimized formulation F_{10} was found to be nearly zero order drug release, governed by dissolution through matrix.

The optimized formulation (F_{10}) was found to be stable under the test storage conditions of 40 ^oC ± 2 ^oC / 75% ± 5% RH as there was no change in tablet properties in between and after completion of three - month stability study.

Table IV: In-vitro release profile of Nitrofurantoin sustained release tablets of F_{10} formulation

Time (hr)	Root T	Log T	Cum. % drug release	Cum % drug retained	Log % cum drug release	Log % cum drug retained	(Percentage retained)$^{1/3}$
1	1	0	29.97	70.03	1.47	1.84	4.12
2	1.414	0.301	61.75	38.25	1.79	1.58	3.36
4	2	0.602	83.48	16.52	1.92	1.21	2.54
6	2.449	0.778	90.41	9.59	1.95	.98	2.12
8	2.828	0.903	95.19	4.81	1.97	.68	1.68

Table V: Kinetics value obtained from in-vitro released data of formulation F_{10}

Kinetic model	Intercept	Slope	Regression (R^2)
Zero-order plot	19.4	7.7667	0.9123
First-order plot	-0.292	2.134	0.9960
Higuchi plot	15.91	24.43	0.8789
Peppas-korsmeyer	0.116	1.472	0.7787
Hixson Crowell	-0.612	4.6	0.9679

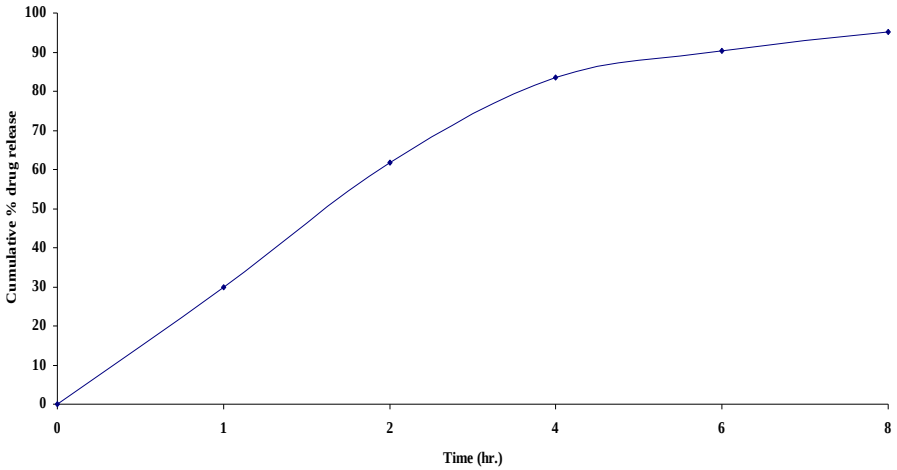

Figure 2: In Vitro cumulative % drug release vs. time for formulation (F10) of nitrofurantoin (Zero order release)

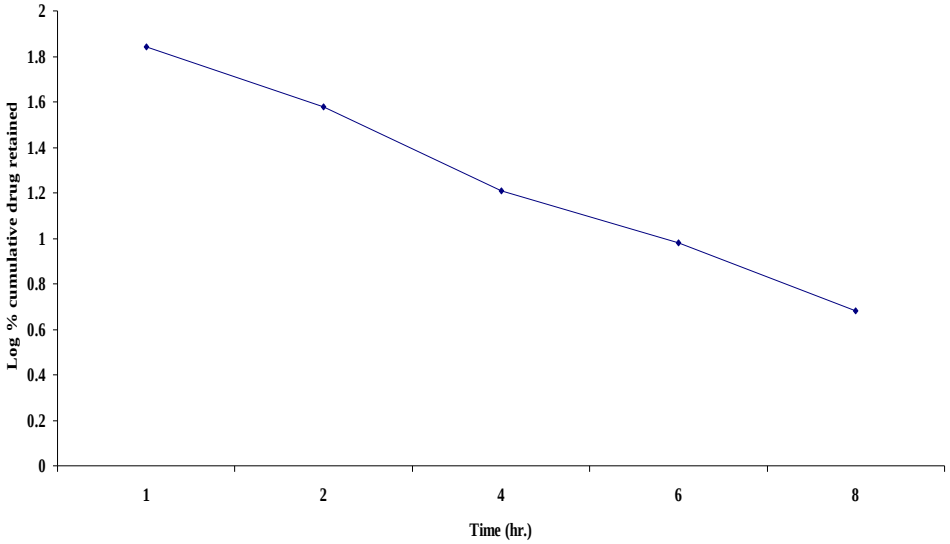

Figure 3: Log cumulative % drug retained vs. time for formulation (F_{10}) of nitrofurantoin (First order plot)

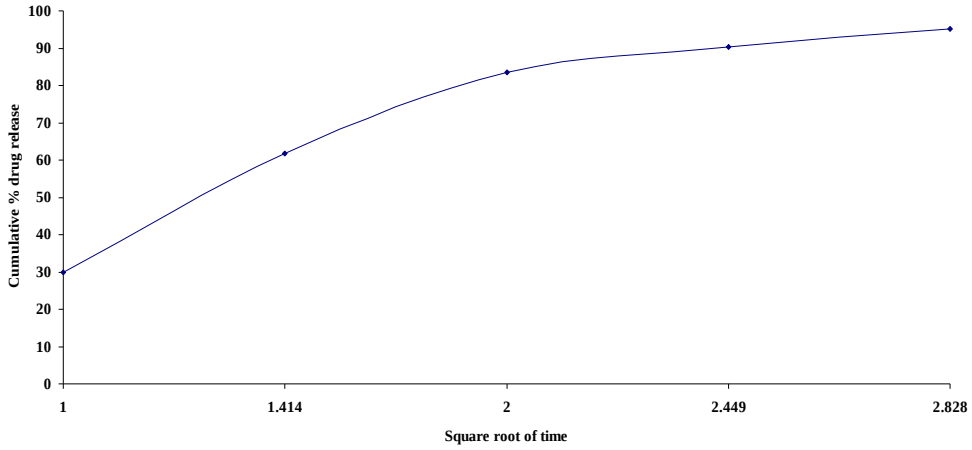

Figure 4: Cumulative % drug released vs. square root of time for formulation (F_{10}) of nitrofurantoin (Higuchi matrix)

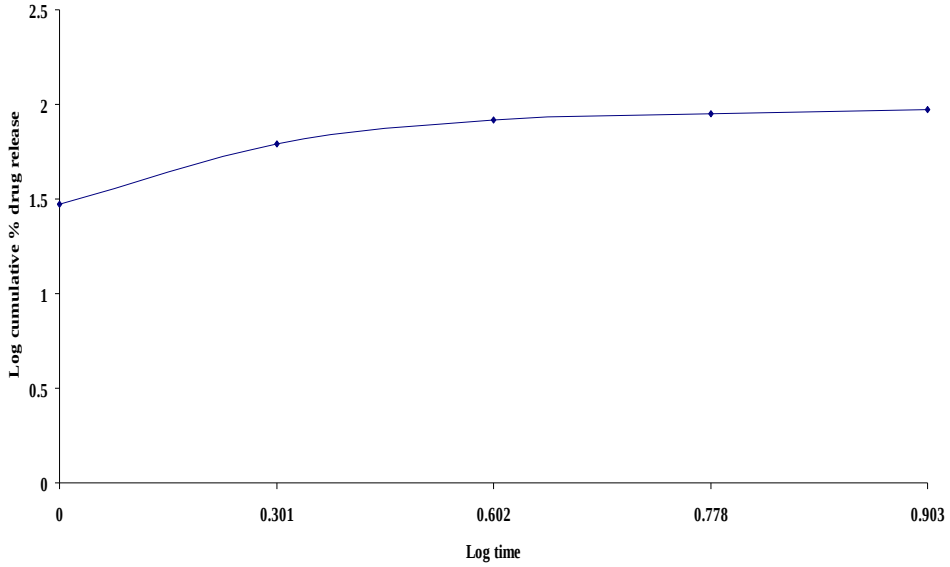

Figure 5: Log cumulative % drug released vs. log time for formulation (F10) of nitrofurantoin (Peppas)

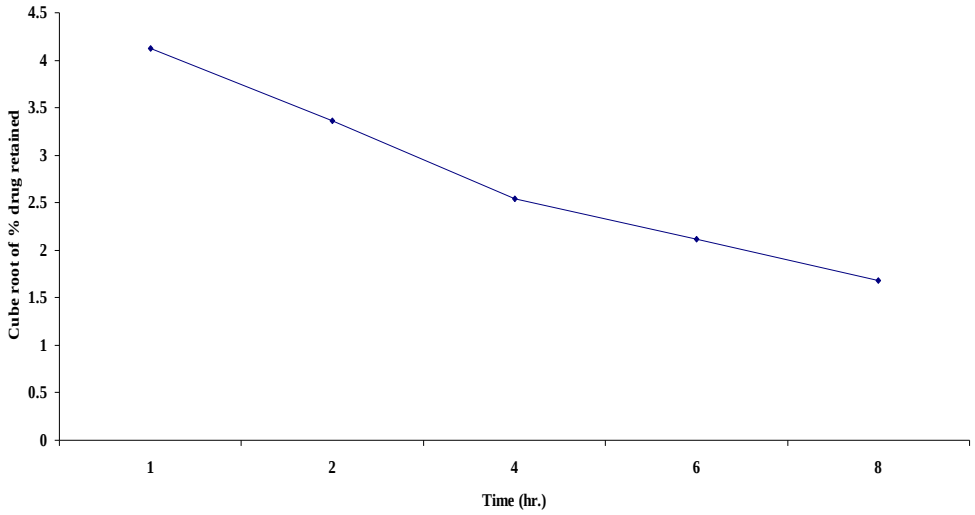

Figure 6: Cube root of % drug retained vs. time for formulation (F10) of nitrofurantoin (Hixson-Crowell)

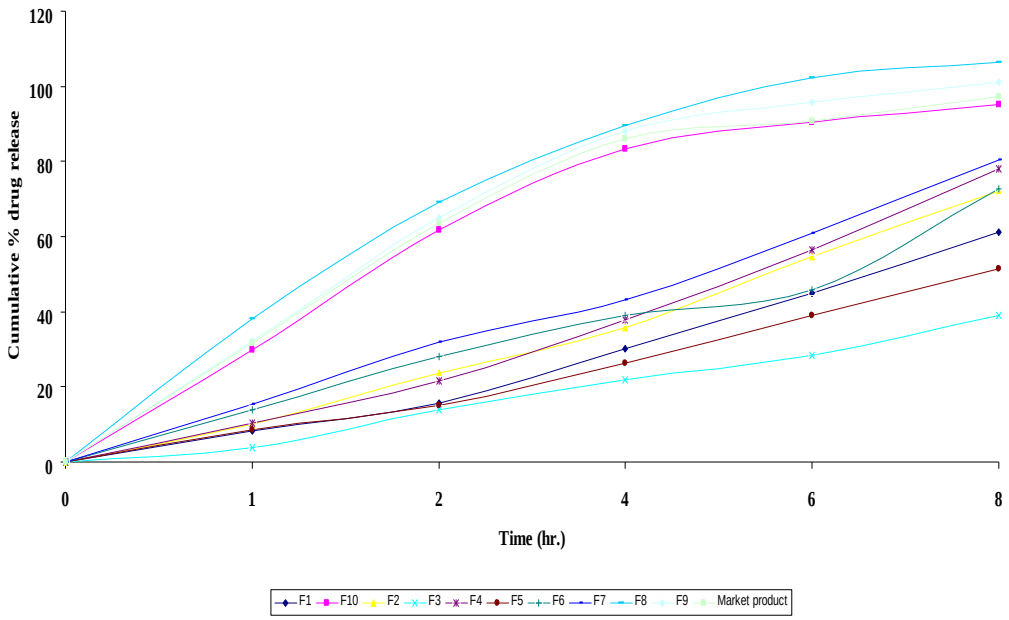

Figure 7: Comparative dissolution profiles of Nitrofurantoin tablets with market product.

Conclusion

The present study was undertaken with the aim to formulate and evaluate Nitrofurantoin sustained release tablet. The study reveals that formulation F_{10} is an ideal or optimized formulation for sustained release tablets, as it fulfills all the requirements for sustained release tablets. The reproducibility and accuracy of formulation was required further in-vivo studies and continuation of stability studies is also recommended.

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