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FORMULATION AND EVALUATION OF NITROFURANTOIN SUSTAINED RELEASE CAPSULE

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ABSTRACT

Urinary Tract Infection (UTI) is a serious medical issue liable for influencing a great many individuals. Nitrofurantoin is a medication of decision for UTIs. Sustained release drug delivery system offers a progression of favorable circumstances. The purpose of the study to develop, optimize and appraise sustained release capsules of nitrofurantoin using polymer such as Methocel K4 Premium and different excipients by wet granulation technique. The evaluation involved physical properties studies (weight variation, drug content uniformity) of capsules and in vitro release kinetics assessment. The USP Type 1 dissolution apparatus was selected to perform the dissolution test and 900 ml phosphate buffer of pH 7.2 at 100 rpm was used as dissolution medium at temperature of 37 °C. The release kinetics was analyzed using zero-order, first order, Higuchi's equations, Hixon-Crowell equation and Krosmeyer-Peppas equation. Noteworthy differences were found among the drug release profile from different level of polymeric matrix. The release kinetics was found governed by the content of polymers in the matrix system. Higher polymeric content in the matrix decrease the release rate of drug, because of increased tortuousity and decreased porosity. All formulations followed Krosmeyer-Peppas kinetics. When the release data was plotted into Krosmeyer-Peppas equation, then it was confirmed that F-1, F-3, F-4 and F-5 exhibited fickian type drug release whereas F2 and F6 exhibited non-fickian type drug release

from the matrix granules of the capsule. In-vitro release studies revealed that the formulation F-2 and F-6 can be taken as an ideal or optimized formulation for sustained release capsule.

KEYWORDS: Sustained release; capsule; nitrofurantoin; Methocel K4 Premium, In-vitro study.

INTRODUCTION

Urinary tract infection (UTI) is a serious bacterial infection affecting both men and women, which happens generally intermittently. UTI treatments are difficult due to its resistant behavior and recurrence.[1] Women are more vulnerable to UTI than men. It is anticipated that one out of five women develops UTI throughout her life.[2] Nitrofurantoin has antiseptic property active against urinary microorganisms which is usually bacteriostatic in nature.[3] Oral route is the most acceptable route for drug administration that provides high advantage and patient compliance. Conventional drug administration causes frequent increase of drug concentration in the blood and causes toxicity. After administration it reaches to therapeutic level for brief interval of time. Then the drug concentration drops in the blood or tissues and needs re-administration of drugs. Sustained release delivery systems have expected and consistent drug release which provides desired therapeutic potential, decreased toxicity and improved patient compliance. Conventional dosage forms usually doesn't offer rate controlled release of drug. Generally, completely different approaches are investigated to modify drug release pattern from dosages. It is modified to render sustained release drug delivery for improved therapeutic response by exploitation capsule, suspension, matrix tablet formulation etc. Formulation of sustained release drug is important to meet the challenges of many clinical needs.[4,5,6] The study is an endeavor to develop a sustained release capsule of nitrofurantoin that is used in treatment of UTI to render sustained release effect, reduced adverse effect and enhanced patient compliance.

MATERIALS AND METHODS

MATERIALS

Nitrofurantoin was a kind gift from Sandog Fangxing Technology Development co. Ltd., Shandog, Chiana and Nintoin SR Capsule; Incepta Pharmaceuticals Ltd (marketed product) was purchased from a local market in Bangladesh. The excipients present in the SR granules are: hydroxypropyl methylcellulose-K4M (HPMC; Methocel K4M Premium, Colorcon Asia Pvt. Ltd., Singapore), Microcrystalline Cellulose- Avicel 101, Povidone- PVPK-30, Colloidal silicone dioxide were obtained from Eskayef Bangladesh Limited as a gift.

METHODS

Preparation of capsules

Single unit capsules were formulated with various proportions of excipients. The drug nitrofurantoin and required quantity of each ingredient for each predetermined formulation were accurately weighed and blended after passing through 20 mesh screens. The blend was kneaded well to make granules and the wet granules were transferred into a dryer for drying at 60 ± 2 ^{0}C until the LOD content of the dry granules was achieved in between 1.5-2.5%. Finally, Aerosil 200 (colloidal silicone dioxide) was passed through 40 mesh screen and mixed well for 2-3 minutes preceding experimental manual filling into the empty capsule shells size #2. The composition of the nitrofurantoin SR Capsule is given in Table 1.

Table 1: Composition of nitrofurantoin SR capsule.

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6
Nitrofurantoin (anhydrous) Potency: 99.50%	5.025 g	5.025 g	5.025 g	5.025 g	5.025 g	5.025 g
Microcrystalline Cellulose (Avicel PH 101)	4.500 g	4.000 g	3.925 g	3.805 g	3.614 g	2.975 g
Methocel K4 Premium	0.400 g	0.380 g	0.475 g	0.570 g	0.760 g	1.425 g
Povidone	-	0.143 g	-	-	-	-
Colloidal Silicone Dioxide	0.100 g	0.100 g	0.100 g	0.100 g	0.100 g	0.100 g
Distilled water	4.2 ml	8 ml	5 ml	4.5 ml	4 ml	4 ml

Evaluation of Capsule

Prepared capsules were assessed for certain physical properties like uniformity of weight variation, content uniformity, in vitro dissolution profile, drug release study etc.

Weight Variation

Weight variation was done by choosing 10 capsules at random and weighing one by one. Average weight was calculated and the weight of individual tablet was compared with it.

Content uniformity

Every individual capsule in a batch should be in uniform weight and weight variation in within permissible limits. Hard capsules containing 25 mg or more of the drug contents should meet content uniformity prerequisites. 10 capsules were assayed exclusively and acceptance value was calculated. The prerequisite meets if the acceptance value of 10 capsules is not exactly or equivalent to 15%. If acceptance value is greater than 15% or is about 25% then, the next 20 units were tested and calculated the acceptance value. The 30

capsules if not exactly or equivalent to 15% and no individual unit is 1 - 25*0.01 nor more than 1 + 25*0.01.

Calculation of acceptance value:

$$(Reference\ value\ -\ mean\ of\ individual\ contents)\ +\ (acceptability\ constant\ *\ sample\ standard\ deviation)$$

In vitro Dissolution studies

The in vitro dissolution study was carried out using USP Type 1 dissolution apparatus. The study was carried out in 900 ml of phosphate buffer pH 7.2 from 1 to 8 h. The dissolution medium was kept in a thermostatically controlled water bath, kept up at 37 ± 0.5 °C. The pre-weighed capsules were then introduced into the basket of the dissolution jar and the basket was rotated at 100 rpm. 5 ml sample was withdrawn at different time intervals by replacing with same dissolution medium and samples were analyzed by measuring the absorbance at 375 nm by UV spectrophotometer.

Analysis of in vitro drug release

To analyze the mechanism of drug release from the capsules the in vitro dissolution data were fitted to zero order (cumulative amount of drug release versus time),[7] first order (log cumulative percentage of drug remaining versus time),[8] Higuchi release model (cumulative percentage of drug release versus square root of time),[9] Hixson and Crowell powder dissolution method (cubic root of percentage drug release versus time)[10] and Korsmeyer and Peppas model (log cumulative percentage drug release versus time).[11] The equations for the said models are given in Table 2.

Table 2: Kinetics of optimized formulation of nitrofurantoin.

Sl. No.	Model	Equation
1	Zero order	$F=k \times t$ (where F is the fraction of drug release, k is the release constant and t is the time)
2	First order	$\ln F=k \times t$ (where F is the fraction of drug release, k is the release constant and t is the time)
3	Higuchi	$F = k\sqrt{t}$
4	Hixon and Crowell powder dissolution method	$F=100(1-(1-kt)^3)$
5	Korsmeyer and Pappas model	$F=kt^n$ (n is the diffusion coefficient)

Dissolution data were likwise fitted according to the notable exponential equation, which is frequently used to depict the drug release behavior from polymeric systems introduced by Krosmeyer –Peppas as:

$M_t/M_\infty=kt^n$

Where, M_t is the amount of drug release at time t, M_∞ is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the capsule and n is the diffusional exponent indicative of the mechanism of drug release. A value of n=0.45 indicates Fickian (case I) release, >0.45 but <0.89 for non-fickian (anomalous) release and >0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-fickian) refers to a combination of both diffusion and erosion controls drug release.

Based on highest regression coefficient value (r^2) the best-fit model for all formulations was Korsmeyer-Peppas model. To characterize the drug release rate in different experimental conditions, MDT (mean dissolution time), $T_{25\%}$, $T_{50\%}$ and $T_{80\%}$ values were calculated from dissolution data according to the following equations using Korsmeyer-Peppas constant:

$T_{25\%}= (0.25/k)^{1/n}$

$T_{50\%} = (0.5/k)^{1/n}$

$T_{80\%} = (0.8/k)^{1/n}$

Mean Dissolution Time can also be calculated by the following equation:

$MDT = (n/n+1).\ K^{-1/n}$

Mean dissolution time (MDT) value is used to characterize the drug release rate from the dosage form and the retarding efficiency of the polymer. A higher value of MDT indicates a higher drug retaining ability of the polymer and vice-versa. The MDT value was also found to be a function of polymer loading, polymer nature and physico-chemical properties of the drug molecule.

RESULTS AND DISCUSSION

Weight variation and Drug content uniformity

The average percentage deviations of 10 capsules of each formulation were less than 5% and hence all formulations passed the test for uniformity of weight as per official requirements. All formulations showed good uniformity in drug content. Table 3 shows the Weight variation and drug content of nitrofurantoin matrix capsules.

Table 3: Weight variation and drug content of nitrofurantoin matrix capsules from proposed formulations.

Formulation	F-1	F-2	F-3	F-4	F-5	F-6
Weight variation (%) ± SEM	200.50 ± 0.79	192.96 ± 0.95	190.50 ± 0.57	190.00 ± 0.89	189.98 ± 0.66	190.50 ± 0.48
Drug content uniformity (%) ± SEM	99.2 ± 1.4	99.36 ± 1.10	98.52 ± 0.79	97.75 ± 0.70	98.86 ± 0.80	97.97 ± 1.60

Values are expressed as mean ± SEM

In vitro drug release studies

The in vitro release pattern of the formulations was analyzed by fitting the dissolution data into various kinetic models. Table 4 shows the in vitro drug release profile for proposed formulations. Figure 1, 2, 3, 4 and 5 shows the drug release model of different formulations of nitrofurantoin sustained release capsule. It was observed from release kinetics parameters (Table 5) that the highest regression coefficient value (r^2) of all formulations (F-1 to F-6) that showed delayed drug release were found to best fit with Korsmeyer model having r^2 values in the range of 0.956 to 0.993. The lower release exponent (n) values of these formulations obtained from the Korsmeyer plot indicated that fickian diffusion was the dominating release mechanism. It might be caused due to the viscous gel formation by the polymer around the API and slowed down the rate of drug diffusion through the polymer. From the Table 6 we can say that F-1, F-3, F-4, F-5 exhibited fickian type drug release whereas F-2 and F-6 exhibited Non-fickian type drug release. Table 7 shows the mean dissolution time calculation using Korsmeyer-Peppas model for proposed formulations. Table 8 represents the time required for different percentages of drug release.

Table 4: In vitro drug release profile for proposed formulations.

Time (hr)	F-1		F-2		F-3		F-4		F-5		F-6		Market products	
	% DR_1	% DR_2	% DR_1	% DR_2	% DR_1	% DR_2	% DR_1	% DR_2	% DR_1	% DR_2	% DR_1	% DR_2	% DR_1	% DR_2
0.5	30.24	69.76	22.35	77.65	37.45	62.55	41.55	58.45	53.66	46.34	22.18	77.82	22.18	77.82
1	43.99	56.01	30.70	69.30	55.12	44.88	56.59	43.41	58.08	41.92	29.01	70.99	30.16	69.84
2	58.51	41.49	43.21	56.79	67.86	32.14	67.15	32.85	76.04	23.96	45.60	54.40	43.91	50.09
3	72.57	27.43	58.22	41.78	74.32	25.68	86.37	13.63	86.92	13.08	55.55	44.45	58.08	41.92
4	85.14	14.86	63.07	36.93	79.37	20.63	87.72	12.28	88.67	11.33	62.12	37.88	62.31	37.69
5	91.85	8.15	66.46	33.54	80.40	19.60	94.26	5.74	91.71	8.29	70.13	29.87	68.22	31.78
6	94.38	5.62	73.63	26.37	81.84	18.16	96.41	3.59	92.37	7.63	71.82	28.18	70.92	29.08
7	94.78	5.22	78.14	21.86	92.11	7.89	97.82	2.18	96.96	3.04	77.82	22.18	77.39	22.61
8	97.45	2.55	84.53	15.47	98.98	1.02	97.88	2.12	98.05	1.95	81.23	18.77	88.24	11.76

Here, % DR_1 = % Drug release, % DR_2 = % Drug remaining

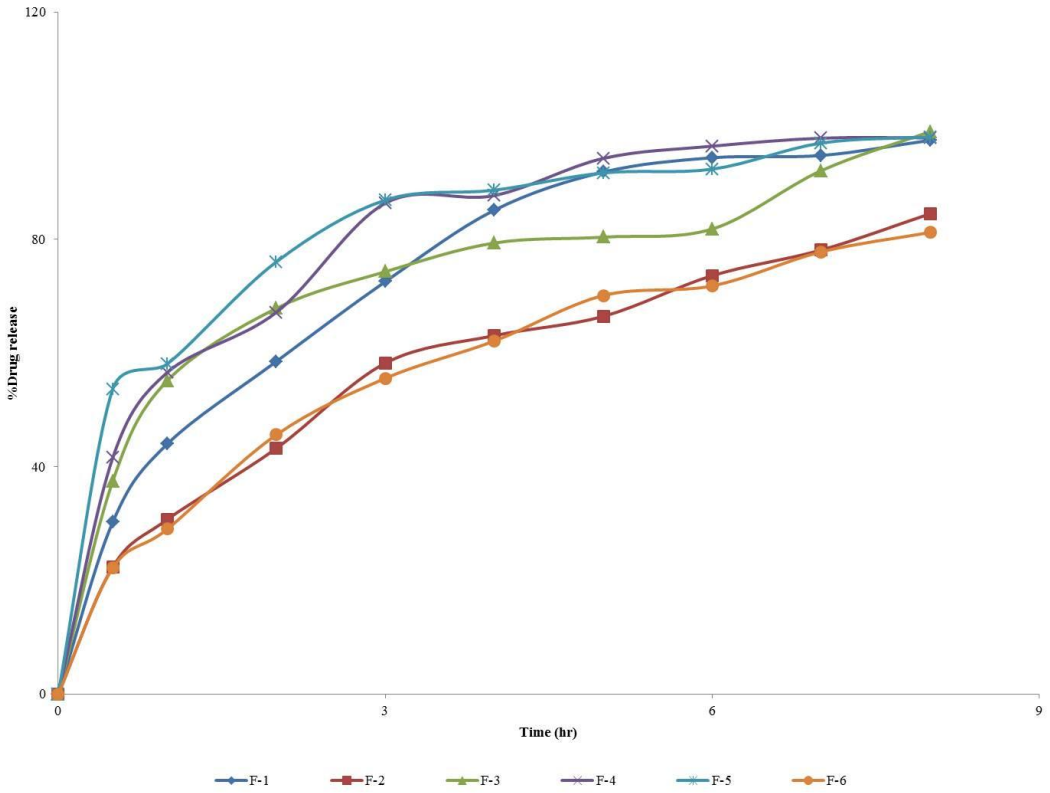

Figure 1: Zero order release model of nitrofurantoin sustained release formulations.

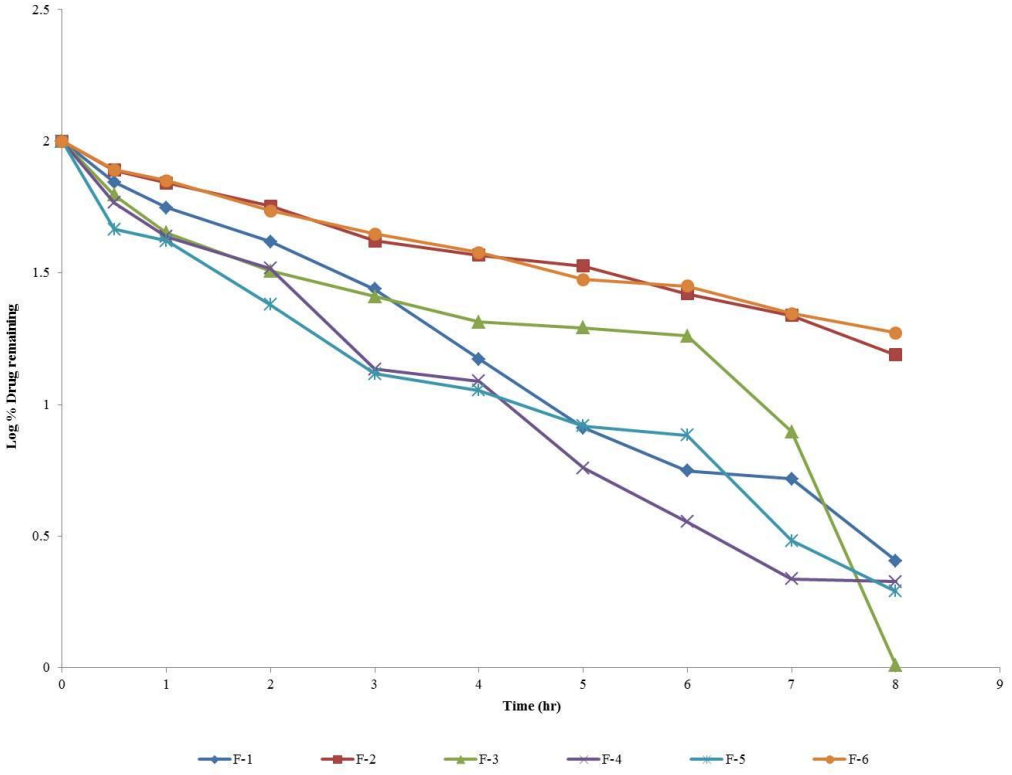

Figure 2: First order release model of nitrofurantoin sustained release formulations.

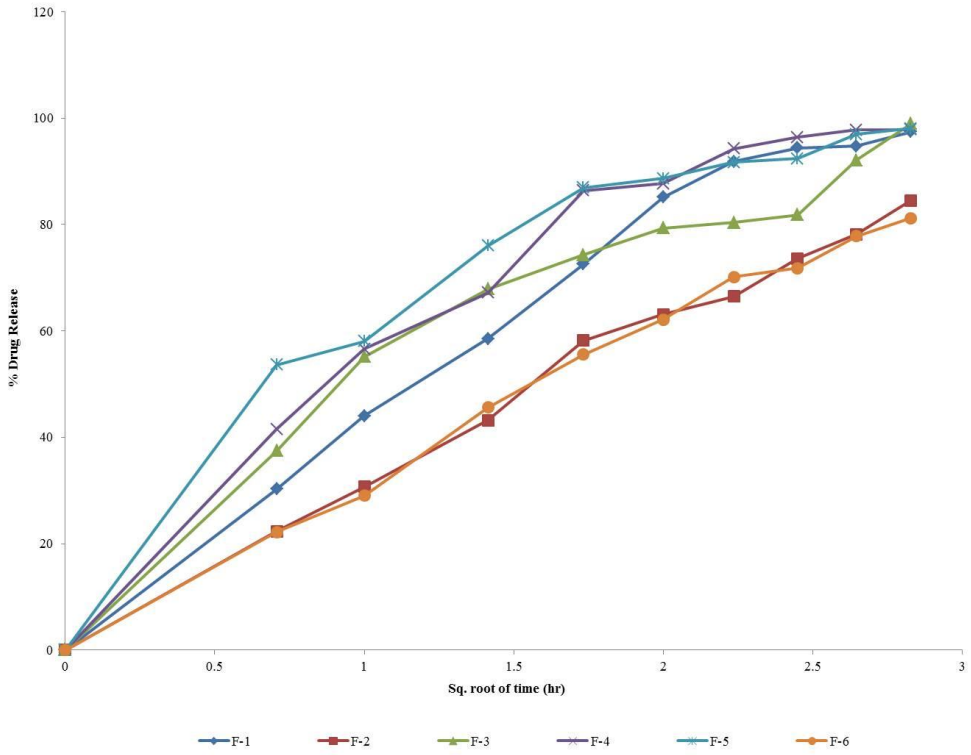

Figure 3: Higuchi release model of nitrofurantoin sustained release formulations.

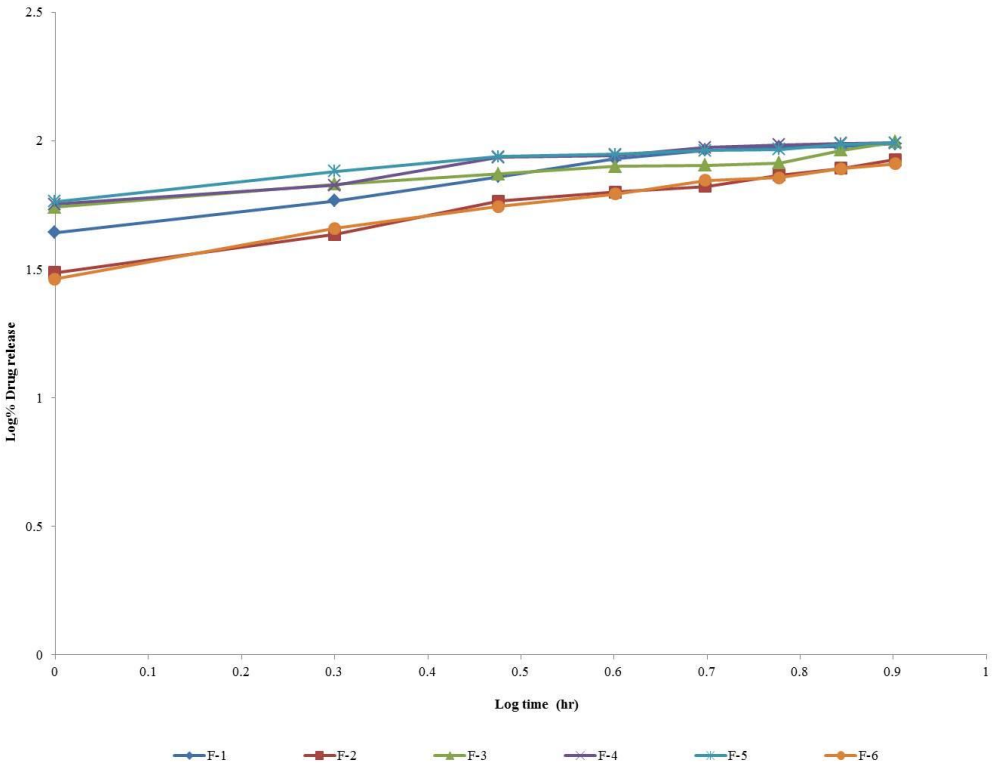

Figure 4: Korsmeyer-peppas release model of nitrofurantoin sustained release formulations.

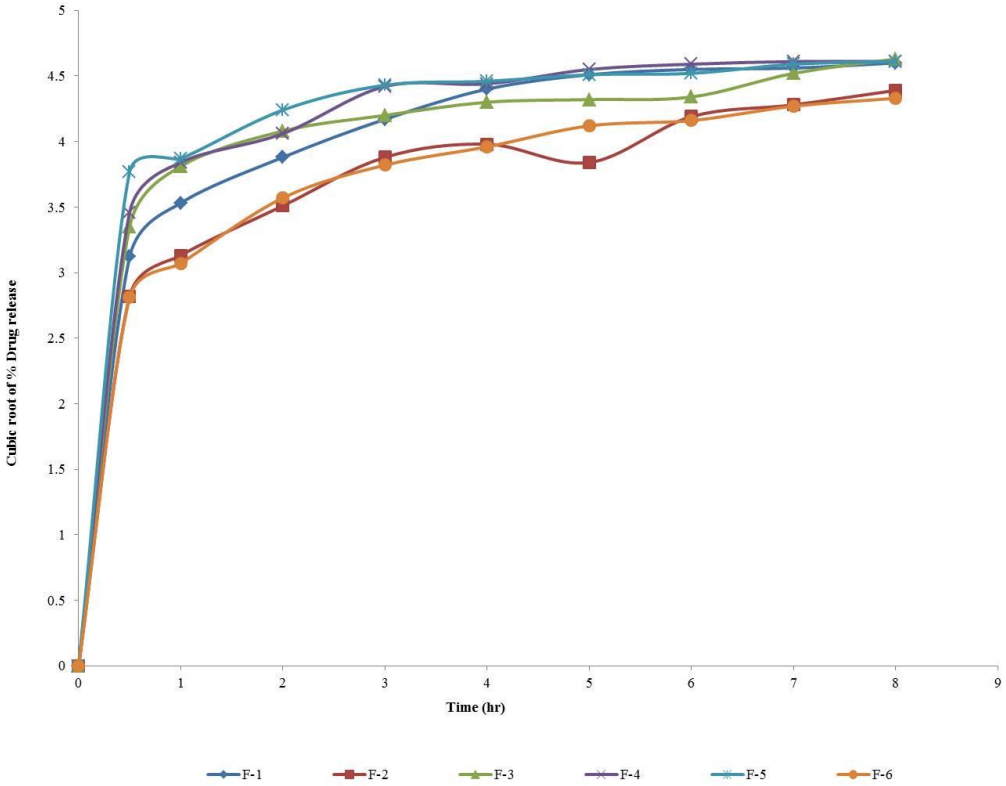

Figure 5: Hixon-Crowell release model of nitrofurantoin sustained release formulations.

Table 5: In vitro drug release kinetics for proposed formulations.

Formulation	Regression co-efficient (R^2) value				
	Zero order	1st order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas
F-1	0.827	0.989	0.970	0.507	0.981
F-2	0.898	0.983	0.993	0.552	0.993
F-3	0.750	0.805	0.928	0.428	0.956
F-4	0.725	0.980	0.921	0.426	0.964
F-5	0.649	0.962	0.870	0.373	0.962
F-6	0.887	0.983	0.992	0.551	0.991

Table 6: In vitro drug release mechanism for proposed formulations using Korsmeyer-Peppas model.

Formulation	Release rate constant (k)	Diffusion exponent (n)	Release type	Comments
F-1	0.433	0.433	Fickian	Diffusion Mediated
F-2	0.314	0.481	Non-Fickian	Non-Diffusion Mediated
F-3	0.511	0.308	Fickian	Diffusion Mediated
F-4	0.550	0.315	Fickian	Diffusion Mediated
F-5	0.627	0.232	Fickian	Diffusion Mediated
F-6	0.310	0.483	Non-Fickian	Non-Diffusion Mediated

Table 7: MDT (Mean Dissolution Time) calculation using Korsmeyer-Peppas model.

Formulation	Release rate constant (k)	Diffusion exponent (n)	Release type	MDT (hr)
F-1	0.433	0.433	Fickian	2.09
F-2	0.314	0.481	Non-Fickian	3.62
F-3	0.511	0.308	Fickian	2.10
F-4	0.550	0.315	Fickian	1.59
F-5	0.627	0.232	Fickian	1.41
F-6	0.310	0.483	Non-Fickian	3.68

Table 8: Time required for 25%, 50% and 75% drug release.

Formulation	$t_{25\%}$	$t_{50\%}$	$t_{75\%}$
F-1	0.281	1.39	3.556
F-2	0.622	2.631	6.111
F-3	0.098	0.931	3.477
F-4	0.082	0.739	2.677
F-5	0.02	0.377	2.164
F-6	0.641	2.691	6.229

Effect of Polymeric content on the release profile of drugs

The release rate of nitrofurantoin mainly controls by the hydration and swelling properties of HPMC that forms a gel layer that controls the water penetration and drug release. The impact of polymer concentration on drug release could be obviously observed from the variation of the dissolution profiles. It absolutely was found that drug release from F-1 to F-6 composed of 4.5%, 4.3%, 5.3% 6.3%, 8.3% and 15.8% HPMC single polymer was slow on increasing the percentage of polymer presented in Figure 6. In formulation F-2 povidone was used as a binding agent which helps to bind the polymer at the surround of the API more uniformly and strongly. So the release rate of nitrofurantoin was slowed in formulation F2 than formulation F-1 (Figure 2). Formulations F-3 to F-6 shows different release rate profile up to 8 hour period. Formulations F-3, F-4, F-5 showed 74.32%, 86.37%, 86.92% drug release whereas formulation F-6 shows 55.55% drug release in 3 hours. In 8 hours F-3, F-4, F-5 formulations show 98.98%, 97.88%, 98.05% release and formulation F6 shows 81.23% drug release. The difference release rate was due to the higher amount of drug release retarding polymers used in formulation F-3 to F-6 (Figure 1).

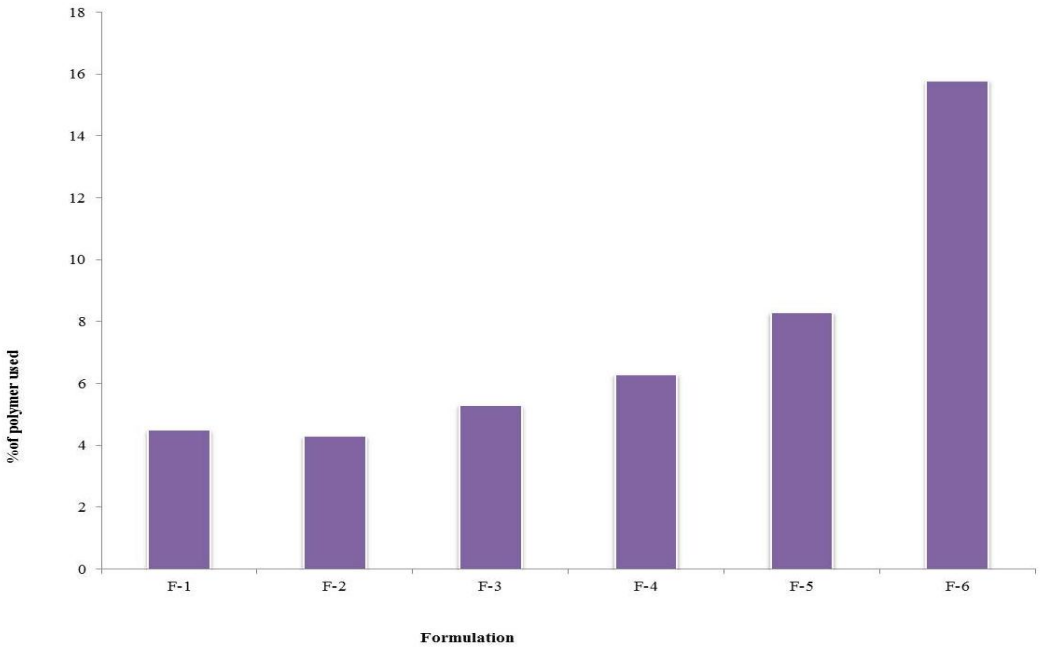

Figure 6: Bar diagram showing effect of polymer content on release rate.

The release rate diminished significantly and the drug release prolonged as the polymer concentration was increased. But among them drug release of the formulation F-2 and F-6 were comparatively slower than the target profile. This might be due to use of polymer with povidone in F1 and of higher proportion of HPMC K4M (Methocel K4 Premium) polymer in F-6. However F-1, F-3, F-4, F-5 showed the faster dissolution profiles.

The hydration rate of HPMC depends on the nature of the substituent like hydroxypropyl group contents. HPMC K4M having viscosity 4000cps forms a strong viscous gel in contact with aqueous media, which controls the release rate of nitrofurantoin. For formulation F-6, containing highest amount of polymer shows more controlled release of drug in both pH 7.2 phosphate buffers. This might be attributable to a more rigid complex formed by presence of higher proportion of HPMC K4M which helped in retaining the drug in matrix and did not allow rapid diffusion of drug from matrix. The rate and amount of drug release were decreased with increasing the amount of HPMC polymers. This polymers ability to retard the drug release rate is depends on its viscosity. The increase in polymer content decreases the total porosity therefore drug release extended for prolonged period because decreased porosity have lower lateral area. The release rate decreased significantly and drug release retarded as the polymer proportion was increased. The drug release became sustained with increasing HPMC concentration because of poorer wet ability, slower hydration and

formation of gelatinous layer. Another important factor is viscosity of the polymers which is higher as the molecular weight of polymer increases. If the viscosity of the polymer increases the gel layer viscosity conjointly will increase so the gel layer becomes resistant to diffusion and erosion. The release rate therefore decreases. Completely different levels of methyl and hydroxypropoxy substitution resulted in intrinsically different hydration rates that affected the performance of the polymer in the initial stages of hydration. When glassy polymer comes into contact with water or any other medium with which it is thermodynamically compatible, the solvent penetrates into the free spaces on the surface between macromolecular chains. Once enough solvent has entered into the matrix, the glass transition temperature of the polymer drops to the extent of the experimental temperature (37 °C). The presence of solvent within the glassy polymer causes stresses that are then accommodated by rise within the radius of the gyration and end to end distance of the polymer molecules. i.e., the polymer chains get solvated. The solvent molecules come in the glassy polymer matrix. The thickness of the swollen or rubbery region increases with time in the opposite direction. This phenomenon is individual characteristic for that particular polymer/solvent system.

CONCLUSION

The results of the study clearly demonstrated that HPMC matrix granules formulation is an effective and promising drug delivery system for twice daily administration of nitrofurantoin. The release of nitrofurantoin from the matrix formulation followed Korsmeye-Peppas kinetics and the mechanism of drug release was both diffusion and erosion. F-2 and F-6 exhibited non-fickian type drug release from the matrix granules of the capsule. The in-vitro release studies revealed that the formulation F-2 and F-6 can be taken as an ideal or optimized formulation for sustain release capsule.

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