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Formulation and Characterization of Sustained Release Microspheres of Nitrofurantoin

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ABSTRACT

The aim behind the present work was to develop a microsphere based novel dosage form for sustained delivery of Nitrofurantoin. Nitrofurantoin is the hydantoin derivative which is used to treat urinary tract infection and kidney infection. It has been used to prevent recurrent infection and for the prevention of bacteriuria after prostatectomy.

The microsphere system is based upon the fact that their structure can entrap the drug within them. The method used for the microspheres preparation is the Ionic gelation method. The microspheres were prepared in various batches depending on the ratio of polymers. The polymer namely Hydroxypropyl methyl cellulose (HPMC), polyvinyl alcohol (PVA) and Sodium alginate (SA) were taken for the preparation of the microspheres. The HPMC and PVA when used in combination with sodium alginate produces microspheres but not individually. The microspheres were evaluated for parameters such as FTIR particle size analysis, production yield, swelling index, encapsulation efficiency, *and in-vitro* dissolution study. The in vitro dissolution studies were done to assess the release pattern of the drug from the microspheres over a twelve-hour period. Microspheres were able to sustain the release of nitrofurantoin up to 12 hrs. From the FTIR study it is found that process parameters do not make any structural changes in Nitrofurantoin.

KEYWORDS: Nitrofurantoin, Ionic gelation, Hydroxypropyl methyl cellulose (HPMC), Polyvinyl alcohol (PVA), Sodium alginate (SA).

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INTRODUCTION

A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. The development of new delivery systems for the controlled release of drugs is one of the most interesting fields of research in pharmaceutical sciences.[1]Microspheres are small spherical particles (typically 1 μm to 1000 μm), sometimes referred to as micro particles. The microspheres can be made up of either natural or synthetic polymers. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. Each particle is basically a mixture of drug, dispersed in a polymer form with release occurs by 1storder process. Drug release is controlled by dissolution/degradation of matrix. Because of their size and shape, Microspheres offer a ball-bearing effect.[2]

Drug loading: The active components are loaded over the microspheres principally using two methods, i.e. during the preparation of the microspheres or after the formation of the microspheres by incubating them with the drug/protein. The active component can be loaded by means of the physical entrapment, chemical linkage and surface adsorption. The entrapment largely depends on the method of preparation and nature of the drug or polymer (monomer if used).Maximum loading can be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables such as method of preparation, presence of additives (e.g. cross linking agent, surfactant stabilizers, etc.) heat of polymerization, agitation intensity, etc. Release of the active constituent is an important consideration in case of microspheres. The release profile from the microspheres depends on the nature of the polymer used in the preparation as well as on the nature of the active drug. Ionotropic Gelation (Polyelectrolyte Complexation) involves simply the interaction of an ionic polymer with oppositely charge ion to initiate cross linking. Unlike simple monomeric ions, the interaction of polyanion with cations (or polyanion with polycation) cannot be completely explained by the electro-neutrality principle. The three dimensional structure and presence of other groups influence the ability of cations (or anions) to conjugate with anionic (or cationic) functionalities and some kind of selectivity is found.[3]

2. MATERIALS AND METHODS

Formulation And Development

The microspheres were prepared by using ionic gelation method. The polymeric solution is firstly prepared by dissolving the required quantity of polymers in the water. The nitrofurantoin (1 g)

is then added to the polymeric solution. The drug and polymeric solution is stirred continuously until a uniform mixture is formed. The solution is the kept for sonication for 30 minutes to remove bubbles. For the formation of microspheres, the dispersion was then extruded manually drop wise into aluminium sulphate solution (5%) using polyethylene syringe (needle size 22 G). the extruded droplets were kept in the aluminium sulphate solution for 30 mins to completed the curing reaction and to produce the spherical microspheres of nitrofurantoin. The prepared microspheres were collected by decantation and washed repeatedly with distilled water to remove excess aluminum impurity and dried at room temperature for 12 hours.

Table:1 Composition of Nitrofurantoin Microspheres.

Sr. No.	Formulation Code	Nitrofurantoin (gm)	HPMC (gm)	PVA (gm)	SA (gm)	D: P Ratio
1	F1	1	0.5	-	0.5	1:1
2	F2	1	1	-	1	1:2
3	F3	1	-	0.5	0.5	1:1
4	F4	1	-	1	1	1:2
5	F5	1	0.2	0.4	0.4	1:1
6	F6	1	0.4	0.8	0.8	1:2
7	F7	1	-	-	1	1:1
8	F8	1	-	-	2	1:2

3.EVALUATION OF THE MICROSPHERES

Percentage Yield

The percentage yield of microspheres is calculated by using completely dried microspheres. Percentage yield of all prepared formulations of Nitrofurantoin microspheres were calculated by formula-

$$Percentage\ Yield = \frac{Mass\ of\ microspheres\ obtaine}{total\ weight\ of\ drug\ and\ polymer} \times 100 \qquad (1)$$

Particle Size Analysis

The particle size of microspheres of nitrofurantoin was studied by using the light microscopy techniques. The micro particles were selected randomly for particle size and analysis and then particle size was determined by using eyepiece micrometer. The microscope is calibrated by using the stage micrometer and eyepiece micrometer.

Swelling Index

Swelling index (pH dependent equilibrium water uptake) of nitrofurantoin microspheres was measured by placing 20 mg in to 20 ml phosphate buffer pH 7.2 and allowed to swell for 24 h at 37˚C. Swelling index was calculated by formula:

$$Swellingindex(\%)=\frac{Final\ weight\ of\ microspheres - Initial\ weight\ of\ microspheres}{Initial\ weight\ of\ microsphere} \quad (2)$$

In Vitro Drug Release:

Dissolution studies were carried out with the USP type-II (rotating paddle) apparatus in phosphate buffer pH 7.2 for 12 hrs. The % drug release upto 12 hrs. was calculated. The drug release rate from microspheres was determined using USP apparatus type II (lab India, India). The dissolution test was performed using 900 ml of Phosphate buffer pH 7.2 for 12 hrs. at 37±0.5°C and 100 rpm. A sample (10 ml) was withdrawn at a specific interval and replaced with fresh dissolution medium of same quantity. Absorbance of the solutions was measured at 367 nm by UV-Visible Spectrophotometer (UV-2450 SHIMADZU). The drug release and drug release kinetics was calculated.

Data Analysis

In order to investigate the mode of release from the tablets the release data were analysed with the following mathematical models,

Zero- Order Kinetic

$Q_0 = Q_t + K_{0t}$ *(3)*

Where,

Qt=is amount of drug release at time t

$K_{0=}$ is zero order release rate constant.

$Q_{0=}$is amount of drug present initially at t = 0

First- Order Kinetic

$ln(100 - Q) = lnQ_0 + K_{1t}$(4)

Where,

Q = amount of drug release at time t

Q0 = amount of drug present initially

K_1 = first order release rate constant.

HIGUCHI EQUATION[3]

$Q = KHt1/2$ (5)

Where,

Q = amount of drug release at time t

KH = Higuchi dissolution constant.

Hixson-Crowell Equation[3]

$W_0^{1/3} - W_t^{1/3} = Kst$ (6)

Where,

W_0=is the initial amount of drug in the pharmaceutical dosage form,

$W_{t=}$ is the remaining amount of drug in the pharmaceutical dosage form at time *t*and

Ks=is a constant incorporating the surface–volume relation.

KORSMEYER- PEPPAS MODEL

$Q = KPtn$ (7)

Where,

Q=is the percent of drug released at time t

KP=is the constant incorporating structural and geometric characteristics of the release device.

n=is the release exponent indicative of the mechanism of drug release.

This equation was further simplified and proposed by Ritger and Peppas,

$Mt / M = Ktn$ (8)

Where,

Mt=is the drug released at time t,

M=is the amount of drug released at infinite time

K is a kinetic constant, and

n=is the diffusional exponent.

The value of n indicates the drug release mechanism.

For a slab the value n = 0.5- indicates Fickian diffusion and values of n between 0.5 and 1.0 or n = 1.0 indicate non- Fickianmechanism.

In case of a cylinder n = 0.45 instead of 0.5, and 0.89 instead of 1.0.

This model is used to analyze the release from polymeric dosage forms, when the release mechanism is not well known or when there is a possibility of more than one type of release phenomenon involved.

4. RESULT AND DISCUSSION

Particle Size Analysis

Calibration of eyepiece micrometer=1 division of eyepiece micrometer is equals to 4.63 micrometer.

Table:2Particle Size Data of Different Formulations.

Sr. No.	Formulation code	Particle size range (µm)
1	F1	379-736
2	F2	333-648
3	F3	282-440
4	F4	217-482
5	F5	509-791
6	F6	384-903
7	F7	240-408
8	F8	148-361

PERCENTAGE YIELD, DRUG CONTENT & ENCAPSULATION EFFICIENCY:

Table: 3 Percentage Yield, Drug Content & Encapsulation Efficiency.

Sr. No.	Formulation code	Percentage yield	Percent Swelling index	Percent Entrapment Efficiency
1	F1	51 %	61 %	82.91 %
2	F2	56 %	73 %	51.54 %
3	F3	70.67 %	17.5 %	89.91 %
4	F4	80 %	41 %	85.71 %
5	F5	67.25 %	49.5 %	95.23 %
6	F6	69.67 %	58.5 %	40.33 %
7	F7	95 %	51.5 %	83.75 %
8	F8	97 %	21.5 %	56.58 %

In Vitro Drug Release

Table: 4 In-vitro Drug Release from Different Formulations

Time (Hrs.)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	26.76774	19.8	27.73548	15.77419	19.60645	22.12258	32.57419	19.99355
1	39.25871	21.95548	33.85011	16.18172	26.59849	26.62645	39.32323	23.89312
2	43.45871	26.04151	37.59204	24.23591	30.35118	32.09312	46.16839	26.45011
3	51.05226	29.18344	46.72968	28.58344	34.84366	41.44366	51.27591	34.6071
4	57.71	33.66	51.86	33.85	42.82	47.15978	55.58989	36.82645
5	65.33	38.55763	58.88667	39.14043	46.78774	53.99634	60.08882	40.72108
6	70.06	44.99849	65.35118	46.55333	54.95978	60.84581	65.75118	54.50602
7	74.95	50.48882	70.06731	51.08667	60.46946	66.14688	71.2329	58.14258
8	79.26	53.83935	76.11892	60.81355	65.75548	71.04366	76.13183	60.50387
9	82.80	58.71462	81.4114	63.4372	71.42645	76.71032	80.05656	64.01355
10	87.67	64.38129	84.95333	68.30387	73.4243	83.54688	84.93828	67.53613
11	91.2157	68.70172	89.6372	73.58344	77.12323	88.26731	92.92753	71.05871
12	94.54473	73.39419	92.78559	79.25441	81.6157	92.57699	94.75763	75.16194

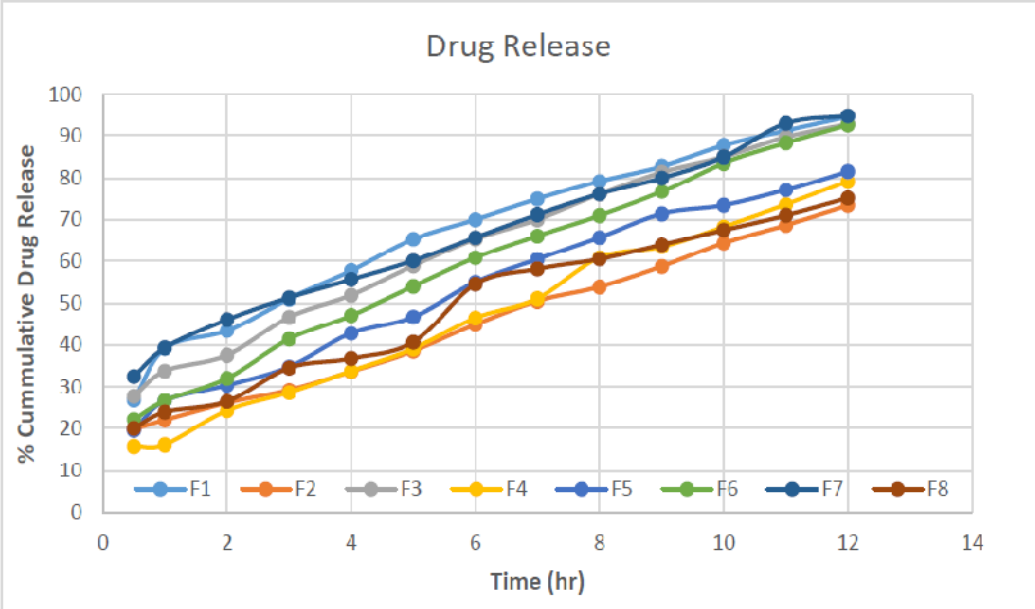

Fig 1 Drug Release Profile of F1 to F8

Kinetics of Drug Release

Table.5 Drug Release Kinetics of Different Formulations

Formulation code	Zero order	First order	Korsemayer- peppas model	Weibull model	Hixon Crowell model	Higuchi model
	R^2	R^2	R^2	R^2	R^2	R^2
F1	0.9687	0.8828	0.9875	0.9387	0.9184	0.9267
F2	0.9974	0.9787	0.925	0.8905	0.9912	0.9528
F3	0.9897	0.9387	0.9685	0.9087	0.9611	0.9619
F4	0.9964	0.948	0.955	0.9222	0.9747	0.9237
F5	0.9888	0.9319	0.969	0.9358	0.9584	0.9808
F6	0.9971	0.9419	0.9715	0.8953	0.9688	0.9781
F7	0.9935	0.9544	0.9652	0.8695	0.973	0.8501
F8	0.9781	0.9354	0.9456	0.9198	0.9547	0.9676

5. CONCLUSION

The aim of present investigation was to develop sustained release microspheres of Nitrofurantoin. The pre-formulation study was performed for both drug and excipients. The Microspheres were prepared by ionic gelation method. The viscosity increasing polymer Hydroxypropy l methyl cellulose and excipients like Polyvinyl alcohol, sodium alginate was used for the formulation of microspheres. The microspheres were evaluated for parameters such as particle size analysis, production yield, swelling index, encapsulation efficiency, in-vitro dissolution study etc. All the drug and excipients obtained were of appropriate standards.

When there is use of the HPMC and PVA, individually both the polymer did not form the microspheres of nitrofurantoin and it is found that both the polymer has lack of cross-linking ability. The SA alginate forms the microspheres when it is used individually with drug and it is found that

the SA possess the cross-linking ability. When there is use of HPMC and PVA in combination with SA both the polymer forms the microspheres of nitrofurantoin. All the microspheres were found to release the drug up to 12 hrs. Most of the formulations followed Hixon Crowell and Korsemayer-peppas model. As the concentration of polymer was increased, a decrease in drug release was observed. Thus the sustained release Microspheres of Nitrofurantoin were prepared.

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