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(RESEARCH ARTICLE)

PREPARATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF NITROFURANTOIN

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ABSTRACT

Aim of the present work was to prepare and evaluate sustained release (SR) matrix tablets of Nitrofurantoin (NF), for the treatment and prevention of urinary tract infections and better patient compliance. The SR-NF matrix tablets were prepared by direct compression method using different ratios of ethyl cellulose, HPMC K4M, sodium alginate and carbopol. Total three sets, each set consisting of three formulations, overall nine formulations viz., F-1 to F-9 were prepared. The prepared SR-NF matrix tablets were evaluated for precompression, postcompression parameters, drug content and in vitro drug release. All formulations (F1 – F9) which shows burst release during initial stages of dissolution. The release of nitrofurantoin from the matrix tablets was controlled up to 12 hr. The cumulative percentage of drug release was decreased with increase in polymer concentration. Among all formulations HPMC K4M released maximum amount of drug as it's a hydrophilic matrix polymer that hydrates, forms a gel layer, and controls drug release by diffusion and erosion. A burst release of 20–30% may occur because drug particles are present on or near the tablet surface. The drug release was independent of its concentration and the mechanism of drug release followed non-fickian diffusion. It is concluded that sustain release matrix tablets of Nitrofurantoin gives all satisfactory results for formulation F1-F9. The increase in polymer ratio was found to influence the release of drug from the formulations.

Keywords: Nitrofurantoin, Ethyl Cellulose, Sodium Alginate, Carbopol.

1 INTRODUCTION

The oral route is the most popular of the different medication delivery methods. However, the traditional dosage form has a few drawbacks that could be fixed by altering the current dosage form. A sustained and regulated drug delivery system prolongs the duration of action by slowing the drug's release rate and assisting in maintaining a steady plasma drug concentration. The matrix tablet is a crucial tool among the several formulation options for sustained release tablets. As a result, issues like saw tooth pattern/variations, numerous dosages, and poor patient compliance can be readily reduced. A range of hydrophilic or hydrophobic polymers can be used to make matrix tablets utilizing the wet granulation process or direct compression. The rate and extent of water penetration, polymer swelling, and drug dissolution and diffusion are the main factors influencing the rate of drug release from the matrix. Therefore, sustained release matrix tablets may improve patient adherence and prove beneficial in the management of long-term illnesses[1]. Any medication delivery system's objective is to deliver a therapeutic dosage to the right location in the body in order to quickly and sustain the required drug concentration[2]. By continuously releasing medication over a prolonged period

of time following the administration of a single dose, sustained release dosage forms allow for this intentional management of drug release[3]. Including it in a matrix system is the most commonly used technique to control the sustained drug release. In order to achieve a desired drug release profile, cost-effectiveness, and widespread regulatory approval, hydrophilic polymer matrix solutions are frequently utilized in oral controlled drug delivery due to their versatility[4]. Additionally, matrix systems are preferred over traditional drug delivery (TDS), which has numerous disadvantages such as recurrent administration and blood concentration fluctuations, because to their ease of use and patient compliance. The drug will be uniformly distributed throughout the crosslink matrix of the linear polymer chain in this kind of drug delivery system[5].

Urinary tract infection (UTI) is a severe medical condition that affects a lot of people. The recommended drug for UTIs is nitrofurantoin. Its precise mode of action is unclear and most likely complex. Bacterial enzymes must reduce nitrofurantoin to produce "extremely reactive electrophilic" metabolites. By interfering with bacterial ribosomal proteins, these subsequently prevent protein synthesis. Nitrofurantoin (NF) is a first line antibiotic that is frequently used for prophylaxis and treatment of simple UTIs[6]. An estimated 25 million prescriptions for nitrofurantoin are filled annually worldwide, and it possesses antiseptic properties that are effective against urinary bacteria. It is typically bacteriostatic in nature. There are bigger crystal forms of NF macrocrystals. Flavoproteins (nitrofuranreductase) within the bacteria quickly convert NF to a number of reactive intermediates. The ribosomal proteins, DNA, and enzymes involved in respiration and pyruvate metabolism within the cell are all targeted by these reactive intermediates. Therefore, it works through a variety of mechanisms, which is perhaps why there isn't much resistance to this medication[7, 8]. It's short biological half -life (30 min to 1hr) calls for frequent daily dosing (3 to 4 times) and therapeutic use in urinary tract infections necessitates its formulation into sustained release dosage form. The aim of the present work was to develop sustained release matrix tablets of NF to reduce the frequency of administration and to improve the patient compliance.

2 MATERIAL

The drug Nitrofurantoin (NF) was obtained as a gift sample from MSN Pharmaceuticals, Hyderabad. Ethyl cellulose, HPMC K4M, Sodium alginate, Lactose, PVP, Galen IQ and Carbopol were produced from SD Fine Chem Ltd, Mumbai.

3 METHODS

3.1 Preparation of sustained release matrix tablets

Table 1: Formulae of NF sustained release matrix tablets

Ingredients in mg	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Nitrofurantoin	100	100	100	100	100	100	100	100	100
Ethyl cellulose	30	30	30	30	30	30	30	30	30
HPMC K4M	25	50	75	-	-	-	-	-	-
Sodium alginate	-	-	-	25	50	75	-	-	-
Carbopol	-	-	-	-	-	-	25	50	75
Lactose	45	20	-	45	20	-	45	20	-
PVP	30	30	30	30	30	30	30	30	30
Galen IQ	10	10	5	10	10	5	10	10	5
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total weight in mg	250	250	250	250	250	250	250	250	250

Sustained release matrix tablets of NF were designed by using ethyl cellulose, sodium alginate, carbopol and HPMC K4M in different proportions by direct compression method. All the ingredients as per the formulae (table 1) were weighed and grinded to fineness in a mortar and passed through sieve no 60 separately and mixed homogeneously. The powder blend was further subjected for precompression studies viz., rheological properties like bulk density, tapped density, compressibility index, angle of repose prior to compression. All studies were carried out in triplicate and results were computed. The powder was lubricated with a mixture of talc and magnesium stearate. The lubricated powder were

compressed into tablets on a rotary multi station tableting machine with required hardness using 8 mm round and flat punches[9-10].

3.2 Evaluation

The prepared powder blend was subjected for precompression characteristics viz., bulk density, tapped density, compressibility index, flow properties (angle of repose) [11-13]. Sublingual tablets were evaluated for their post compression parameters i.e., thickness, diameter, weight variation, hardness, friability, drug content and *in vitro* dissolution studies[14-15]. All studies were carried out in triplicate and mean values were reported.

3.3 *In vitro* dissolution study

In vitro drug dissolution studies were carried out for sustained release matrix tablets using USP XXII dissolution apparatus type II (Campbell electronics, Mumbai). Dissolution volume: 900 ml, Temperature: 37± 0.5 °C, RPM: 50, Withdrawal volumes: 5 ml. Initially the dissolution was carried out in 0.1N HCl for first 2 hr to mimic the simulation of gastric fluid. After 2 hr, 0.1 N HCl was replaced with phosphate buffer pH 6.8 and continued the dissolution for further 12 hr. In each time interval specified amount of fluid was withdrawn and same was replaced with fresh dissolution medium to maintain the sink conditions. The drug release at different time intervals was measured at 364.5 nm using a double beam UV spectrophotometer. The study was conducted in triplicate and data were computed by using dissolution software PCP Disso V3.0.

4 RESULTS

4.1 Precompression studies

The NF sustained release matrix tablets formulations viz., F1 to F9 with varied concentrations of HPMC K4M, sodium alginate, carbopol were prepared and its evaluation was carried out in two steps precompression and postcompression parameters. The prepared powder blends were subjected for various precompression studies. The results were presented in the table 2.

Table 2: Precompression parameters for Nitrofurantoin sustained release matrix tablet powder blend.

Batches	Bulk density gm/cc±*SD	Tapped density gm/cc±*SD	Carr's index (%)	Hausner's ratio	Angle of repose θ
F1	0.555±0.06	0.833±0.16	33.37	1.509	21.21±0.33
F2	0.500±0.04	0.625±0.03	20	1.25	25.24±0.01
F3	0.500±0.04	0.714±0.09	29.97	1.425	22.12±0.04
F4	0.550±0.05	0.650±0.04	27.38	1.35	22.36±0.01
F5	0.500±0.04	0.833±0.16	33.37	1.509	23.21±0.03
F6	0.555±0.06	0.714±0.09	29.87	1.425	24.36±0.06
F7	0.550±0.05	0.625±0.03	20.04	1.25	21.35±0.05
F8	0.500±0.04	0.650±0.04	27.38	1.35	19.22±0.04
F9	0.500±0.04	0.714±0.09	29.97	1.425	21.11±0.09

4.2 Post compression studies

The tablets were prepared and subjected for post compression evaluation tests and results are given in table 3.

Table 3: Postcompression evaluation parameters for matrix tablets.

Batches	Weight variation mg±*SD	Diameter mm±*SD	Thickness mm ±*SD	Friability in % ±*SD	Hardness kg/cm^2 *SD	Drug content % ±*SD
F-1	249.55±0.03	8.08±0.03	4.09±0.02	0.320±0.102	5.5±0.110	94.61%
F-2	249.35±0.02	8.04±0.01	4.04±0.03	0.200±0.110	5.9±0.102	92.25%
F-3	249.15±0.06	8.08±0.03	4.09±0.02	0.321±0.102	5.2±0.112	92.75%
F-4	249.90±0.03	8.02±0.01	4.12±0.04	0.804±0.112	5.8±0.101	91.91%
F-5	249.35±0.01	8.03±0.01	4.04±0.03	0.220±0.110	5.6±0.113	93.60%
F-6	249.20±0.02	8.02±0.01	4.06±0.04	0.281±0.119	5.2±0.112	94.94%
F-7	249.85±0.07	8.04±0.01	4.06±0.04	0.241±0.110	5.4±0.116	94.64%
F-8	249.51±0.06	8.02±0.01	4.03±0.02	0.361±0.103	5.2±0.112	92.92%
F-9	249.75±0.05	8.04±0.01	4.12±0.04	0.240±0.109	5.2±0.112	93.60%

4.3 Dissolution studies

In vitro dissolution of designed Nitrofurantoin sustained release matrix tablets were studied using USP apparatus-2 paddle method. The dissolution profile is presented in figures 1-3.

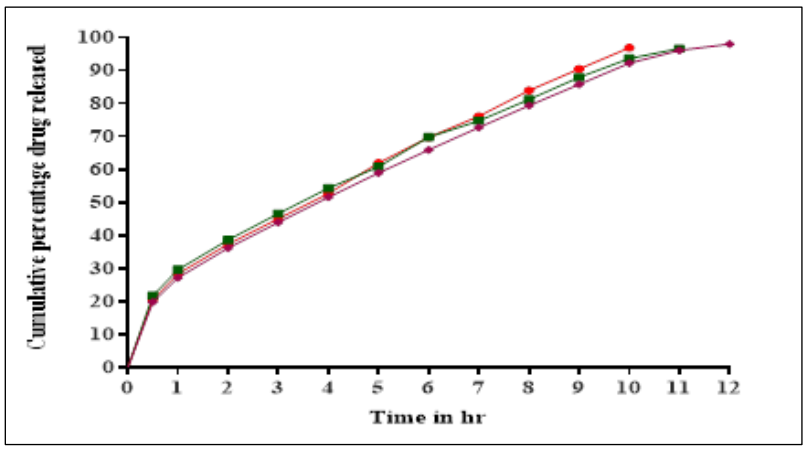

Figure 1: Comparative dissolution profile of formulations F1 to F3

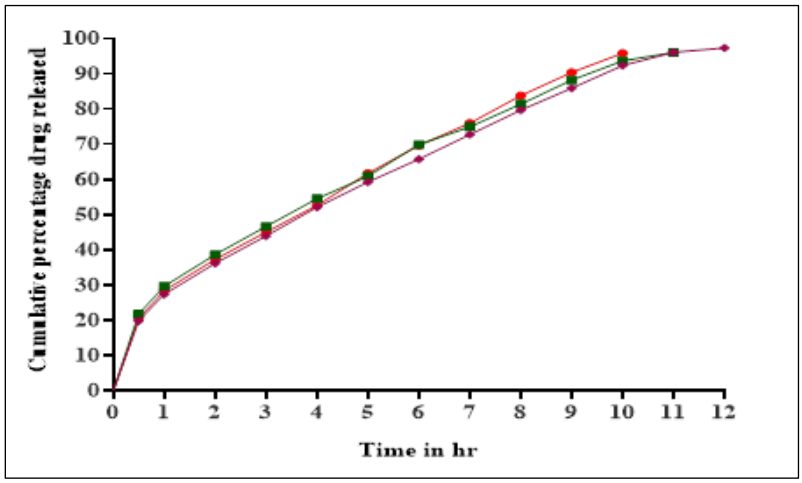

Figure 2: Comparative dissolution profile of formulations F4 to F6.

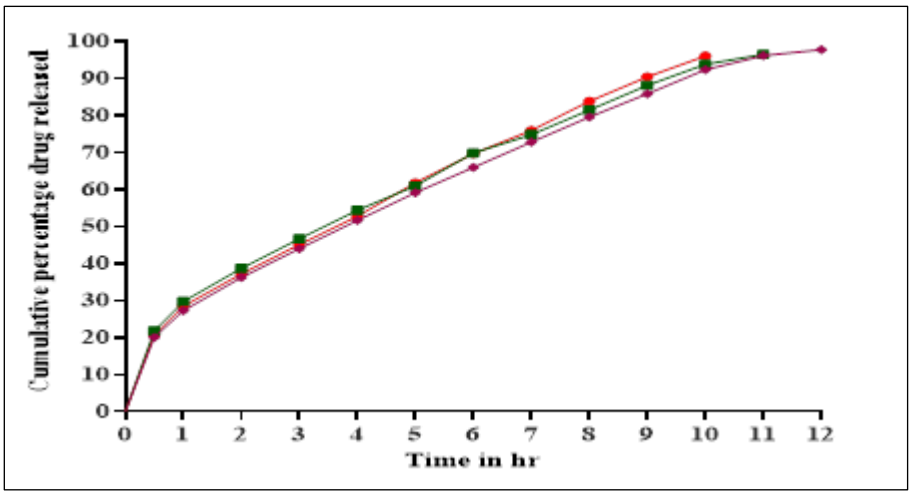

Figure 3: Comparative dissolution profile of formulations F7 to F9.

5 DISCUSSION

The present study was an attempt to prepare and evaluate sustained release matrix tablets of Nitrofurantoin using various polymers i.e., ethyl cellulose, HPMC K4M, sodium alginate and carbopol in the ratio of 1:0.25, 1:0.5, 1:0.75 for the treatment of urinary tract infections. The purpose of developing these tablets is for prolong the drug release up to 12 hr, which is very convenient for administration. The sustained release matrix tablets of NF were prepared by direct compression technique using 8 mm punch. Total three sets were prepared, each set consisting of three formulations. F1-F3 formulations were prepared with HPMC K4M, F4-F6 formulations were prepared with sodium alginate and F7-F9 formulations were prepared with carbopol. Ethyl cellulose as hydrophobic polymer is kept constant in all the formulations. The prepared powder blends of above batches were evaluated for precompression characteristics viz., bulk density, tapped density, Hausner's ratio, angle of repose. These fabricated tablets were evaluated for post compression evaluation parameters viz., thickness, diameter, weight variation, drug content uniformity, hardness, friability, and *in vitro* dissolution. All formulations (F1 to F9) were found to be lemon yellow in colour, odourless, round flat without break line on one side.

5.1 FTIR Studies

Drug polymer compatibility studies were carried out using Fourier Transform Infrared spectroscopy to establish any possible interaction of Nitrofurantoin with the Ethyl cellulose, HPMC K4M, sodium alginate and carbapol polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FT-IR spectra of the pure drug. The results indicated that the principal peaks obtained from the combinations were almost similar to that of pure drug without any significant change in their position, indicating no chemical interaction between drug and polymers.

5.2 Precompression studies

The bulk density was found to be in the range of 0.500±0.04 g/cm^3 to 0.555±0.06 g/cm^3; tapped density was found to be in the range of 0.625±0.03 to 0.833±0.16 g/cm^3; and Hauser's value was found to be in the range of 1.25 to 1.5009 indicates a powder with good flow properties. All the formulations showing that the blend of powder for formulation having good flowability. The angle of repose was found to be 19'22º to 25'24º indicates blend was free flowing and can be used for direct compression.

5.3 Postcompression studies

Thickness of the matrix tablet was found to be in the range of 4.03±0.02 mm to 4.12±0.04 mm for F-1 to F-9 formulations. The results were within the limits and are in accordance with pharmacopeial standards. The hardness of the tablets was found to be in the range of about 5.2±0.112 kg/cm^2 to 5.9±0.102 kg/cm^2 and friability was found to be in the range of 0.200±0.110 % to 0.804±0.112 % which was below 1% indicating the sufficient mechanical integrity and strength of the prepared tablets. The hardness and friability data indicates good mechanical strength/resistance to the tablets. The weight variation results revealed that average percentage deviation for 20 tablets was less than ±10%, which provide good uniformity of the tablets and were found to be within acceptable limits as per the pharmacopeial specifications, whereas the percentage drug content was found to be in the range of 91.91% to 94.94%. The low SD values indicate the drug content was uniform in all the formulated tablets.

5.4 *In vitro* drug release study

The cumulative percentage drug release for F1, F2, F3 formulations prepared with HPMC K4M as polymer in the ratio of 1:0.25, 1:0.5, 1:0.75 respectively showed 37.40, 38.71 and 36.20 after 2 hr in simulated gastric fluid pH 1.2; 96.93, 96.63 and 98.01 at the end of 10 hr, 11 hr and 12 hr in simulated intestinal fluid pH 6.8 for F1-F3 formulations respectively. The cumulative percentage drug release for F4, F5, F6 formulations prepared with Sodium Alginate as polymer in the ratio of 1:0.25, 1:0.5, 1:0.75 respectively showed 35.93, 36.49 and 34.60 after 2 hr in simulated gastric fluid pH 1.2; 95.83, 96.04 and 97.32 at the end of 10 hr, 11 hr and 12 hr in simulated intestinal fluid pH 6.8 for F4-F6 formulations respectively. The cumulative percentage drug release for F7, F8, F9 formulations prepared with Carbopol as polymer in the ratio of 1:0.25, 1:0.5, 1:0.75 respectively showed 36.82, 37.79 and 35.49 after 2 hr in simulated gastric fluid pH 1.2; 96.03, 96.44 and 97.71 at the end of 10 hr, 11 hr and 12 hr in simulated intestinal fluid pH 6.8 for F7-F9 formulations respectively. The *in vitro* dissolution studies suggest a direct relationship of concentration of polymers with drug release irrespective of diluents used in the studies. Formulations prepared using ethyl cellulose and HPMC K4M exhibited the most desirable sustained-release profile. HPMC K4M rapidly hydrated on contact with the dissolution medium and formed a uniform, stable gel barrier around the tablet. This gel layer effectively controlled water penetration and drug diffusion while maintaining matrix integrity throughout the dissolution period. Ethyl cellulose, being hydrophobic, further restricted the penetration of dissolution medium, thereby providing an additional barrier to drug release.

6 CONCLUSION

Sustained release matrix tablets of Nitrofurantoin were conveniently formulated by direct compression method using ethyl cellulose, HPMC K4M, sodium alginate, carbopol. The combined effect of these polymers produced a controlled and predictable release of nitrofurantoin over 12 hours.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

There are no conflicts of interest.

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