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PREPARATION AND EVALUTION OF SUSTAINED RELEASE MATRIX TABLET OF NITROFURANTOIN

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Abstract

Aim: In the present study an attempt was made to Preparation and Evaluation of Sustained Release Matrix Tablet of Nitrofurantoin by wet granulation method using various polymers like HPMC 4000 & PVPK 30

Materials and Methods: A variety of physicochemical characteristics, including rheological characteristics, weight variation, thickness, hardness, in vitro release studies, and drug content, were assessed for the prepared tablets.

Results: All of the physicochemical parameters met the official standards, according to studies. The extended release profile of the formulation, which has better bioavailability and lower dosing frequency with lower doses, is confirmed by the in vitro release studies, which show release up to 90.02 % over an extended period of time.

Conclusion: Nitrofurantoin sustained release matrix tablets have shown improved potency, efficacy, and bioavailability. According to the drug release study, PVPK 30 and HPMC4000 could maintain the drug release. The drug release was sustained for over twenty-four hours when both polymers were combined with the drug.

Keywords: Nitrofurantoin, Bioavailability, matrix, sustained release, characterization.

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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 seesaw 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 illnesses1.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 is 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. In Australia, nitrofurantoin has been on the market since the 1970s, and since 1953. 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 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 nitrofurantoin (macrocrystals). Flavoproteins (Nitrofuranreductase) within the bacteria quickly convert nitrofurantoin 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].

Methods

Physical Appearance: A variety of organoleptic properties, including color, state, odor, and taste, were used to evaluate the drug's physical appearance[8].

Melting Point Determination: Using the capillary fusion method, the drug's (nitrofurantoin) melting point was ascertained. A tiny quantity of medication was put into a capillary that was sealed at one end. The capillary was then kept upside down, or sealed end down, inside the melting point apparatus. Using the provided thermometer, the temperature at which the solid drug turns into a liquid was recorded[8].

Infrared Spectral Assignment: The IR analysis of sample was carried out for qualitative compound identification. The infrared spectra of Nitrofurantoin was performed on fourier transformed infrared spectrophotometer. The pellet of approximately 01mm diameter of drug was prepared grinding 3-5mg of sample with 100-150mg of potassium bromide in pressure comparison machine. The sample pellet was mounted in IR compartment and scanned at wavelength 4000cm-1-500cm-1 .9

Determination of Absorption Maxima (λ max) A UV absorption maxima of the drug was determined by scanning (10µg/ml) solution of drug in methanol between 200-400nm.

Preparation of Calibration Curve in Phosphate Buffer (pH 6.8)

a**) Preparation of phosphate Buffer (pH 6.8):**Take 28.80gm of disodium hydrogen phosphate and 11.45 gm of Potassium dihydrogen phosphate in sufficient water to produce 1000ml.

b) **Preparatrion of calibration curve:** 50mg of drug dissolved in small amount of methanol and dilute to 100ml with phosphate buffer pH 6.8,50ml of this solution was taken and dilute to 100ml with phosphate buffer pH 6.8 to prepare stock solution of 250 µg/ml.From this solution take 0.1,0.2,0.3,0.4,0.6 and 0.8ml and transferred it into 10 ml volumetric flask and volume make upto 10 ml with phosphate buffer and take absorbance at 238 nm using phosphate buffer as blank.

Preparation of Calibration Curve in Methanol

50mg of drug dissolved in 100ml of methanol,50ml of this solution was taken and dilute to 100ml with methanol to prepare stock solution of 250 µg/ml.From this solution take 0.1,0.2,0.3,0.4,0.6 and 0.8ml and transferred it into 10 ml volumetric flask and volume make upto 10 ml with methanol and take absorbance at 238 nm using methanol as blank.

Preparation of Calibration Curve in Water

50mg of drug dissolved in 100ml of methanol,50ml of this solution was taken and dilute to 100ml with methanol to prepare stock solution of 250 µg/ml.From this solution take 0.1,0.2,0.3,0.4,0.6 and 0.8ml and transferred it into 10 ml volumetric flask and volume make upto 10 ml with water and take absorbance at 238 nm using water as blank.

Drug Excipients Interaction Studies

While designing tablets, it was imperative to give consideration to compatibility of drug and polymer used within the system. It is therefore necessary to confirm that drug is not interacting with the polymer under experimental conditions(40±20C and 75±5 % RH) for 4 weeks. The infrared absorption spectra of drug, polymer and mixture of polymer and drug were run between 4000 cm-1-500cm-1.

Preparation of Solid Dispersions of Nitrofurantoin

Nitrofurantoin solid dispersions were made using the kneading method. The ingredients for making solid NF dispersions with hydroxy propyl methyl cellulose and PVP K30 in different ratios are shown in the table. PVP K30 and NF with hydroxy propyl methyl cellulose were weighed using various weighed ratios. In a glass mortor, the NF, hydroxy propyl methyl cellulose, and PVP K30 mixture was thoroughly kneaded for 30 minutes after being wetted with ethanol. The resulting paste was vacuum-dried for a full day. After passing through sieve number 60, the dried powder was kept in a desiccator pending additional analysis10.

Characterization of Physical Mixtures and Solid Dispersions[11]

Drug content, solubility studies, Fourier transform infrared (FTIR), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), X-ray diffraction (XRD), in vitro drug release, and dissolution efficiency were all assessed for the prepared physical mixtures and solid dispersions.

Determination of Drug Content

After precisely weighing 100 mg of drug:carrier, it was transferred to a 100 ml volumetric flask, and the volume was adjusted using phosphate buffers with a pH of 6.8. From this, 1 ml was transferred to a 10-ml volumetric flask, and the same solvent was used to adjust the volume to the desired level. Using the proper blank, the absorbance of the solution was measured at 241 nm. Using a calibration curve, the drug content of nitrofurantoin was determined.

Determination of Solubility

Solubility tests were conducted using the methodology described by Higuchi and Connors. Ten milliliters of distilled water were mixed with an excess of nitrofurantoin, and the mixture was shaken in a rotary shaker for a full day. The solution was filtered after shaking, and the absorbance at 241 nm was recorded.

In vitro Drug Release

Nitrofurantoin solid dispersions were dissolved in vitro using a basket stirrer in a USP dissolution apparatus (Electro lab). At 50 rpm, 900 ml of pH 6.8 phosphate buffer was employed as the dissolution medium. The experiment was conducted at a constant temperature of 37 + 0.5°C. Each test used solid dispersions equal to 10 mg of NF. At predetermined intervals, 5 ml of the dissolution medium sample was extracted using a syringe fitted with a pre-filter. The absorbance at 241 nm was then measured to determine the drug release following an appropriate dilution with phosphate buffer. At each time interval, a new amount of dissolving medium was added to replace the volume that was removed. Plotting the amount of NF released against time and comparing it with with pure drug.

Fourier Transform Infrared (FTIR) Spectroscopy.

Samples prepared in potassium bromide (KBr) disks were subjected to Fourier Transform Infrared (FTIR) spectra of pure drug, HPMC AND PVP K30, physical mixture, and solid dispersion. KBr disks were used to prepare the samples using a hydrostatic press. The resolution was 4 cm–1, and the scanning range was 400–4000 cm–1.

Differential Scanning Calorimetry (DSC) Analysis

The samples were analyzed by DSC using a Mettler Toledo SR system. The samples (5 mg each) were placed into pierced aluminum container. The studies were performed under static air atmosphere in the temperature range of 20°C to 400°C at a heating rate of 10°C/min. The peak temperatures were determined after calibration with standard.

Powder X-Ray Diffraction (XRD) Analysis.

Using an X-ray diffractometer, the powder X-Ray Diffraction (XRD) pattern of solid dispersion, physical mixture, HPMC, PVP K30, and pure drug was recorded. In the circumstances listed below: At room temperature, target CuKamonochromatized radiation with a voltage of 40KV and a current of 40mA. The conditions scan mode was used to collect the data, with a step size of 0.010 at 20/s. The range that was scanned was 50–500.

FORMULATION OF BLENDS

NF:HPMC:PVP K30 solid dispersion and excipient like Lactose were co-grounded in pestle mortor(except talc and magesiumsterate) and were passed through mesh. no. 60. Finally talc and magnesium stearate were added and mixed for 5 minutes.

Characterization of Blends

Once a tablet is formulated according to a rule, its quality is typically determined by the blends' physicochemical characteristics. The properties of the blend that is produced can be influenced by a variety of formulations and process variables that are involved in the mixing step. The flow property of the powders was used to characterize the mixed blend. Additionally determined are the bulk density, tapped density, Hausner's ratio, compressibility index, and angle of repose.

Bulk Density

Bulk density is defined as the mass of powder divided by the bulk volume and is expressed as g/cm3. Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of powder (M) was determined. The bulk density was calculated using the formula.

$$\rho b = M/Vb$$

Tapped Density

Tapped density (ρt) can be defined as mass of blend in the measuring cylinder divided by its tapped volume. The measuring cylinder containing a known mass of blend was tapped 100 times using density apparatus. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the formula.

$$t = M/Vt$$

Compressibility Index

The simplest way for measurement of flow of powder is its compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as follows:

$$I = \rho t - \rho b/\rho t \times 100$$

Where, ρt = Tapped density, ρb = Bulk density.

Carr's Index (%)	Type of flow
>12	Excellent
12.0-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Hausner Ratio

Hausner ratio (HR) is an indirect index of ease of powder flow. It is calculated by the following formula

$$Hr = \rho t/\rho b$$

Where, ρt is tapped density and ρb is bulk density.

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones(> 1.25).

Angle of Repose

Angle of Repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a specified cone height (h) was obtained.

Radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula.

$\tan\theta = h/r$; Therefore; $\theta = \tan^{-1}(h/r)$

Table 2: Angle of Repose as an Indication of Powder Flow Properties

Angle of repose(°)	Type of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Evaluation tests

After tablet compression, tablets are subjected various evaluation tests to ensure the tablets withstand sufficient mechanical strength, etc.

General appearance: it includes overall appearance of the tablet like size, shape, odor, taste, color, surface, consistency, textures physical flaws. Tablet thickness should be controlled with ± 5% variation ofstandard value.

Weight varaiation test: Twenty tablets are weighed randomly in a batch , and the average weight of the tablet is determind. As per the IP specification,if the tablest weight is: < 80mg- deviation upto 10% is allowed 80-250mg - deviation upto 7.5% is allowed

>250 mg- deviation upto 5% is allowed If any tablet deviates from the specification, another 10 tablets are selected from the batch and the same procedure is repeated. In case of 30 tablets, not more than one tablet should deviate.

Hardness test: It is defined as the force required to break the tablet. This test is prefomed in order to ensure that the tablet withstands mechanical shocks during manufacture packaging and shipping of tablet. Various types of hardness testers are used to measure the hardness of the tablet like: Monsanto hardness tester, strong cobbtestre, pfizer tester etc.The tablet hardness should be 2.5- 5kg/cm2 (for conventional tablets), for extended release tablets hardness should be 5-7.5 kg/cm2.

Friability test: Friability test is performed ,in order to ensure the mechanical strength of the tablet during transporation , packing etc. Roche friabilator is the instrument, used to carry out the friability test, in which tablets are weighed before friabilation , and subjected to friabilation with a speed of 25 rpm. Thus the tablets are weighed after friabilation, and the percantgefriabilaty is determined. The deviation should be between 0.5-1%.

Disintegration test: Disintegartion is the breakdown of tablet into finely divided pariculates or granules in GI tract. Disintegration time for uncoated tablets should be 15 minutes, 60minutes for sugar coated tablets, and 30 minutes for film coated tablets.

Dissoultion test: the time required for the given percentage of drug in tablet, to go into solution, under specified set of conditions as in invitro test. It can also be considered as solubilisation of drug in dissoultion media. Several dissolution apparatus like paddel over disk, flow through cell, cylindrical apparatus, paddle over disk, etc. used depending on the type of dosage form. For tablets rotating basket and rotating paddle type is most commonly used.The similarity factor (f2) was used as a basis to compare dissolution profile. The dissolution profile of optimized formulation before and after stability testing were compared using a similarity factor (f2) which is calculated from the following formula:

f2=50.log{1+(1/n)€}

hereRt and Tt are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively. When the two profiles are identical, f2=100. An average difference of 10% at all measured time point's results in a f2 value of 50. FDA has set a public standard of f2 value between 50 to 100 indicate similarity between two dissolution profiles.

Results and Discussion

Physical Appearance

Physical appearance of drug was studied by its various organoleptic properties. The sample of Nitrofurantoin was found to be off white, non hygroscopic, crystalline solid powder. The melting point was found to be in the range of 1540C by Capillary method.

Differential scanning Calorimetry:

The DSC of the pure drug sample as shown below in figure

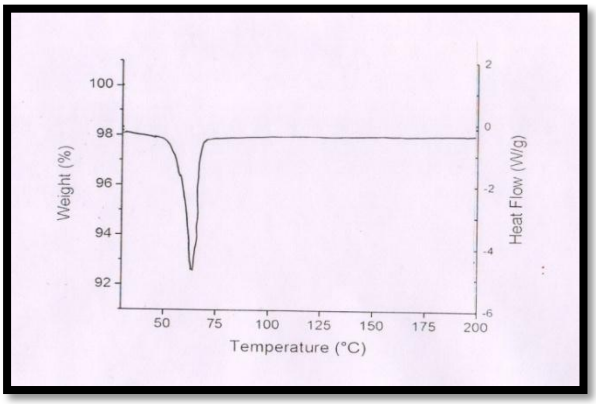

Figure 1: DSC Thermogram of Nitrofurantoin

FTIR

IR spectra of pure drug have been performed and no major differences were observed in characteristic absorption peaks of the IR spectra of the reference spectra given in literature and pure sample drug, spectra of pure drug shown in Figure 2.

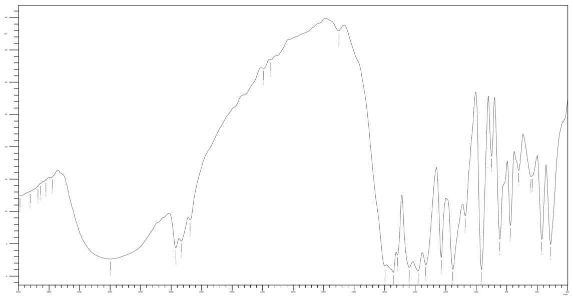

Figure 2: FTIR of Nitrofurantoin

Table 3 :Observed Peaks of Nitrofurantoin

Functional groups	Peaks(cm^{-1})
C≡N	2393.66
N-H	3396.64
C=O	1153.43,1228.66
C-H	1381.03,1438.92

Absorption Maxima

Absorption maxima (λ max) of Nitrofurantoin were observed in different solvents.

Table 4 :Absorption maxima (λmax) of the NF in different solvent

Solvent	(λmax)nm
Phosphate buffer	241nm
Water	240nm
Methanol	239nm

Solubility

The solubility studies of Nitrofurantoin were determined in different solvents.

Table 5: Solubility of NF in different solventsmean ± S.D (n=3)

Solvent	Solubility
Phosphate buffer	4.026±0.554
Water	1.648±0.326
Methanol	2.668±0.122

Solubility of the Nitrofurantoin found to be higher in phosphate buffer as compared to other solvents.

Drug Excipient Compatibility Studies

Physical mixtures of both Nitrofurantoin and excipients HPMC and PVP K30 are prepared and Drug-Exciepient studies were carried out. No major changes were observed in the drug like there was no discoloration of the drug, No liquefaction between drug and polymer, No odour changes in the pure form of the drug was noticed which confirms the compatibility between the drug and excipients. The FTIR spectra of Nitrofurantoin and HPMC / PVP K30 physical mixture are shown below which indicate that Nitrofurantoin compatible with the HPMC and PVP K30.

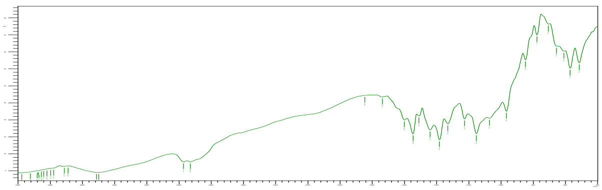

Figure 3: IR Spectra of Mixture of Drug & HPMC:PVP

Table 6: Drug Excipient compatibility study between Drug and polymers

	Week 1	Week 2	Week3	Week 4 Peaks(cm^{-1})
Drug				1330.88, 1516.05, 1597.0, 2393.66, 2933.73 , 3396.64
Drug +polymers				1382.96, 1440.83, 1546.91, 1600.92, 1845.88, 3498.87, 3689.83

Standard curves

The calibration curve of Nitrofurantoin was found to be linear in the concentration range of 2.5-15 µg/ml at 241 nm in Phosphare buffer buffer (pH 6.8), methanol and water. The absorbance at different concentrations is shown in table and graph is represented in figure respectively.

Standard Curve of NF in Phosphate Buffer (pH6.8)

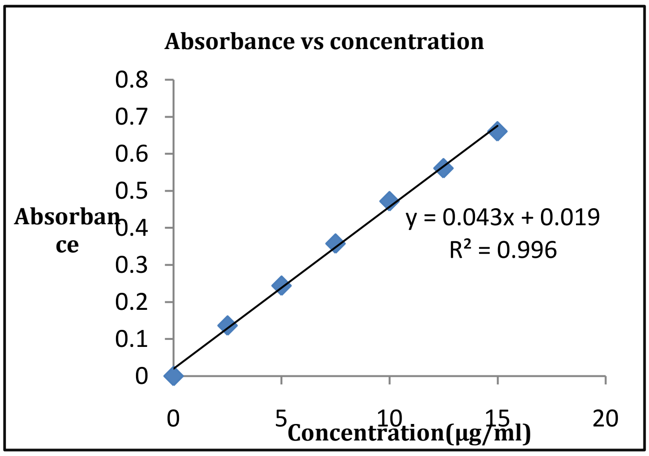

Figure 4: Standard Curve of NF in Phosphate Buffer (pH6.8)mean ± S.D (n=3)

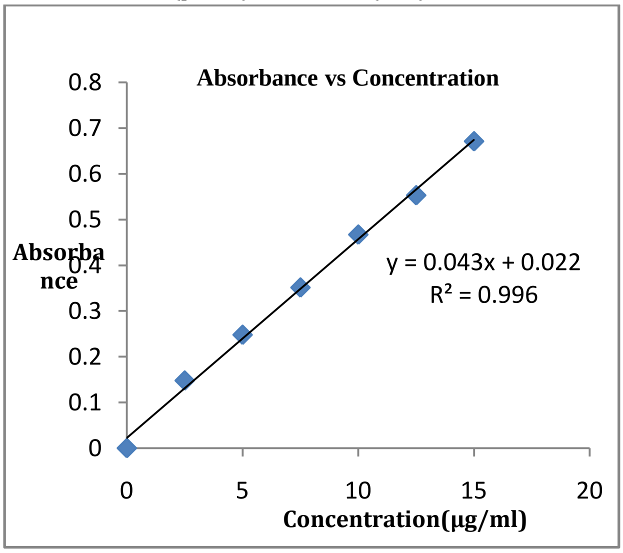

Figure 5: Standard Curve of NF in Distilled water

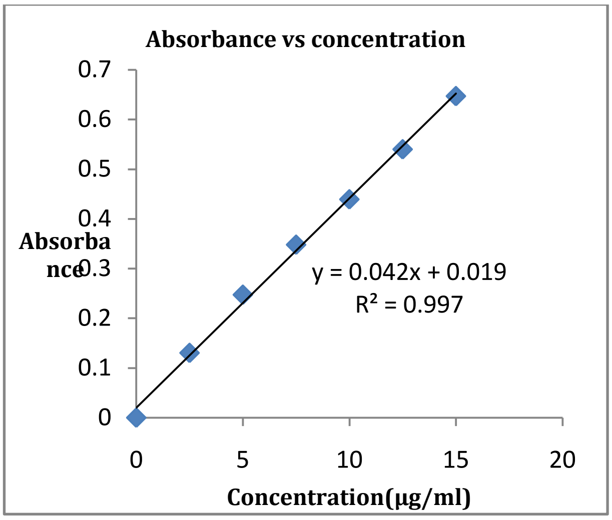

Figure 6: Standard Curve of NF in Methanol

Dissolution studies

The dissolution profile of pure drug and solid dispersion were carried out in Phosphate buffer (pH 6.8). The presence of HPMC:PVP increases the dissolution of Nitrofurantoin from the solid dispersion, which increases the dissolution rate as shown in figure . The figure indicates that the solid dispersion (1:7) of Nitrofurantoin: HPMC: PVP gives fastest dissolution of drug as compared to other formulation. The In vitro release of pure drug and different solid dispersions were determined and plotted the graph between % drug released vs time.

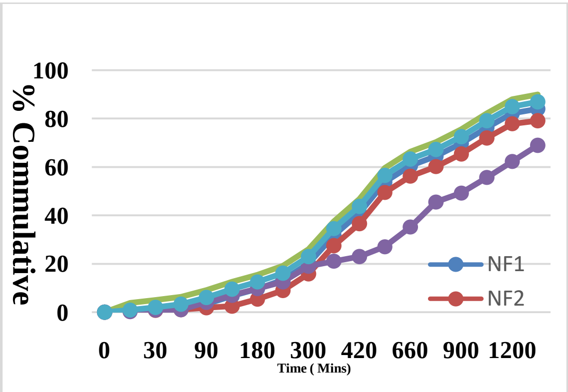

Figure 7:- Dissolution profile of pure drug and solid dispersions

Differential Scanning Spectroscopy

The DSC thermogram of Optimised Ratio (1:7) shows absence of sharp peaks, the possible interaction between the pure drug, polymers and their formulations were confirmed by Differential Scanning Calorimetry

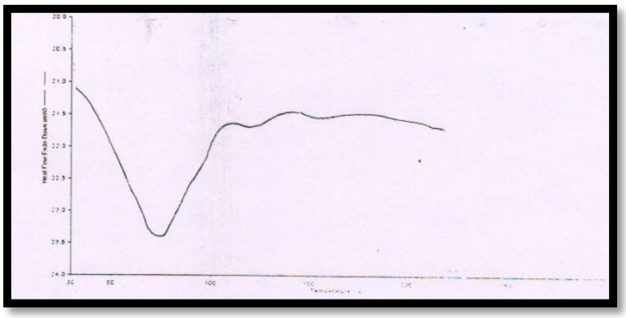

Figure 8: DSC Thermogram of optimized batch

Infrared Spectroscopy

The IR Spectra of **Nitrofurantoin** and optimized solid dispersion of combination of HPMC and PVP shown in figure 9. The spectra peaks of drug were almost unchanged in the optimized solid dispersions which indicate that the overall symmetry of molecule was not affected with polymers

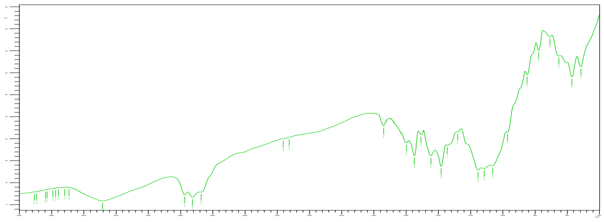

Figure 9: FTIR of Optimized batch

X-ray diffraction studies

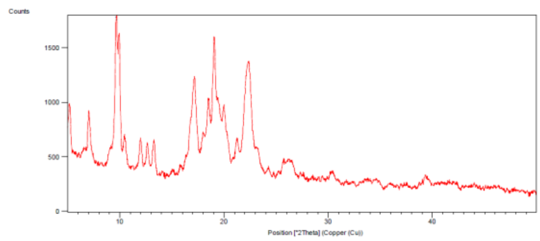

Figure 10: XRD of optimized batch

Characterization of Blends

The X-ray diffraction studies of optimized solid dispersion is shown in figure. Peaks of optimized solid dispersion shows the reduction in peak height area which indicates the reduction in the crystallinity nature of the **Nitrofurantoin** as some of the drug converted into the amorphous form in the solid dispersions

Table 7: Blend Characteristics mean ± S.D (n=3)

Parameters	Results
Carr"s index (%)	11.6
Angle of repose (°)	46^{0z}
Bulk Density (g/cc)	0.7

Identification tests for tablet dosage form:

Table 8: Characterization of Tablet Dosage form mean ± S.D (n=3)

S. no	Hardness (kg/cm)	Wt. Variation (mg)	Disintegration Time (min)	Drug Content (%)	Percent Yield (%)
NF1	4.5±0.096	101.1±1.123	6.22	84.03±0.168	76.25 ±0.263
NF2	4.1±0.049	100.3±1.068	6	79.22±0.268	78.26 ±0.169
NF3	4.3±0.169	100.8±1.268	7 .46	90.02±0.144	81.65 ±0.259
NF4	4.2±1.026	99.1±2.569	7	69.01±0.206	75.66 ±0.305
NF5	4.3±0.009	98.3±1.201	5.99	87.03±0.125	77.88 ±0.25

Conclusion

Nitrofurantoin has a low absolute bioavailability and a comparatively short plasma half-life. Patient compliance may be lowered if larger doses must be administered two or three times per day. For daily dosing of nitrofurantoin, a sustained release formulation that would sustain plasma levels for 8–24 hours might be adequate. For nitrofurantoin to increase patient compliance and extend its duration of action, sustained release products are required. This study's main goal was to create an oral sustained-release nitrofurantoin tablet using the combination of HPMC4000 and PVPK30 as a rate-controlling factor. According to the drug release study, PVPK 30 and HPMC4000 could maintain the drug release. The drug release was maintained for over twenty-four hours when both polymers were combined with the drug.

Disclosure Statement

There are no conflicts of interest.

Acknowledgment

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