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Formulation and Evaluation of Sustainedrelease Matrix Tablet of Nitrofurantoin

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ABSTRACT

The main objective of the present work was to develop sustained release matrix tablets of Nitrofurantoin. To reduce the frequency of administration and to improve the patient compliance, a twice daily sustained release formulation of Nitrofurantoin is desirable. So sustained release Matrix tablet of Nitrofurantoin was designed by using different polymers viz. Hydroxyl Propyl Methyl Cellulose (HPMC K4M, K100M), and natural polymer like xanthan gum at varying ratios of drug and polymer were selected for the study. The IR examine found out that there has been no chemical interplay among drug and excipients. The tablets were prepared by direct compression method. Pre-compressional parameters such as angle of repose, percent compressibility, and Hauser's ratios were studied. These results indicate that powder blend had good flow characteristics. After assessment of physical properties like Weight variation, Hardness, Thickness, Friability of tablet, the different formulations were checked for the percentage Drug content, which showed good uniformity. The in vitro release study was performed in 0.1N HCl for first 2 hrs and in phosphate buffer pH 6.8 up to 12 h. The effects of polymer concentration were studied. Dissolution records become analyzed via way of means of Percentage cumulative drug release Matrix capsules studied for the distinct polymer ratios and overall performance checked for different concentration ratios. The effects of drug dissolution research confirmed advanced drug release, retardation effects of the polymers and could achieve better performance. It was observed that matrix tablets contained mixture of natural and synthetic polymer successfully sustained the release of drug up to 12 hrs. Stability studies (40±2ºC) for three months indicated that Nitrofurantoin become stable in the matrixtablets.

KEYWORDS: Nitrofurantoin, Hydroxyl Propyl Methyl Cellulose (HPMC K4M, HPMC K100M), Xanthan gum, Sustained release.

I. INTRODUCTION

[1]Diseases and problems are the principle elements for which pharmaceutical enterprise make the drug treatments and make certain that excellent of existence for the human beings is improved. Everyone is going through paintings pressure, they're going thru stress, abnormal weight-reduction plan habits, and negligence closer to exercising has made the human beings extra vulnerable to diseases. Once the people reach their 40s, they start acquiring one or more common diseases like high blood pressure, high cholesterol level, Diabetes etc. As they grow older, the list of medication increases and so do their frequency of medication. The market is changing and new technological improvements are taking place and drug delivery systems are changing rapidly. The market is now more focusing on modified release drug deliverysystems.Most conventional drug products, such as tablets and capsules, are formulated to release the active drug immediately after administration to obtain rapid and complete systemic drug absorption.The conventional dosage form gives prompt release of drugs showing fluctuations in drug concentration in the body and necessitates multiple dosing to maintain the therapeutic level. So, to achieve and maintain uniform concentration of drug in the therapeutic range the modified dosage formsare developed.

[2]Sustainedrelease drug delivery system.Any dosage form that maintains the therapeutic blood or tissue levels of drug by continuous release of medication for a prolonged period of time, after administration of a singledose. Sustained release tablet owing a twofold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form. It is designed to

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maintain constant levels of a drug in the patient's blood stream by releasing the drug over an extended period. Maintaining constant blood levels of the drug in the bloodstream increases the therapeutic effectiveness of the drug.Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. The basic rationale of sustained release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure/treatment of the disease is achieved. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SRdosage form.

II. MATERIALS AND METHODS:

Materials:

Table 1: List of Ingredients

Sl. No	Materials	Supplied by
1	Nitrofurantoin	QMED pvt ltd Bhaktapur,Nepal
2	HPMC K4M	Yarrow chem pvt ltd, Mumbai
3	HPMC K100M	Yarrow chem pvt ltd, Mumbai
4	Xanthan gum	Yarrow chem pvt ltd, Mumbai
5	Anhydrous Lactose	Mehta chemicals, Bangalore
6	Magnesium stearate	Signet Chemical Corporation Pvt. Ltd, Mumbai
7	Talc	Karnataka Fine Chem, Bangalore

Table 2: List of Equipments

Sl. No	Equipment	Model/ Manufacturer
1	Electronic analytical balance	Sartorius
2	Bulk density apparatus	Singhla lab
3	FTIR Spectrometer	Jasco, FT-IR 460 Plus
4	UV-Visible spectrometer	UV-117/ Systronics
5	Single head rotary tablet compression machine	Cadmack
6	Tablet hardness tester	Monsanto
7	Vernier calipers	Mitutoyo, SXR629
8	Roche friabilator	Electro lab
9	USP Dissolution apparatus	DS 8000/Lab India

Formulation procedure: -

Nitrofurantoin tablets were prepared by direct compression method. Specified quantity of nitrofurantoin, polymers such as HPMC K4M, HPMC K100M, xanthan gum, other excipients like lactose, magnesium stearate and talc weighed accordingly to the formula given in table. All the materials except magnesium stearate and talc were transferred in a mortar and pestle and mixed thoroughly. This powder was passed through sieve no #80. To this add weighed quantity of magnesium stearate andtalc.Each batch formulation powder blend was weighed to accurate single total tablet weight (710mg). Tablet was compressed with Single head rotary tablet compression machine. Fill the weighed powder in to the die cavity(12mm). Adjust the hardness suitable for sustained drug release and punch the tablet. The different batches of nitrofurantoin tablet were collected and stored in container.

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Table 3: Formulation for the preparation of Nitrofurantoin tablet (F1-F9)

Batch Code									
Ingredients in mg	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nitrofurantoin	200	200	200	200	200	200	200	200	200
Xanthan gum	300	-	-	-	150	150	150	75	75
HPMC K4M	-	300	-	150	150	-	75	150	75
HPMC K100M	-	-	300	150	-	150	75	75	150
Anhydrous lactose	200	200	200	200	200	200	200	200	200
Magnesium Stearate	7	7	7	7	7	7	7	7	7
Talc	3	3	3	3	3	3	3	3	3
Total weight(mg)	710	710	710	710	710	710	710	710	710

Characterization of Nitrofurantoin:

Melting point: The melting point of pure drug nitrofurantoin was determined by open capillary method.

Determination of organoleptic properties: The physical appearance of the drug was observed and compared with thePharmacopeial specifications.

Solubility:[3]Small increments of Nitrofurantoin were added to 10ml of solvent (acetone, ethanol, diethyl ether, acetic acid) in a 25ml stoppered standard flask with vigorous shaking. Visually observed the solution, if the solution was clear and no undissolved particles were observed if it was insoluble again another increment of particular solvent was added and the procedure was continued until undissolved Nitrofurantoin wasfound.

Pre compression studies

Angle of repose (θ):[4]flow property was determined by measuring the angle of repose.

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

Where, θ = angle of repose, h = height of the cone, r = radius of the cone base

Bulk density (Db)-The Bulk density of the powder was evaluated using bulk density apparatus. It is the ratio of total mass of powder to the bulk volume of powder.Db =M/Vb

Where, M= Mass of the powder, Vb= Bulk volume of powder

Tappeddensity (Dt): It is the ratio of total mass of powder to the tapped volume of powder.

$$D_t = M/V_t$$

Where, M= Mass of the powder, Vt= Tapped volume of powder

Compressibility index (CI) and Hausner's ratio (HR):

Carr's index or compressibility index and Hausner's ratio measure the propensity of powder to be compressed and the flow ability of powder. Carr's index and Hausner's ratio were calculated using the followingformula,

Carr's index= [(Tapped density –Bulk density)/tapped density] x 100

Hausner's ratio= Tapped density / Bulk density

Table 9: Effect of Carr's index and Hausner's ratio on flow properties

Flow properties	**Angle of repose (θ)**	**Carr's index (%)**	**Hausner's ratio**
Excellent	25-30	1-10	1.00-1.11

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Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>66	＞38	＞1.60

POST COMPRESSION STUDIES: -

Shape and appearance:

The formulated tablets were visually observed for its shape and color.

Thickness and Diameter:

Thickness and diameter of the tablets were measured using a Vernier caliper. Three tablets of each formulation were picked randomly and the dimensions of each three tablets were measured in mm. This was done in triplicate and standard deviation was calculated.[5]

Weight variation test:

[5]The Weight variation test was carried out in order to verify the uniformity of the weight of tablets in each formulation. 20 Tablets were selected randomly and weight individually to check for the weight variation. The following percentage deviation in weight wasallowed.

Table 4: Limits for weight variation (USP)

Average weight of a tablet	Percentage deviation (%)
130 mg or less	±10
More than 130mg and less than 324mg	±7.5
324mg or more	±5

Friability of tablets:

[5]It is measure of tablet strength. It is related to tablet ability to withstand both shock and abrasion without crumbling during the handling of manufacture, packing, shipment and consumer use.

$$\% \text{ Friability} = \frac{\text{Initial weight (w1)} - \text{Final weight(w2)}}{\text{Initial weight (w1)}} \text{ X } 100$$

Hardness of tablets:

[5]For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured.

Uniformity of drug content:

[5,6,7]From each batch 10 tablets were taken and finely powdered. A weight equivalent to 100 mg of Nitrofurantoin was accurately weight and dissolved in 100 ml of 0.1 N HCl. The drug was allowed to dissolve in the solvent, the solution was filtered and 1 ml of the filtrate was suitably diluted to 10 ml with the same buffer.Again from the II stock solution 1ml was pipette out and diluted to 10 ml with 0.1 N HCl and analyzed Spectrometric ally at 330nm. The amount of Nitrofurantoin was estimated using standard calibration curve of thedrug.

In-Vitro dissolution studies:

[8]Dissolution rate of Nitrofurantoin was

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studied by using USP type –II apparatus (USP XXII Dissolution test apparatus at 50 rpm using 900ml of 0.1N HCl (1.2 pH buffer) for first 2 hrs and remaining 10 hrs in phosphate buffer pH (6.8) as dissolution medium. Temperature of the Dissolution medium was maintained at 37±0.5℃. 5ml of dissolution medium was withdraw at regular intervals and replaced with the same volume off dissolution medium. The samples Were analyzed at 330 nm by UV Spectrometer and the results were reported. The absorbance were recorded and percentage drug release was calculated.

Stability studies: -

The selected formulation was tested for its stability studies. Short term stability studies were performed at temperature 40±2℃ over a period of 3 months. 5 tablets were packed in amber colored screw capped bottle and kept in stability chamber maintained at 40±2℃. Samples were taken at 1-month interval for their drug content estimation including physical parameters. At the end of 3 months period, dissolution test was performed to determine the drug release profile.

III. RESULTS AND DISCUSSION: -

Characterization of Nitrofurantoin

Table no 5: Organoleptic properties of Nitrofurantoin-

Sl. No.	Parameter	Reported	Inference
1	Nature	Crystalline powder	Crystalline powder
2	Color	Yellow	Yellow
3	Melting point	270℃	270℃
4	Odor	Odorless	Odorless
5	Taste	Tasteless	Tasteless

Preparation of Standard calibration curve of Nitrofurantoin in 0.1N HCl:

25mg of Nitrofurantoin was weighed accurately and transferred to a 100 ml volumetric flask and dissolved with little amount of acetone and then the volume was made up by adding the same solvent. Then 5 ml was sifted to 50 ml volumetric flask and then volume was adjusted up to mark with same solvent to achive concentration 100microgram /ml from accurate stock solution 0.5 ml was transferred to 25 ml volumetric flask and volume adjusted upto mark with same solvent to obtain concentration 5 microgram/ml. The absorbance of above solutions were scanned in UV region and found that nitrofurantoin showed absorbance at 330nm. Calibration curve was prepared by plotting concentrationV/s absorbance.

Sl.No.	Concentration (µg/ml)	Absorbance
1	0	0.00
2	2	0.077
3	4	0.161
4	6	0.244
5	8	0.318
6	10	0.385

Table no 6: Standard calibration curve of Nitrofurantoin in 0.1N HCl

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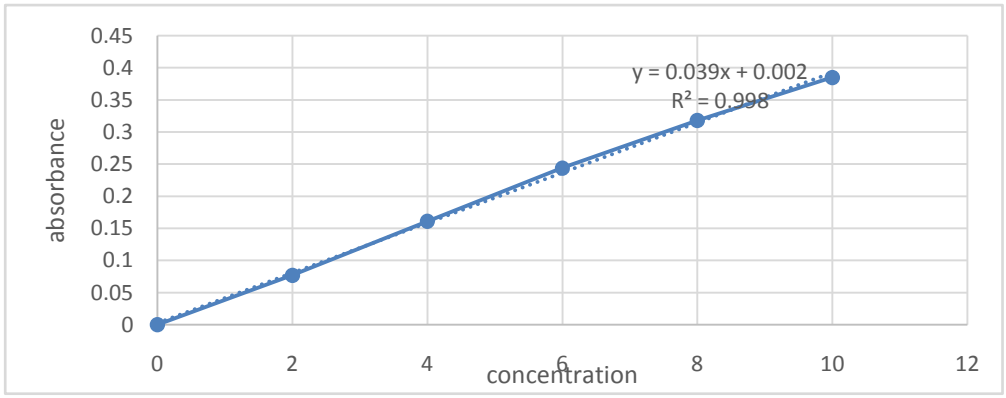

Figure 1: Standard calibration curve of Nitrofurantoin in 0.1N HCl

Preparation of Standard calibration curve of Nitrofurantoin in Phosphate buffer pH 6.8:

Phosphate buffer solution pH 6.8:

10 mg of Nitrofurantoin was weighed accurately and transferred to a 100 ml volumetric flask and dissolved with little amount of ethanol and then the volume was made up by adding the Phosphate buffer in 100 ml volumetric flasks. Then ten ml from above solution was taken into another 100ml volumetric flask and volume was made up with stock solution. Volumes of 2ml, 4ml, 6ml, 8ml & 10 ml were taken in 10 ml volumetric flask from the prepared solution and diluted up to the mark with Phosphate buffer. The absorbance of above solution was scanned in UV region and found that nitrofurantoin showed absorbance at 330nm. Calibration curve was prepared by plotting concentration V/sabsorbance.

Table 7: Standard calibration curve of Nitrofurantoin in Phosphate buffer pH6.8

SL.NO	**Abs**	**Conc**
1	0	0
2	0.076	1
3	0.111	2
4	0.153	3
5	0.194	4
6	0.235	5
7	0.279	6
8	0.321	7
9	0.359	8
10	0.402	9
11	0.448	10

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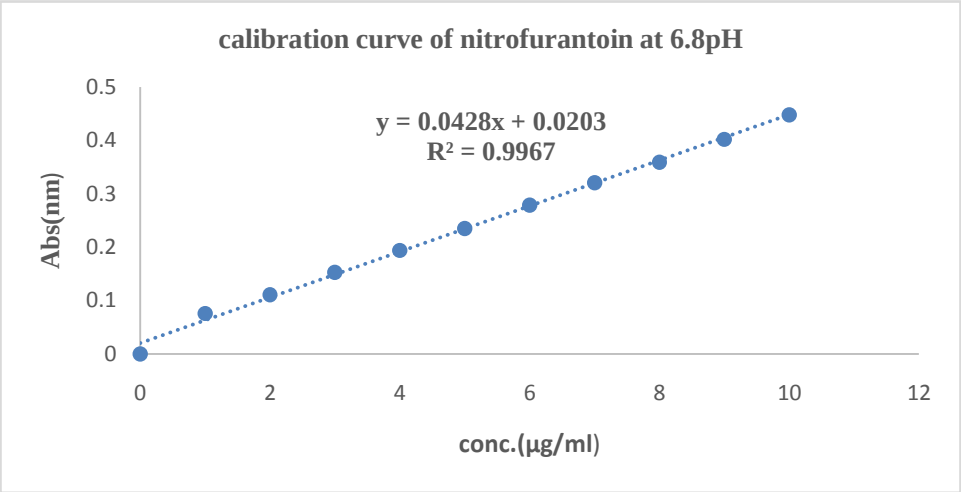

Figure 2: Standard calibration curve of Nitrofurantoin in Phosphate buffer pH6.8

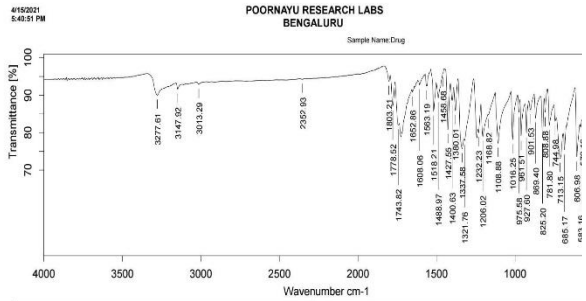

Figure 3: Infrared spectrum of Nitrofurantoin

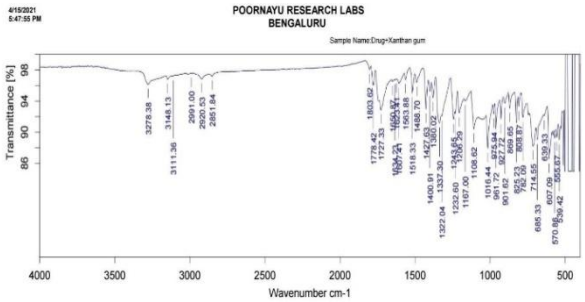

Figure 4: Infrared spectrum of Nitrofurantoin + xanthan gum

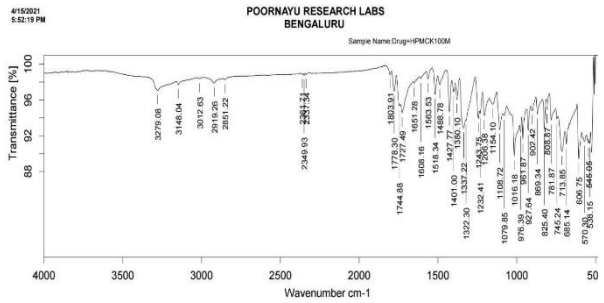

Figure 5: Infrared spectrum of Nitrofurantoin + HPMC K100M

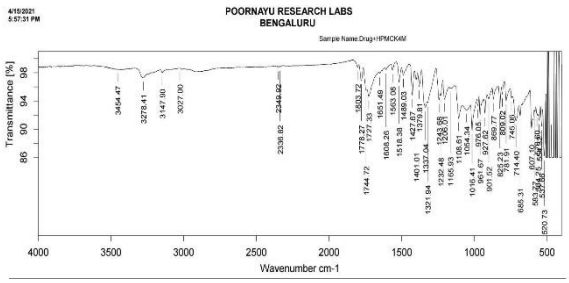

Figure 6: Infrared spectrum of combination of Nitrofurantoin andHPMC K4

PRE COMPRESSION STUDIES

Table no 8: Evaluation properties of powder blend

Formulation Code	**BD (g/ml)**	**TD (g/ml)**	**Car's Index**	**Hauser's Ratio**	**Angle of Repose(Ɵ)***
F1	0.39	0.48	18.75	1.23	32.72±1.605
F2	0.389	0.49	13.55	1.15	32.015±2.326

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F3	0.424	0.53	20	1.25	35.14±0.056
F4	0.429	0.53	20.23	1.23	30.725±2.029
F5	0.441	0.509	13.35	1.15	26.99±0.806
F6	0.45	0.506	11.06	1.12	26.865±1.534
F7	0.42	0.56	25	1.33	24.39±0.367
F8	0.374	0.481	22.24	1.28	27.80±0.813
F9	0.389	0.484	17.76	1.21	27.99±0.848

POST COMPRESSION STUDIES

Table no 9 : Evaluation of tablets

Formulation Code	Hardness	Thickness	Friability%	Average weight	Drug content (%)
F1	7.5±0	5.5	0.74	710.3	98.29±0.05
F2	6.66	5.5	0.47	710.17	99.54±0.64
F3	6.5±0	5.4	0.72	710.42	99.05±0.4
F4	6±0	5.48	0.70	709.36	100.35±0.16
F5	7.33±0.288	5.01	0.50	709.4	101.76±0.52
F6	6.5±0	5.02	0.83	710.5	100.63±0.09
F7	6.16±0.288	5	0.49	710.16	98.49±0.2
F8	6.33±0.288	5.01	0.75	710.34	101.8±0.4
F9	6.83±0.288	5.02	0.70	709.56	97.35±0.14

*All the values of mean of three reading

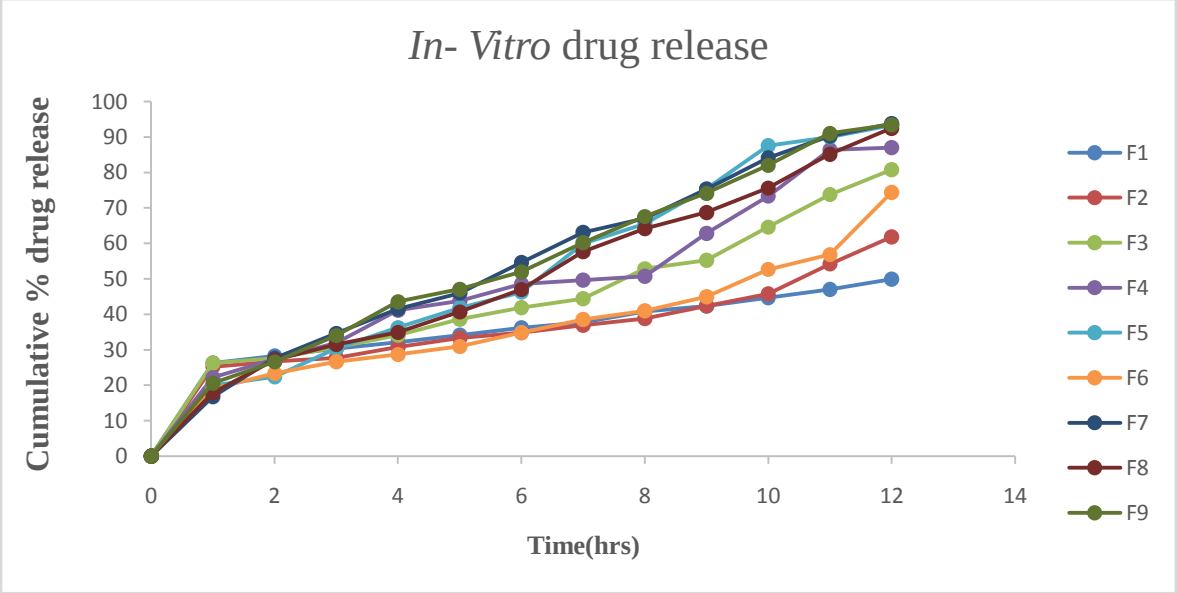

Figure No 7: *In- vitro* drug release curve for formulation F1-F9.

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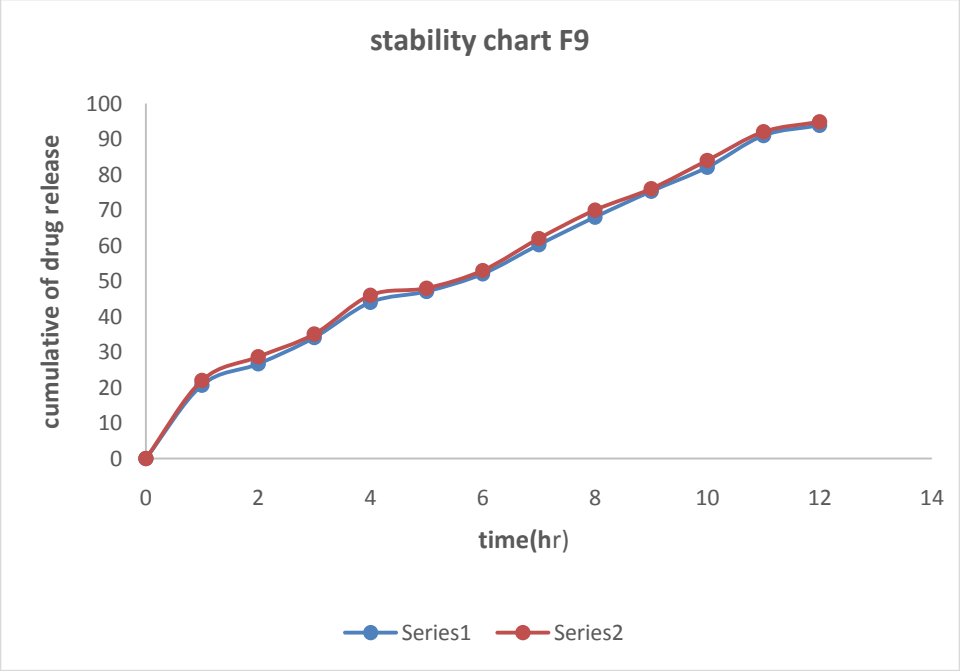
Table 10: In-vitro drug release study for stability testing of formulation F9 at 30±2°C

S. No.	Time (hrs)	90^{th} day cumulative % drug release
0	0	0
1	1	22.01
2	2	28.66
3	3	35.07
4	4	46.02
5	5	48.01
6	6	53.00
7	7	62.01
8	8	70.01
9	9	76.02
10	10	84.01
11	11	92.05
12	12	94.89



FigureNo8:In-vitrodrugreleaseofF9 beforeStabilityandAfterstabilityat30±2°C.

Discussion

Successful attempt was made to formulate and evaluate sustain released matrix tablets of Nitrofurantoin employing direct compression technique. In-vitro dissolution study was carried out in order to investigate the drug release from various formulations. Various physio-chemical, pre- compression, post-compression parameters of the formulated sustain released matrix tablets of Nitrofurantoin were characterized.

PREFORMULATION STUDIES OF PURE DRUGS:

Identification of Pure Drug

- ✓ Appearance: Nitrofurantoin is a yellow odorless crystallinepowder.
- ✓ Melting Point Determination: The melting point of pure drug was found to be 270^0C. As per the Pharmacopoeia, the melting point of Nitrofurantoin was reported to be 270^0C, thus indicating purityof sample.
- ✓ Solubility: Nitrofurantoin is soluble in organic solvents such as ethanol, DMSO and dimethyl formamide at room temperature i.e. 22 – 25^0C whereas it is sparingly soluble in aqueous buffers.

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- ✓ IR Spectroscopy: The FT-IR spectrum of Nitrofurantoin recorded by FT-IRspectrometer was

compared with standard functional group frequencies of Nitrofurantoin. The frequencies of functional group of the obtained sample were in the range which indicated that the obtained Nitrofurantoin was of pure quality.

- ✓ Drug-Excipients Compatibility Studies: FT-IR spectrum obtained for the drugwith formulation excipients showed characteristic peaks of the drug at their respective wavelength with no major shifts indicating compatibility of drug with the used excipients.
- ✓ Standard calibration curve of Nitrofurantoin: Standard solution of Nitrofurantoin was scanned inthe range of 200-400nm and showed maximum absorbance at 330nm in 0.1N HCl and 6.8 pH Buffer with slope, intercept and regression co-efficient tabulated in 27 and depicted in figure 21 & 22. Good linearity was observed in the plot with regression value 0.998 in 0.1 N HCl and 0.996 in 6.8 pH buffer with the slope 0.0428 and 0.049 respectively, hence obeyed "Beer Lambert's Law." The calculation of drug content and in-vitro drug release study are based in this standard calibration curve.

EVALUATION OF GRANULES AND TABLETS OF ALL FORMULATIONS

❖ **Pre-compression Evaluation Parameters:** The formulation blend was subjected for pre- compression evaluations such as angle of repose, bulk and tapped density, compressibility index and hausner's ratio. Results of the pre-compression parameters performed for the blend for each batch are reported in thetable 16.

The angle of repose for all the formulations was found to be within the range of 24.495 to 32.72 showing excellent flow properties. Hausner's ratio was found to be in the range of 1.12 to 1.33 and compressibility index was found to be in the range of 11.06 to 22.44 indicating good compressibility of the tablet.

❖ **Post-compression Parameters**

- ✓ **Weight Variation Test:**Prepared tablets of all the formulations were evaluated for weight

variation and percentage deviations from the average weight (n=10) are reported in the table no.17. The average weights of all the formulations are within the range of 710mg. All the tablets passed the weight variation test, i.e. the average percentage. weight variation was found to be within the prescribed pharmacopeial limit of ±5%.

- ✓ **Friability**: The friability of the formulations was found to be 0.47% to 0.89% as reported

in the table no.17. The obtained results were found to be within the approved range (<1%) in all the formulations indicating tablets possess good mechanical strength.

- ✓ **Tablet thickness and hardness**: The thickness of the tablets for all the batch wasfound

between 5±0.1 to 5±0.5 mm whereas hardness was found to be within the range of 5.5±0 to 7.5±0.288Kg/cm^2 as reported in the table no.17. The low standard deviation values indicate that the thickness as well as hardness of all the formulations was almost uniform and also the tablet possess good mechanical strength with sufficient hardness.

- ✓ **Drug Content Uniformity**: The percentage of drug content was found to be in the rangeof98.29±0.05 to 101.98±0.44% as shown in the table no.17. The results were within the limit (NLT 98% and NMT 102%) as specified in the Pharmacopoeia. The cumulative percentage drug released from each tablet in the in-vitro release studies was based on the average drug content present in thetablet.
- ✓ **In-vitro dissolution studies**:In-vitro dissolution studies were performed for all thebatches

of tablets containing Nitrofurantoin using USP dissolution test apparatus – I at 50 rpm, 900ml of 0.1 N HCl for 2hours and 6.8pH buffer for 10 hours. The in-vitro drug release data are reported in tables 18 to 26 From the above result showed that the F9 formulation showed maximum drug release at the end of 12 hours

- ✓ **Drug Release Kinetics:** The data obtained from in-vitro dissolution studies were fittedto mathematical model viz. Higuchi Model and the co-efficients of regression value were compared. From the table no 27. It was observed that the formulations followed Higuchi Model as the co-efficient of regression value was more nearer to one. Among the 9 formulations, F9 was selected as the best formulation as its co-efficient of regression value of korsmeyers-peppas model was morenear to unity. After, the data was subjected to Korsmeyer-Peppas equation for determination of release mechanism the

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acceptable linearity was observed for all the developed formulation. The release co-efficient "n" varied from 1.645 to 0.803 that indicates both non-fickian and super case – II transport of a drug from polymer i.e. drug release follows both diffusion and relaxation of polymer chain.

✓ **Stability Studies**: From the stability studies, it was clear that the formulationF9 was Physically and chemically stable for 90 days and there was no significant change in the physical parameters, drug content and in-vitro dissolution release profiles shown in table 28 &29.

Determination of ʎmax and Standard calibration curve of nitrofurantoin: Standard solution of nitrofurantoin was scanned in the range of 200-400 nm and showed maximum absorbance at 330nm in 0.1N HCl, with slope, intercept and regression co-efficient tabulated in table no. 14 and depicted in figure no.21.Good linearity was observed in the plot with regression value and hence obeyed "Beer-Lambert's Law." The calculationofdrugcontentandin-vitrodrugreleasestudyarebasedinthisstandardcalibration curve

IV. CONCLUSION

Matrix tablet of nitrofurantoin were successfully prepared by direct compression method, using different types of matrixes forming polymers like HPMC K4M,HPMC K100M,Xanthan gum. Matrix tablets are easy to prepare. They are cost effective and exhibit predictable release behavior. So, the ultimate aim of the present study was to prepare twice daily sustained release matrix tablets of Nitrofurantoin for improved patient compliance, better therapeutic efficacy, less side effects and reduced dosage regimen with less toxicity for treatment of urinary tract infection. In conventional dosage form it undergoes First pass metabolism, that is way it shows poor bioavailability of 45-56%. So due to this disadvantage to improve bioavailability sustained release matrix tablet wasformulated.

Following conclusions have been drawn from the presentstudy.

- Compatibility of drug and polymer was confirmed by FTIR studies.
- The formulation blend was subjected for pre-compressional evaluations such as angle of repose, bulk and tapped density, compressibility index and hausner'sratio and was found to be in the specified limit.
- The evaluation data for properties such as hardness, thickness, friability, weight variation, drug content indicated that the prepared matrix tablet were within the specified standards.

The in-vitro dissolution studies closely indicate that among Nine formulations, F9.wasfound to be best with good drug release.

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