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FORMULATION OF NITROFURANTOIN TABLETS FULFILLING THE PHARMACOPOEIAL SPECIFICATIONS

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ABSTRACT

The USP XXII specifies that the disintegration time for nitrofurantoin tablets must be not less than 30 minutes, not less than 25% of the drug is dissolved in 60 minutes and not less than 85% is dissolved in 120 minutes. These specifications were done to minimize the side effects and to achieve a proper bioavailability for the drug.

On testing the market tablet preparation (Furadantin), it was found that it does not fit to the USP specifications. Nine nitrofurantoin tablet formulations were then tried and each was studied for disintegration time and % dissolution in the first and second hours. The best formula was found to be consisted of adding 2% of collodion in 40% of the starting granules, coated with 4% CAP and adding another 2% of collodion to the remaining 60% of the granules.

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INTRODUCTION

Many trials were made to reduce or minimize the gastrointestinal intolerances of nitrofurantoin as well as to maximize its bioavailability. Adjusting the particle size of nitrofurantoin in both tablets and capsules was studied[1-4]. Controlling the in-vitro dissolution and in-vivo absorption characteristics of nitrofurantoin was achieved either by increasing the solubility[5,6] or by adjusting the pH[7,8]. The rate of excretion of enteric-coated tablets was greater than plain uncoated nitrofurantoin tablets[9].

No attempts were done to solve the above two problems of nitrofurantoin tablets by changing the components of the tablet formulation.

The aim of this paper is to control these side effects and to maximize bioavailability of nitrofurantoin tablets through formulation of tablets that comply with the USP XXII specifications[10].

MATERIALS AND METHODS

MATERIALS

Nitrofurantoin was a kind gift from Kahira Pharm. and Chem. Ind. Co., (Cairo, Egypt). Maize starch, lactose, povidone (30), starch, talc and magnesium stearate were of analytical grade. Cellulose acetate phthalate (CAP) and collodion CL were from B.D.H. Chemicals Ltd. (Poole, England).

METHODS

Formulation of Nitrofurantoin Tablets

Nitrofurantoin tablets were manufactured from the starting formula (F) by mixing nitrofurantoin with maize starch and lactose, granulating by the aqueous solution of PVP, passing through sieve No. 16 and

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retaining on sieve No. 20. Then starch, talc and magnesium stearate were added to the granules. After drying,the granules were sieved again and that retained on sieve No. 20 were compressed on 8 mm set of punches and dies.

Formulations, F_1 and F_2, contained 4 and 5% of CAP, respectively, were prepared by sprinkling the solution of CAP in acetone on 50% of the prepared starting granules to form a coat around the coarse granules. After drying, mixed with the rest of the granules and then retained on sieve No. 20. Then, proceed as above.

Formulations, F_3 and F_4, contained 2 and 3% of collodion CL, respectively, were prepared by adding collodion CL together with starch, talc and magnesium stearate and mixed with the prepared granules.

Formulae from F_5 to F_8 were prepared by dividing each formula into two parts. The first part was consisting of chosen percentage of the starting formula excluding the lubricants. To this part, CAP solution was added as a coat. The other part of the granules was mixed with collodion CL. The two parts were then mixed together, and lubricants were added and proceed as above.

F_9 was prepared by mixing 40% of the starting formula with 2% collodion CL and granulated by PVP solution. The finished granules were sprayed with 4% CAP in acetone, dried in air. The other 60% of the granules wax mixed with 2% collodion CL. The 2 parts were mixed, lubricants were added and then the final granules were compressed. Table (1) illustrated the different formulae studied and the amount of each ingredient.

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Table I

The Different Formulae of Nitrofurantoin Tablets and Their Compositions.

Formulations	F	F_1	F_2	F_3	F_4	F_5		F_6		F_7		F_8		F_9	
Tablet composition						I	II	1	II	I	II	I	II	I	II
Nitrofurantoin	100	100	100	100	100	50	50	40	60	30	70	30	70	40	60
Maize starch	20	20	20	20	20	10	18	8	12	6	14	6	14	8	12
Lactose	38	38	38	38	38	19	19	15.2	22.8	11.4	26.4	11.4	26.6	15.2	22.8
P.V.P.	10	10	10	10	10	5	5	4	6	3	7	3	7	4	6
Starch	8	8	8	8	8	--	8	--	8	--	8	--	8	--	8
Talc	3	3	3	3	3	--	3	--	3	--	3	--	3	--	3
Magnesium stearate	1	1	1	1	1	--	1	--	3.5	--	5	--	6.5	--	7.5
CAP	--	4%	5%	--	--	11%	--	11%	--	10%	--	5%	--	4%	--
Collodion	--	--	--	2%	3%	--	5%	--	5%	--	5%	--	5%	2%	2%

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Disintegration Test

The disintegration time of 6 tablets of each formulation was determined at 37°C in 900 ml of distilled water, using Erweka disintegration tester ZT4 (G.M.B.H., Germany).

Dissolution

The in-vitro dissolution studies were carried out on commercial tablets (Furadantin) and on each of the prepared formulations using the USP dissolution apparatus I with a 100 rpm basket rotation. The dissolution medium was 900 ml of phosphate buffer pH 7.2 at 37°C. Samples were withdrawn at the end of 1st and 2nd hour of dissolution and assayed spectrophotometrically at 266 nm.

RESULTS AND DISCUSSION

On testing one form of nitrofurantoin commercial tablets in the local market, the disintegration time (DT) obtained was only one minute the amount of the drug dissolved at the end of the first hour and second hours was 39% and 59%, respectively which is not approved. The less dissolution percent on the second figure will declare improper therapeutic effect where only 59% of the dose assumed to be absorbed.

Tablets containing nitrofurantoin, in the starting formula (F), disintegrated completely after 11 min. and amounts of the drug dissolved at the 1st and 2nd hour were found to be 25 and 52%, respectively which is far from USP specification.

The addition of 4% CAP as a coating material in F_1 increased the DT from 11 to 15 min., but decreased the amount dissolved from 25 to 21.8% in 60 min., and from 52 to 33.6% in 120 min. The 5% addition in F_2 showed similar results with small variation as observed in

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Table (2). On the other hand, the addition of 2% collodion CL as a protectant in F_3 decreased the DT to be 8 min., and increased the amount dissolved of the drug to be 56 and 67% in 60,and 120 min., respectively. The 3% addition in F_4 showed more decrease in DT (5 min.) and more increase in the amount dissolved (78 and 93%). Thus, increasing the concentration of CAP from 4% to 11% and collodion CL from 2% to 5% separately in formula F showed the same sequence of results i.e. CAP increase the DT and decrease the amount dissolved while collodion CL decrease the DT and increase the dissolved amount of the drug. These results suggest the addition of CAP to a chosen percentage of formula F as a coat, then mixing these granules with the remaining part containing collodion CL in order to control both DT and the dissolved drug, as shown from the remaining formulations.

The addition of 11% of CAP to 50% of the granules and 5% collodion CL to the other half in F_5 improved both DT (15 min.) and the dissolution (56 and 74%). Increasing the amount of magnesium stearate from 1 mg to 3.5 mg in the above formula with adjusting the granules ratio to be 40:60, as shown in F_6, increased the DT to be 16 min., and improved the dissolved amount after the first hour (65%) but decreased them to 71% after the second hour. Another increase in magnesium stearate (5 mg) with decreasing the concentration of both CAP (10%) and collodion (5%), to be added to 30:70 granules ratio in F_7, showed a more increase in DT (18 min.) and improved the dissolution after the first hour (39%) but decreased the dissolution after the second hour from 71% to 55%. Further increase in magnesium stearate (6.5 mg) with further decrease in CAP (5%) and remaining the concentration of collodion CL as in F_7 and using the same granules ratio (30:70) showed an

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Table II
Disintegration Time and Dissolution of Nitrofurantoin Tablets of Different Formulae.

Tablet formula	Disintegration time (minutes)	Percent drug dissolved after 60 min.	120 min.
Comm.tablet	01	39	59
F	11	25	52
F_1	15	21.8	33.6
F_2	20	20	32.6
F_3	08	56	67
F_4	05	78	93
F_5	15	56	74
F_6	16	65	71
F_7	18	39	55
F_8	21	45	70
F_9	30	53	87

increase in DT (21 min.) and an increase for both dissolution values, 45% and 70% after 60 and 120 min., respectively.

F_9,last trial,the amount of collodion CL was divided into two equal parts. The first part was added to 40% of the prepared granules and then sprayed by CAP. The other part of collodion CL was added to 60% of the granules. The results obtained were found to be complying with the USP's specifications where the DT was 30 min., and the amount of drug dissolved was 53% and 87% after 60 and 120 min., respectively.

The results of all tested formulations are summarized in Table(2).

Controlling the disintegration time and modification of the absorption pattern of individual nitrofurantoin doses by controlling release into the GIT might reduce the undesirable side effects of nitrofurantoin.

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Another point, which arose in this work, is the importance of the amount of magnesium stearate added to formulae F_5 to F_9. On increasing its amount from 1 mg to 7.5 mg prolonged DT of the tablets probably due to the hydrophobic characters of magnesium stearate is obtained.

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