RESEARCH PAPER

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Controlled Release Pellets of Nitrofurantoin

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A prototype formula, which is amenable to Spheronization, was designed for the drug cores of Nitrofurantion. Effect of excipient variables and process variables to obtain a product giving desired drug release for a period of 8-10 hours was studied. The successful formulation was subjected to *in vitro* and *in vivo* evaluation and stability.

THE present investigation was aimed at development of controlled multiunit dosage form of Nitrofurantoin, an urinary antiseptic, which has a biological half life of 30 min and is given orally in a dose of 50-100 mg four times a day[1]. To maintain clinically acceptable urinary concentrations, it is necessary to give the drug in a controlled release form which also minimises the side effects of the drug. Since local effects of an irritant drug can be reduced by multiparticulate systems,[2] controlled release pellet formulation offers most desirable form of administration of an irritant drug like Nitrofurantoin. The drug release characteristics of the pellets can be modified by changing the nature and concentration of the excipients used in the formulation.[3]

The present investigation deals with the development and evaluation of a matrix type multiparticulate controlled release preparation of Nitrofurantoin.

EXPERIMENTAL

Materials

Nitrofurantoin I.P., Micro crystalline cellulose U.S.NF, (MCC), Avicel PH 101 and Avicel RC-581 (F.M.C corporation U.K.), Dicalcium Phosphate I.P (DCP), Lactose I.P., Starch I.P, Hydroxy Propyl Methyl Cellulose U.S.P. (H P M C), Polyvinyl Pyrrolidone (B D H Chemicals U.K.) (P V P), Talc I.P., urea I.P.

All other materials, solvents and reagents used were of analytical grade. **All the analyses of Nitrofurantoin were carried out to protect the drug from light.**

METHODS

a) Fabrication of drug cores

Pellets were prepared by Extrusion-spheronization. Based on Pharmacokinetic parameters, dose of the drug chosen was 170 mg. The drug and matrix materials were sieved through 80 mesh, mixed and kneaded followed by extrusion through 16 mesh screen. The extrudates were rotated on spheronizer (Marumerizer, Fuji Paudal, Japan) fitted with 1 mm cross hatch pattern friction plate until the bed rotated axially and showed good fluidization. The studies were carried out using Acivel pH 101 as the main filler excipient, a spheronizer speed of 1100 r.p.m, a spheronization time of 3 min and batch size of 10 g. The pellets obtained were dried on paper lined trays at 50° for 2 h.

The prototype was subjected to different formulation variables such as filler type, filler concentration, moisture content, binder type and lubricants.[4,5]

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Table 1 : Process Variables

Code	Extruder Screen size (mesh)	Spheronizer speed (rpm)	Spheronization time (min)
1	16	1100	3
2	16	1100	5
3	16	1100	3
4	16	290	1)
		570	1) 5
		830	1)
		1100	2)
5	20	1100	3
6	30	1100	3

Of the various formulations studied, the selected one was subjected to different process variables[4,5] as shown in Table 1 and effect on pellet characteristic such as percent yield, mean particle size, sphericity[6] and drug release profile was observed.

b) Scale up studies

After standardisation of the excipients and process conditions the best formulation was investigated for successful scale up with respect to different independent variables. The batch size was increased from 10 g to 250 g and extrusion was carried out on a Fuji Paudal Ex - DS 60 extruder. The extruder speed and the spheronizer speed were held constant at 23 r.p.m. and 1100 r.p.m. respectively and the spheronization time was varied according to the need.

c) Evaluation of the pellets

1) Percent drug content : The pellets were extracted using DMF (dimethyl formamide). The filtered solution was then diluted with distilled water and the absorbance was measured at 367 nm using Bausch and Lomb Spectronic 2000 spectrophotometer. The drug concentration was determined from the standard curve of the drug in distilled water over a range of 0 - 25 mg/ml.

2) In vitro release profile : This was determined using USP XXI Type II dissolution apparatus, with the dissolution fluid maintained at 37° and the paddle operated at 100 r.p.m. The fluid consisted of standard buffer of pH 1-2 for one hour, pH 4.5 for the second hour and pH 7.0 for the rest of the dissolution period.

The pellets were also evaluated for percent friability, density, porosity, flow properties and surface area.

In Vivo evaluation : The **in vivo** behaviour of the developed formulation (170 mg) was studied on three healthy male volunteers in the age group of 20- 26 years, weighing 50-70 kg and compared with that of a conventional formulation (100 mg).

Urine samples were collected at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 24 and 48 hours and frozen immediately. For analysis, to 1 ml of urine sample, 4 ml of 1% urea solution was added. The mixture was heated on a boiling water bath for 15 min. The absorbance of the resulting solution was measured at 400 nm on spectronic 2000 spectrophotometer. The concentration of the drug was determined from the standard curve of the drug in urine over a range of 0-25 μg/ml.

d) Stability Studies

The formulation was subjected to accelerated stability studies by storing them at 37° ± 1°, 45° + 1°, 60° + 1° and 85% R.H. for a period of 1 year and evaluating them for appearance, drug content and **in vitro** release profile.

RESULTS AND DISCUSSION

A) Effect of Formulation variables

The results of the study revealed that Avicel and locally available M C C formed good pellets. Avicel in combination with D C P formed pellets with rough

Table 2 : Effect of process variables

Code	Percent yield (%)	Sphericity (%)	Mean Particle Size (mm)	Flow rate (g/Sec)
1	76.533	97.8	0.872	20.42
2	85.31	98.12	0.894	18.63
3	60.29	89.25	0.811	19.41
4	91.00	94.22	0.912	20.24
5	90.19	95.12	0.802	17.43
6	19.84	91.25	0.596	18.06

surface due to extrudate shark skinning, whereas, Avicel in combination with lactose formed pellets with smooth surface characteristics. Of the two grades of Avicel used, Avicel RC-581 formed pellets with a very good sphericity of 98.29%. Avicel RC-581 is considered to be an excellent excipient in formulations for extrusion as it contains sodium CMC which improves the binding properties and imparts elasticity to the mass.[7]

However the desired properties for obtaining a narrow particle size distribution are proper elasticity and plasticity of the mass which could be achieved by combining Avicel pH 101 and Avicel RC-581 in a ratio of 60:40 yielding pellets with sphericity of 97.5% and a per cent yield of 76.53% in the desired size range of 0.8 - 1 mm.

As the diluent concentration was increased the pellet formation was better, A drug - diluent ratio of 35 : 65 formed good pellets with 92.18% sphericity.

For a drug-diluent ratio of 35:65, 50% moisture content yielded only 25.72% of the pellets in the desired size range whereas with 52.24% moisture content; the percent yield was 60.24%. However as the moisture content was increased further there was a tendency of lump formulation. Thus determination of optimum moisture content for different excipient combinations was necessary.

PVP solution, H P M C solution and starch paste offered good pellet characteristics with respect to pellet strength. But formulation containing Avicel RC-581 did not require any additional binder other than water, since sodium CMC present itself acts as the binder.

It was observed that addition of lubricants at any stage of spheronization did not offer any additional advantage with respect to pellet characteristics.

B) Effect of Process Variables

The study indicated that as extruder screen size was decreased, a decrease in mean particle size was observed. However, moisture content, Spheronizer speed and spheronization time are the other factors governing the mean particle size.

At low Spheronizer speed (290 r.p.m.) incomplete Spheroids were formed, whereas, at higher speed (1100 r.p.m.) complete Spheroids were formed at a dwell time of 3 minutes. A gradual increase of speed overtime was found to be the best processing condition where highest percent yield of 91% was obtained.

At low residence time, the process stops at dumbell stage and as the residence time is increased

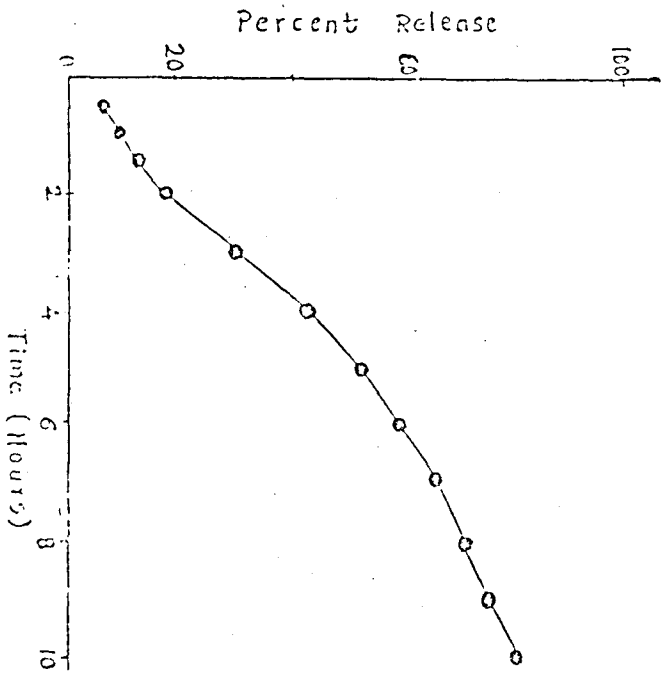


Fig 1 : Release profile of Nitrofurantoin pellets

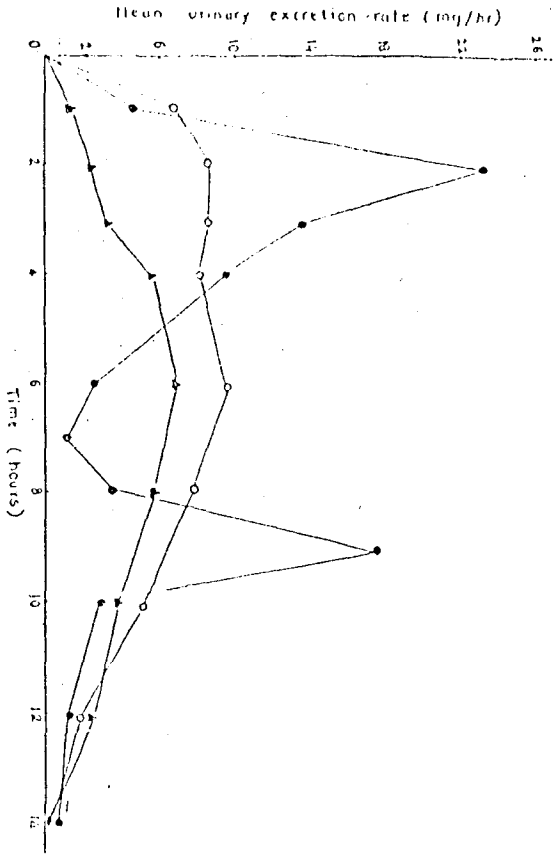
beyond a certain limit the process tends to form agglomerates. A 3 minutes dwell time was found to be satisfactory but as it was increased to 5 min. the percent yield was also increased by 10% and hence it was considered to be optimum.

Thus Nitrofurantoin pellets were fabricated using Avicel pH 101 - Avicel RC-581 (60 : 40) as the filler base, with a drug, diluent ratio of 35:65, using water as the binder by extrusion through a screen size of 16 mesh and spheronizing at a variable speed (290 r.p.m. (1 min), 570 r.p.m. (1 min) and 830 r.p.m. (3 min) for 5 minutes on the spheronizer plate.

C) Scale up Studies

The successful formulation was subjected to scale up studies which revealed that for a batch size of 250 g, moisture content required to get extrudates of proper consistency was 44.84% for extruder which was less than that for sieve (45.8%). A 6 min dwell time was found to be optimum to give a percent yield of 77.42%.

Fig. 2: Urinary excretion rate profiles of Nitrofurantoin pellets in human volunteers



Key : O—O Conventional
Δ — Δ Controlled release
O—O Conventional + controlled release.

D) Evaluation of pellets

Nitrofurantoin being a slightly soluble drug the nature amount of the filler excipient influenced the release rate. A mixture of Avicel pH 101 and Avicel RC-581 gave the desired release profile for a period of 10 h. The sodium CMC present in the filler acts as the swelling polymer which in presence of the dissolution fluid forms a gel around each pellet and helps in the slow release of the drug without desintegration of the pellets upto the end of dissolution period.

Table 3 : Pellet Characteristics

	Parameter	Value
1.	Mean percent drug content (%) ± SD	98.23 ± 1.92
2.	Percent friability	0.143
3.	Mean particle size (mm)	0.912
4.	Surface area ($mm^{2)}$	2.611
5.	Sphericity (%)	99.25
6.	True density(g/ml)	1.522
7.	Bulk density (g/ml)	
	a) Aerated	0.714
	b) Tapped	0.769
8.	Angle of Repose (^{o})	22.55
9.	Flow rate (g/sec)	20.25

A first order release profile was obtained with and t_{50} and t_{75} valves of 4.9 and 8.8 h respectively (fig.1). All other pellet characteristics were found to be satisfactory as shown in table 3.

The **in vivo** evaluation of the pellets showed maintenance of the required therapeutic urinary drug levels for a period of 10 h without any dose dumping and common side effects like nausea and gastric irritation. In comparison, the conventional formulation showed peak through fluctuations in the urinary levels. (fig. 2).

F) Stability studies

Accelearated stability studies revealed that the release profile was slightly changed at higher temperature at the end of the study period although drug content was unaffected. However, the formulation was stable on storage at room temperature for a period of one year.

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