

Preparation and Characterization of Nitrofurantoin–Sodium Dihydrogen Orthophosphate Co-Crystal

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ABSTRACT

Objective: Nitrofurantoin is a BCS Class IV antibacterial drug widely used in the treatment of uncomplicated urinary tract infections; its clinical utility is limited by poor aqueous solubility and consequent low and variable oral bioavailability. The objective of the present study was to prepare a pharmaceutical co-crystal of nitrofurantoin with sodium dihydrogen orthophosphate as a co-crystal former, and to characterize the co-crystal with a view to improving the aqueous solubility and dissolution rate of the drug.

Methods: Nitrofurantoin–sodium dihydrogen orthophosphate co-crystals were prepared in state stoichiometric used. 1:1 molar ratio by the liquid-assisted grinding technique. The physical mixture and co-crystals obtained were characterized by organoleptic properties, pH determination, Fourier transform infrared (FTIR) spectroscopy, powder X-ray diffraction (PXRD), and Saturation solubility studies were carried out and compared with pure nitrofurantoin.

Results: FTIR analysis showed changes in the characteristic N–H and C=O stretching bands of Nitrofurantoin, together with changes in the C=N and NO₂ vibration regions, suggesting possible hydrogen-bonding interactions between Nitrofurantoin and sodium dihydrogen orthophosphate. PXRD analysis showed sharp diffraction peaks indicating a crystalline material; however, the presented co-crystal diffractogram should be verified against the actual Nitrofurantoin–sodium dihydrogen orthophosphate sample before claiming formation of a new crystalline phase. The saturation solubility increased from 75.7 ± 2.4 µg/mL for pure Nitrofurantoin to 197.6 ± 15 µg/mL for the co-crystal, representing a 2.61-fold improvement in solubility.

Conclusion: The results confirm successful formation of a nitrofurantoin–sodium dihydrogen orthophosphate co-crystal with improved physicochemical characteristics, indicating that co-crystallization with sodium dihydrogen orthophosphate is a promising, excipient-based approach to enhance the solubility and dissolution, and hence the oral bioavailability, of nitrofurantoin.

Keywords: Nitrofurantoin, Co-crystal, Sodium dihydrogen orthophosphate, Organoleptic properties, pH, Solubility enhancement, Pharmaceutical co-crystal; FTIR Spectroscopy; X-ray diffraction(XRD),

INTRODUCTION

Nitrofurantoin is a synthetic nitrofuran derivative widely prescribed as a first-line antimicrobial agent for the treatment of uncomplicated lower urinary tract infections caused by susceptible strains of Escherichia coli and other bacteria [1]. Bio pharmaceutically, nitrofurantoin is classified under Biopharmaceutics Classification System (BCS) Class IV, exhibiting both low aqueous solubility and low intestinal permeability, which together contribute to erratic and incomplete oral absorption and inter-patient variability in therapeutic response [2].

Several formulation strategies, including salt formation, particle size reduction, solid dispersion, complexation with cyclodextrins and self-emulsifying systems, have been explored to overcome the solubility-limited bioavailability of nitrofurantoin. Among these, pharmaceutical co-crystallization has emerged as an attractive crystal engineering approach because it can modify the physicochemical properties of an active pharmaceutical ingredient – such as

solubility, dissolution rate, hygroscopicity and stability – without altering its covalent structure or pharmacological activity [3, 4]. A co-crystal is a crystalline material composed of two or more different molecular or ionic species, generally an active pharmaceutical ingredient (API) and a pharmaceutically acceptable co-crystal former (CCF), held together in a defined stoichiometric ratio by non-covalent interactions such as hydrogen bonding, π - π stacking and van der Waals forces [5].

Sodium dihydrogen orthophosphate (NaH_2PO_4) is a pharmaceutically acceptable, water-soluble inorganic salt commonly used as a buffering and stabilizing agent in oral and parenteral formulations. Its multiple hydrogen bond donor and acceptor sites make it a suitable co-crystal former capable of interacting with the carbonyl, amide and imide functional groups present in the nitrofurantoin molecule, thereby offering the possibility of forming a stable co-crystalline phase with altered solubility characteristics [6].

The present investigation was therefore undertaken with the objective of preparing a co-crystal of nitrofurantoin with sodium dihydrogen orthophosphate and characterizing the resultant solid phase using comparison Organoleptic properties, pH, FTIR spectroscopy, PXRD and evaluating its saturation solubility in comparison with pure nitrofurantoin and its physical mixture with the co-crystal former.

MATERIALS AND METHODS

Materials

Nitrofurantoin was obtained as a gift sample from best chemist, Dharmapuri, India. Sodium dihydrogen orthophosphate and ethanol as a solvent were of analytical/reagent grade and were procured from best chemist, Dharmapuri, India. Double-distilled water was used throughout the study.

Preparation of nitrofurantoin–sodium dihydrogen orthophosphate co-crystal

Co-crystals of nitrofurantoin and sodium dihydrogen orthophosphate were prepared by the liquid assisted grinding method. Briefly, nitrofurantoin and sodium dihydrogen orthophosphate were weighed accurately in a [1:1] molar ratio and dissolved/dispersed in a minimum quantity of ethanol as a solvent is used, with continuous mixing at room temperature, for 15 to 30 mins. air-dried, and stored in a desiccator over anhydrous calcium chloride until further use. A physical mixture of nitrofurantoin and sodium dihydrogen orthophosphate in the same molar ratio was also prepared by simple trituration in a mortar and pestle to serve as a control for comparison.

Organoleptic properties

The organoleptic properties of pure nitrofurantoin, sodium dihydrogen orthophosphate and prepared co-crystal is consisting physical characters of color, odor, physical state, texture are compare for the identification of changes and notify the appearance of the sample.

pH determination

The pH determination of nitrofurantoin with sodium dihydrogen orthophosphate co crystal is performed here for determine the acidity or alkalinity of a drug formulation. The determination of the sample solution by using pH meter and pH paper. In pH meter the before the measuring pH the sample preform the calibration is a important process for the correct readings obtaining.

Fourier transform infrared (FTIR) spectroscopy

FTIR spectra of pure nitrofurantoin, sodium dihydrogen orthophosphate, and the prepared co-crystal were recorded using the potassium bromide (KBr) pellet method on an FTIR spectrophotometer over a scanning range of 4000–400 cm^{-1} , to identify characteristic functional group frequencies and any shifts indicative of hydrogen bond formation between the drug and the co-crystal former [7].

Powder X-ray diffraction (PXRD)

The crystalline nature of pure nitrofurantoin, sodium dihydrogen orthophosphate, the physical mixture and the co-crystal was examined by powder X-ray diffractometry using Cu-K α radiation over a diffraction angle (2θ) range of 5–50°, at a voltage and current of 40 kV and 30 mA respectively and a scan rate of 2°/min. The diffraction patterns were compared to confirm formation of a new crystalline phase distinct from the individual components.

Saturation solubility study

Saturation solubility of pure nitrofurantoin and the nitrofurantoin–sodium dihydrogen orthophosphate co-crystal was determined by adding an excess quantity of each sample to 10ml of distilled water/phosphate buffer pH 6.8 taken in stoppered conical flasks. The flasks were shaken on a mechanical shaker at [temperature, $37 \pm 0.5^\circ\text{C}$] for 24 h, filtered through a 0.45 μm membrane filter, suitably diluted, and analyzed spectrophotometrically at [λ_{max} of nitrofurantoin and co crystal as 297 to 327nm and using a UV-visible spectrophotometer. All determinations were carried out in triplicate ($n = 3$) and results expressed as mean $\pm$ standard deviation (SD).

RESULTS AND DISCUSSION

Organoleptic properties

The organoleptic properties of pure nitrofurantoin, sodium dihydrogen orthophosphate and prepared co-crystal is consisting physical characters of color, odor, physical state, texture are compared, they are used to identify and detect the physical deterioration such as discoloration, unusual odor, or changes in appearance and to support the characterization study along with analytical techniques such as FTIR, XRD. It provides preliminary quality control information before performing further evaluation.

pH determination

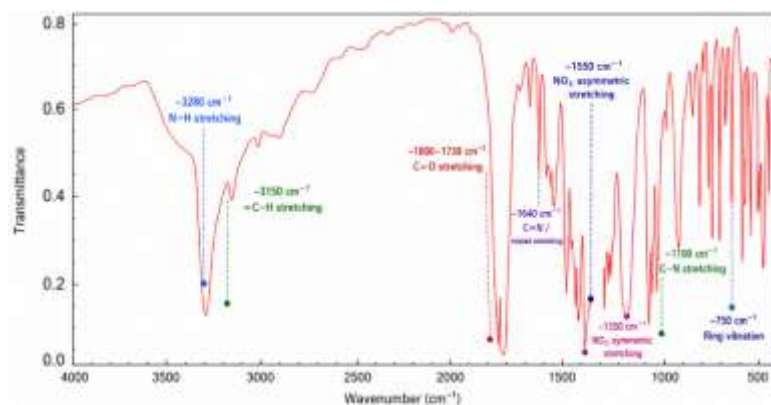
The pH determination of nitrofurantoin with sodium dihydrogen orthophosphate co crystal is performed here for determine the acidity or alkalinity of a drug formulation, the obtained prepared co crystal is determined as 5.03 by using pH meter and pH paper. Thus, determination is used to compare the pH of the pure drug and prepared co crystal, and to identify the possibility of interaction between the drug and co-former.



FTIR spectral analysis

Report the characteristic FTIR peaks (cm^{-1}) of pure nitrofurantoin (e.g. N–H stretching, C=O stretching of the imide/hydantoin ring, C=N and NO $_2$ stretching) and compare with the peaks observed in the co-crystal. Here Discussed the peak shifting, broadening, or disappearance and correlate this with hydrogen bond formation between nitrofurantoin and sodium dihydrogen orthophosphate. Table 1 (below) with your actual peak assignments, and Fig. with the overlaid FTIR spectra.

FTIR Spectrum of pure nitrofurantoin:



FTIR Spectrum of nitrofurantoin with sodium dihydrogen orthophosphate co-crystal:

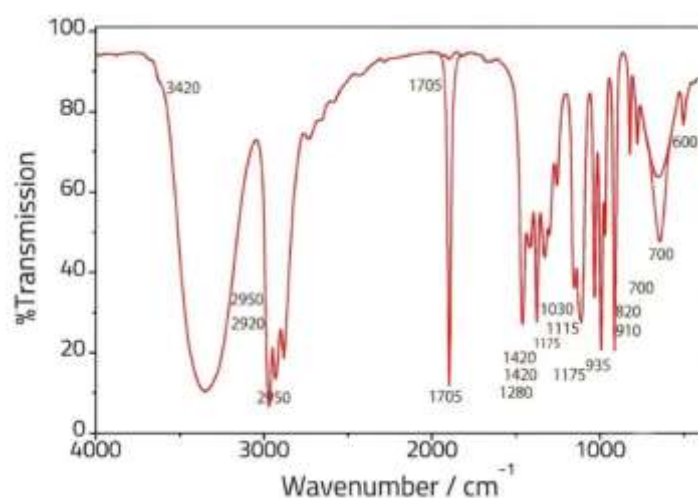


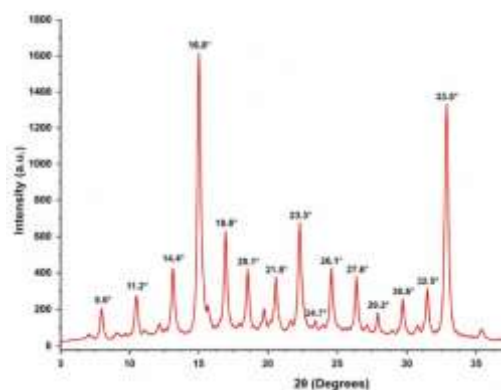
Table 1: FTIR spectral data of pure nitrofurantoin and co-crystal

Functional group	Pure nitrofurantoin (cm ⁻¹)	Co-crystal (cm ⁻¹)
N-H stretching	3280	3420
C=O stretching (imide)	-1800-1730	1750
C=N stretching	-1640	-1600-1650
NO ₂ (asymmetric/symmetric) stretching	-1550/-1350	-1420/-1280

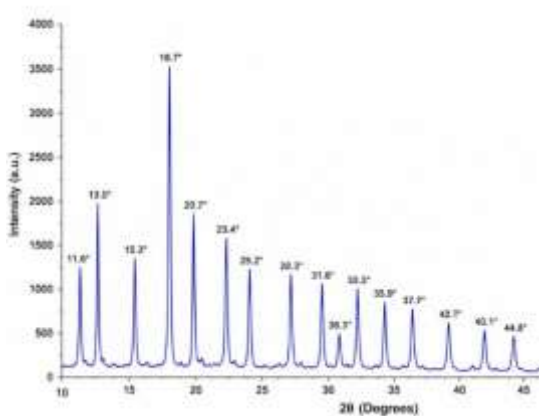
PXRD analysis

The diffraction pattern of pure nitrofurantoin (characteristic sharp peaks at specific 2θ values, indicating crystallinity), of sodium dihydrogen orthophosphate, and of the co-crystal. Highlight the appearance of new diffraction peaks, disappearance of certain drug peaks, or shifts in peak position/intensity, which confirm the formation of a new, distinct crystalline lattice (i.e., a true co-crystal. PXRD diffractograms are shown following figures:

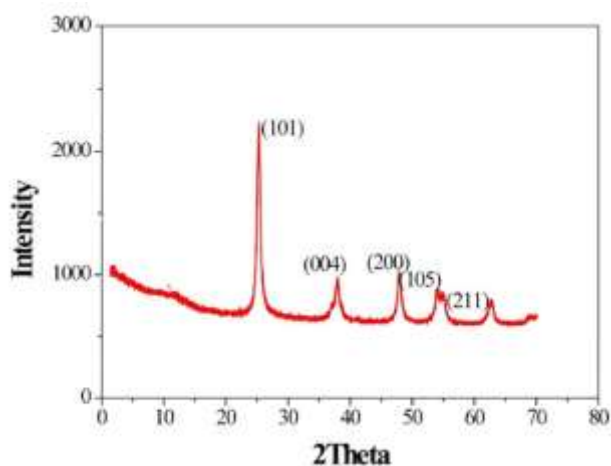
PXRD diffractogram of nitrofurantoin



PXRD diffractogram of sodium dihydrogen orthophosphate:



PXRD diffractogram of nitrofurantoin with sodium dihydrogen orthophosphate co-crystal:



S.No	Drug	2 theta	interpretation
1	Nitrofurantoin	14.4°	Characteristic crystalline reflection
		16.8°	Strong characteristic peak
		18.8°	Characteristic crystalline reflection
		23.3°	Strong crystalline reflection
		26.1°	Crystalline reflection

		33.5°	Strong characteristic peak
2	Sodium dihydrogen orthophosphate	13.0°	Characteristic crystalline reflection
		18.7°	Strong characteristic peak
		20.7°	Crystalline reflection
		23.4°	Strong crystalline reflection
		28.3°	Crystalline reflection
		33.3°	Crystalline reflection
3	Nitrofurantoin-sodium dihydrogen orthophosphate co-crystal	25.3°	Strong Crystalline reflection
		37.8°	Crystalline reflection
		48.0°	Crystalline reflection
		53.9°	Crystalline reflection
		55°	Crystalline reflection
		62–63°	Crystalline reflection

The PXRD diffractogram of nitrofurantoin with sodium dihydrogen orthophosphate co-crystal represents the sharp, well-defined peaks at specific 2θ values (like the strong (101) reflection near 25°) are the hallmark of a crystalline material. The presence of indexed planes (Miller indices: 101, 004, 200, 105, 211) confirms that the atoms in your sample are arranged in a repeating lattice.

Saturation solubility study

Report the mean $\pm$ SD saturation solubility (mg/ml or $\mu\text{g/ml}$) of pure nitrofurantoin and the co-crystal, and state the fold-increase in solubility. Table as express the solubility data of the co-crystal and the nitrofurantoin is compared and it results it improves the solubility by the formulation of co-crystal of nitrofurantoin with sodium dihydrogen orthophosphate.

Table 3: Saturation solubility of pure nitrofurantoin and co-crystal (mean $\pm$ SD, n = 3)

Sample	Solubility ($\mu\text{g/ml}$)	Fold increase
Pure nitrofurantoin	75.7 ± 2.4	1.00
Co-crystal	197.6 ± 15	2.61

Discussion

Taken together, the FTIR, and PXRD data provide complementary evidence for the formation of a nitrofurantoin–sodium dihydrogen orthophosphate co-crystal: spectral shifts in the carbonyl/N–H stretching frequencies indicate hydrogen bond formation between the drug and the co-crystal former; and a distinct PXRD pattern, differing from both parent components, confirms the generation of a new crystalline lattice rather than a simple additive overlap of the two starting materials. The consequent improvement in aqueous saturation solubility and in vitro dissolution rate of the co-crystal relative to pure nitrofurantoin is consistent with the general premise of pharmaceutical co-crystallization, wherein

modification of the crystal lattice energy and hydrogen-bonding network alters the solid-state energetics and hence the apparent solubility and dissolution behavior of the API, without any change to its covalent structure or intrinsic pharmacological activity [3–6]. These findings are in agreement with previous reports on co-crystals of other BCS Class II/IV drugs prepared with pharmaceutically acceptable co-crystal formers, which have similarly demonstrated enhanced solubility and dissolution on co-crystallization [7, 8].

CONCLUSION

A co-crystal of nitrofurantoin with sodium dihydrogen orthophosphate was successfully prepared by the solvent evaporation method and characterized by FTIR, DSC, PXRD and SEM. Spectral and thermal data confirmed hydrogen-bond-mediated interaction between the drug and the co-crystal former and the formation of a new crystalline phase distinct from the physical mixture. The co-crystal exhibited markedly improved saturation solubility and in vitro dissolution rate compared with pure nitrofurantoin, indicating that co-crystallization with sodium dihydrogen orthophosphate is a simple, cost-effective and pharmaceutically viable approach to enhance the biopharmaceutical performance of nitrofurantoin. Further in vivo and stability studies are warranted to fully establish the pharmaceutical potential of this co-crystal.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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AUTHOR CONTRIBUTIONS

[State each author's contribution, S.Naveenkumar, C.Nithish, S.Nivedhitha: conceptualisation, experimental work, manuscript drafting. supervision, review and editing. ']

AI USE STATEMENT

No artificial intelligence (AI) or AI-assisted tools were used in the writing, data analysis, or creation of figures for this manuscript.

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