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Biomedical Approach to Developing and Characterizing Chitosan Nanoparticles Encapsulating Urapidil for Hypertension Management

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Abstract

The aim of this study was to create Chitosan Nanoparticles loaded with Urapidil to achieve controlled drug release, enhance solubility, and reduce dosing frequency to improve patient adherence to therapy for hypertension. Urapidil was formulated into nanoparticles via the ionic-gelation method using Chitosan as a polymer, Sodium tripolyphosphate as a cross-linking agent, and filled into hard gelatin capsules after lyophilization. Pre-formulation studies including melting point determination and absorption maximum (268 nm) indicated stability, safety, and effectiveness of the drug and excipients within the specified range. Different concentrations of Chitosan (0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.4%, and 0.5%) were used to prepare Urapidil-loaded Chitosan Nanoparticles, along with Sodium tripolyphosphate as a cross-linking agent and Tween 80 as a disaggregating agent. Characterization of all seven formulations revealed a percentage yield within the range of 78.84% to 87.25% and entrapment efficiency between 83.40% to 93.15%, with higher concentrations of the polymer resulting in increased entrapment efficiency. Solubility analysis showed improvement after formulation, with the solubility of formulation F5 increased to 9.4933 mg/ml in distilled water and 13.251 mg/ml in phosphate buffer pH 6.8. In vitro release studies demonstrated controlled release with formulation F5 releasing 95.03% of the drug after 12 hours. This formulation was selected as the optimized one due to its higher entrapment efficiency, drug content, and prolonged drug release profile. Accelerated stability studies showed no significant changes in appearance, drug content, or entrapment efficiency of formulation F5 after 90 days at different storage conditions. Overall, formulation F5 containing 0.3% Chitosan concentration emerged as the optimal formulation for achieving controlled drug release.

Keywords: Formulation, Characterization, Urapidil, Chitosan Nanoparticles, biomedical

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INTRODUCTION

In the last 50 years, material researchers have been extensively studying how to exploit nanoparticles and nanostructured materials in different biomedical and healthcare sectors [1]. The term "NP" usually defines minute particles of matter (1 to 100 nm in diameter), but other names can be used to describe larger particles (up to 500 nm in diameter). For example, nanorods, nanowires, and nanofibers are nanoparticles with a diameter in the 1–100 nm range but with one dimension outside the nanoscale dimension [2]. Nanostructured materials are nanomaterials with one dimension in the nanoscale range (<100 nm) and are made of a single material or multiple materials. Therefore,

nanostructured materials are composed of interlinked parts in the nanoscale range [3]. Nanoparticles and nanostructured materials can be made of simple materials (e.g., metal, carbon, polymer) [4], of composites (e.g., polymer-metal, silica-metal, graphene-metal), or in the core-shell form [5–8]. Nanomaterials are typically synthesized by one of two main approaches, i.e., bottom-up approach and top-down approach. Among all the methods, recently, the synthesis of nanomaterials by physical vapor deposition, chemical vapor deposition, electrospinning, 3D printing, biological synthesis, and supercritical fluid have gained importance, which is mingled with other methods to improve the synthesis efficiency [9, 10]. Nanomaterials display many interesting features, such as superior mechanical performance, the possibility of surface functionalization, large surface area, and tunable porosity, compared to their bulk materials [11–13]. These outstanding features explain why nanomaterials are the perfect candidates in the biomedical sector for the production of tissue-engineered scaffolds (e.g., blood vessels, bone), drug delivery systems (gene therapy, cancer treatments, drugs for chronic respiratory infections), chemical sensors biosensors and wound dressings [14, 15]. Remarkably, several studies suggest that ancient civilizations in India, Egypt, and China used nanotechnology (metallic gold) for therapeutic purposes in 2500 BC [16]. Nanomaterials' discrete features can complicate the assessment of the effects and the toxicity risk associated with their use in a biological environment. Indeed, nanomaterials' chemical composition, size, shape, surface charge, area, and entry route in the body can influence their biological activities and effects [17].

In bioimaging, tailored fluorescent nanoparticles could outperform traditional molecular probes as fluorescent indicators, particularly in terms of sensitivity [18]. Tissue-engineered nanofiber scaffolds are considered the best option to manage tissue loss and end-stage organ failure and have already helped millions of patients worldwide. Three-dimensional nanofibrous scaffolds are polymer-based structures with balanced moisture, absorption, strongly organized porosity (60–90%), and gas permeability, comparable to native extracellular matrices. One and two-dimensional nanomaterials can be used for signal amplification, are nanosized (≤100 nm), have high electrical conductivity, and are compatible with drugs and biological molecules. They have also been used for the early detection of diseases (e.g., virus, bacterial, cancer). Antimicrobial nanomaterials (e.g., Ag, Au, CuO NPs) are frequently employed in dermatology because they contribute to accelerating wound healing and preventing/treating bacterial infections [19, 20].

To formulate Urapidil loaded Chitosan Nanoaparticles containing Chitosan as polymer by Ionic gelation method. Characterization and optimization of formulated Urapidil loaded Chitosan Nanoparticles. To enclose Urapidil loaded Chitosan Nanoparticles in Hard Gelatin Capsule and their character to be evaluated.

MATERIALS AND METHODS

Materials Used in Formulation

For the formulation of Chitosan nanoparticles of Urapidil the following materials procured from the following manufacturer/suppliers.

METHODOLGY

Preformulation Studies

Preformulation studies entail examining the physical and chemical attributes of a drug substance independently and in conjunction with excipients. These studies represent the initial phase in the systematic design of drug dosage forms. Their purpose is to apply biopharmaceutical principles to assess the physicochemical characteristics of the drug, aiming to create a stable, bioavailable dosage form suitable for large-scale production. The specific data required varies based on the intended dosage form, as outlined in Table 1.

Thus the goals of the final study are,

1. To determine the physical properties

2. To assess its compatibility with the excipients
3. To determine kinetic rate profile

Compatibility Studies

The chosen drug and excipients for the formulation underwent assessment for physical and chemical compatibility

Physical Compatibility Study

Each 100 mg of powder drug, polymer and cross linking agent were weighed. The drug alone, along with the polymer (Chitosan) and sodium tripolyphosphate, as well as a combination of the drug and excipients, were placed in airtight screw cap vials. These vials were stored at room temperature and at 40ºC with a relative humidity of 75±2%. Any alteration in the color of the physical mixture was visually examined

Chemical Compatibility Study by FTIR

The chemical compatibility studies were conducted using Fourier Transform-Infrared (FTIR) spectroscopy, which was performed using a Shimadzu FTIR 8400 Spectrophotometer from 4000 to 400 cm^{-1} region. The method employed was Potassium bromide pellet method. In this method a small amount of finely ground solid samples (drug alone, Mixture of drug and excipients and the optimized formulation) intimately mixed with about 100 time its weight of powdered potassium bromide. The finely ground mixture was then passed under very high pressure in a press (at least 25,000 psig) to form a small pellets (1-2 mm thick and 1 cm in diameter). The resulting pellet was transparent to IR radiation and was run as such as seen in Table 2.

Determination of Melting Point

The melting point of Urapidil was determined by the capillary tube method as per USP. A Sufficient quantity of Urapidil powder was filled into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in electrical melting point apparatus and the temperature was raised. The temperature at which the last solid particle of Urapidil in the tube passed into liquid phase was noted as melting point.

Preparation of 6.8 pH Phosphate Buffer

- 0.2 M solution of potassium dihydrogen phosphate was prepared by dissolving 27.218 gm of substance in 1000 ml of distilled water.
- 0.2 M solution of sodium hydroxide solution was prepared by dissolving 8 gm of substance in 1000 ml of distilled water.
- 250 ml above prepared potassium dihydrogen phosphate solution & 112 ml of sodium hydroxide solution were mixed together and made up to 1000 ml and pH was adjusted to 6.8.

Table 1. List of material used in formulation

S.N.	Name of the material	Procured from	Use in formulation
1.	Urapidil	Adcock Ingram, Bangalore.	Active pharmaceutical ingredient
2.	Chitosan 50 kD	Lab chemicals, Chennai.	Polymer
3.	Acetic acid	Lab chemicals, Chennai.	Solvent
4.	Sodium tripolyphosphate	Lab chemicals, Chennai.	Cross linking agent

Table 2. Composition of drug and excipients for FT-IR spectra

S.N.	Ingredients
1	Drug
2	Drug + Chitosan
3	Drug + sodium tripolyphosphate
4	Drug + Chitosan + sodium tripolyphosphate

Determination of lambda Max (λ_{max})

100 mg of Urapidil was weighed and transferred to 100 ml of volumetric flask. The drug was dissolved in 10 ml of ethanol and volume was made up to 100 ml using phosphate buffer pH 6.8 to obtain a stock solution of 1000 µg/ml (stock solution I). 10 ml of this stock solution was again diluted with phosphate buffer pH 6.8 up to 100ml to obtain a solution of 100 µg/ml (stock solution II). From the stock solution-II, 10 ml was pipette out in 100 ml volumetric flask. The volume was made up to 100 ml using phosphate buffer pH 6.8 get a concentration of 10 µg/ml. this solution was then scanned at 200–400 nm in UV-Visible spectrophotometer to attain the absorption maxima (λ_{max}).

Standard curve for Urapidil

100 mg of Urapidil was weighed and transferred to 100 ml of volumetric flask. The drug was dissolved in 10 ml of ethanol and volume was made up to 100 ml using phosphate buffer pH 6.8 to obtain a stock solution of 1000 µg/ml (stock solution I). 10 ml of this stock solution was again diluted with phosphate buffer pH 6.8 up to 100 ml to obtain a solution of 100 µg/ml (stock solution II). From the stock solution-II 2, 4,6,8,10,12 ml were transferred to series of 100 ml volumetric flasks. The volume was made up with phosphate buffer pH 6.8. The absorbance of these solutions was measured at 268 nm against the blank.

Solubility Studies of Pure Urapidil

Solubility of Urapidil pure drug was tested in distilled water and phosphate buffer pH 6.8. An excess amount of Urapidil pure drug was added in the pertinent media. The mixtures were stirred in a mechanical shaker at speed 50 rpm for 24 hours and the temperature was maintained at 37±0.5ºC. Visual inspection was carefully made to ensure there were excess Urapidil solids in the mixture, indicating saturation had been reached. Then the mixtures were filtered using 0.45 µm filter and filtrates were suitably diluted with same media. The absorbance of the solution was measured at 268 nm in UV-Visible spectrophotometer.

FORMULATION DEVELOPMENT

Preparation of Chitosan Nanoparticles–Ionic Gelation Method

The preparation of Chitosan nanoparticles was based on ionic interaction between positively charged Chitosan solution and negatively charged STPP solution, with and without drug and it was prepared in the presence of Tween 80 as a re-suspending agent to prevent particle aggregation, at ambient temperature while stirring and Chitosan solution were raised to pH 4.6 to 4.7. Seven formulations (F1,F2,F3,F4,F5,F6,F7) of Urapidil loaded Chitosan nanoparticles were prepared by dissolving Urapidil in 30 ml of Chitosan with varying concentrations (0.1,0.15,0.2,0.25,0.3,0.4,0.5%w/v) containing 0.5% w/v tween 80, TPP (0.1%w/v) was added drop wise under magnetic agitation (1000 rpm).The formed nanoparticle suspensions were lyophilized at -40°C for 24 hrs as seen in Table 3.

Table 3. Composition of Nanoparticles

Formulation	Polymer			DRUG (mg)	Tween 80 (%w/v)	Sodium Tripolyphosphate		
	Chitosan (%w/v)	*1% Aqueous acetic acid (ml)*	*Chitosan (mg)*			*TPP (%w/v)*	*Distilled water (ml)*	*TPP (mg)*
F1	0.1%	30 ml	30	60	0.5	0.1	30	30
F2	0.15%	30 ml	45	60	0.5	0.1	30	30
F3	0.2%	30 ml	60	60	0.5	0.1	30	30
F4	0.25%	30 ml	75	60	0.5	0.1	30	30
F5	0.3%	30 ml	90	60	0.5	0.1	30	30
F6	0.4%	30 ml	120	60	0.5	0.1	30	30
F7	0.5%	30 ml	150	60	0.5	0.1	30	30

Freeze Drying

Lyophilization is a promising way to increase the chemical and physical stability over extended period of time. Lyophilization is necessary to attain prolonged stability for a product containing drugs prone to hydrolysis or to create a suitable formulation for oral administration.

The Urapidil loaded Chitosan suspension is kept in the freeze dryer at -20ºC in overnight and the flask were covered with parafilm sheets on the next day and perforated. After 24 hours the sample were kept inside the lyophilizer at temperature -40ºC and pressure below 15 Pascal (0.1 pa) to remove the water from the samples. After lyophilization the dried powder is used for further studies as seen in Table 4.

RESULTS AND DISCUSSION

Pre-formulation Studies

- The optimization of a formulation can be done only after a thorough investigation of its physicochemical properties of the drug and excipients. The drug and the polymer must be compatible for a successful formulation.

COMPATIBILITY STUDIES

Physical Compatibility Study

Inference

The Physical compatibility study was performed for 3 months. There was no change of color therefore the drug and excipients are physically compatible with each other as seen in Table 5.

MELTING POINT

The melting point of Urapidil was measured using capillary tube method.

Inference

The melting point of drug was studied and tabulated, which confirms the identification of Urapidil as seen in Table 6.

Table 4. Physical compatibility study of drug and excipients.

S.N.	Drug/Excipients	Description and Condition						
		Initial	*At room temperature (in days)*			*At 40ºC ± 2ºC and 75% RH ± 2% (in days)*		
			I	II	III	I	II	III
1	Urapidil	White coloured powder	NC	NC	NC	NC	NC	NC
2	Chitosan	Pale yellow coloured powder	NC	NC	NC	NC	NC	NC
3	Sodium tripolyphosphate	White coloured powder	NC	NC	NC	NC	NC	NC
4	Urapidil + Chitosan	Pale yellow coloured powder	NC	NC	NC	NC	NC	NC
5	Urapidil + Sodium tripolyphosphate	White coloured powder	NC	NC	NC	NC	NC	NC

*NC – No Change

Table 5. FT-IR spectral Interpretation of urapidil + chitosan + sodium tripolyphosphate.

Type of vibration	Wave number (cm^{-1})
Aromatic C-H	3055.02
C-N Stretching	1380.93
N-H Stretching	3209.31
C=0 stretching	1604.66
C-H Stretching	2947.01
N-C Stretching	1234.35, 1056.91
C-0-C Stretching	1350.07
C-O Stretching	1296.07
Na	570.89

Table 6. Melting point of drug.

S.N.	Drug/Excipients	Specification	Observation
1	Urapidil	157ºC-160ºC	157ºC-158ºC

Table 7. Saturation solubility of urapidil in phosphate buffer pH 6.8 and distilled water.

Medium	pH	Solubility (mg/ml)
Phosphate buffer pH 6.8	6.8	0.004093
Distilled water	7.0	0.000216

Table 8. Data for standard curve of urapidil in phosphate buffer pH 6.8.

S.N.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.1153±0.000374
3	4	0.2203±0.000287
4	6	0.3445±0.000432
5	8	0.4686±0.000455
6	10	0.6035±0.000424
7	12	0.7089±0.000497

Table 9. Characterization of urapidil loaded chitosan NPs.

Formulations	Percentage yield (%)	Entrapment Efficiency (%)	Drug content
F1	79.09	83.40	77.16
F2	80.53	86.08	79.98
F3	81.90	88.65	82.52
F4	85.81	90.42	86.19
F5	87.25	93.15	91.83
F6	81.16	89.59	85.62

SOLUBILITY STUDY

The solubility study of Urapidil in different dissolution medium is performed by saturation solubility method as seen in Table 7.

Inference

The solubility of the drug at pH 6.8 was significantly higher than in that of distilled water. Pure drug of Urapidil in distilled water and phosphate buffer pH 6.8 was found be insoluble.

D ETERMINATION OF LAMBDA MAX (λ_{max}) FOR URAPIDIL

The maximum absorbance of the Urapidil was studied. The maximum absorbance of the Urapidil was found to be 268 nm. Hence the wavelength of 268 nm was selected for analysis of drug in dissolution media as seen in Table 8.

CALIBRATION CURVE FOR URAPIDIL

CHARACTERIZATION OF URAPIDIL LOADED CHITOSAN NPs

The formulated Urapidil loaded Nanoparticles are characterized for Percentage yield, Drug content, Entrapment efficiency and the results were tabulated below as seen in Table 9.

COMPARATIVE *IN VITRO* DRUG RELEASE FOR ALL FORMULATION

The formulated Nanoparticles preparation containing drug and polymer were evaluated for drug release and results were tabulated below as seen in Table 10.

Table 10. *In vitro* drug release for all formulations.

Time (h)	*In Vitro* Drug Release for Nanoparticles Formulations						
	F1	***F2***	***F3***	***F4***	***F5***	***F6***	***F7***
0.5	17.25	17.45	16.04	15.09	13.19	9.71	8.32
1	20.12	19.89	19.2	18.99	16.17	11.14	10.14
2	36.4	29.13	28.83	27.02	24.02	17.35	14.14
3	44.8	38.03	37.92	36.21	34.52	31.3	29.27
4	60.2	50.08	47.22	44.1	41.23	34.02	31.73
5	72.27	63.07	59.12	53.8	50.14	36.37	32.13
6	82.29	79.02	69.03	61.78	57.71	42.13	39.92
7	97.04	89.9	78.97	73.2	64.21	50.12	43.78
8	-	96.02	89.17	86.51	73.22	62.79	59.11
9	-	-	94.18	91.52	78.01	71.23	69.24
10	-	-	-	94.47	86.22	79.13	75.17
11	-	-	-	-	91.89	83.2	81.2

SUMMARY AND CONCLUSION

The aim of this study was to develop Urapidil-loaded Chitosan Nanoparticles to achieve controlled drug release, enhance solubility, and reduce dosing frequency, thereby improving patient compliance with therapy. Urapidil was formulated into nanoparticles using the ionic-gelation method with Chitosan as the polymer and Sodium tripolyphosphate as a cross-linking agent. Preformulation studies, including melting point determination and UV absorption spectroscopy, confirmed the stability and safety of the drug and excipients. Physical compatibility studies demonstrated the compatibility of the drug with the excipients, while chemical compatibility was assessed using FTIR spectroscopy, indicating no interaction between the drug and polymer. Standard graphs were constructed for Urapidil, showing linearity and adherence to Beer-Lambert's law.

Various formulations of Urapidil-loaded Chitosan Nanoparticles were prepared with different polymer concentrations, cross-linking agents, and deaggregating agents. Characterization revealed satisfactory percentage yield and entrapment efficiency, with higher polymer concentrations leading to increased entrapment efficiency. Solubility analysis indicated improved solubility profiles for the formulations compared to the pure drug. In vitro release studies demonstrated controlled release, with formulation F5 exhibiting the highest drug release percentage and a controlled release profile. Based on entrapment efficiency, drug content, and in vitro drug release, formulation F5 was identified as the optimized formulation. FTIR analysis confirmed the absence of chemical interactions in this formulation. Further characterization through SEM analysis, particle size analysis, and zeta potential measurements revealed spherical nanoparticles with a smooth surface, a mean particle size of 188.3 nm, and stable zeta potential.

Flow property measurements showed good flow properties for Chitosan Nanoparticles compared to the pure drug, allowing for easy filling into hard gelatin capsules without the need for additional glidants. Post-formulation evaluations, including uniformity of weight, disintegration test, drug content, and in vitro drug release, met official specifications. Dissolution data were fitted to various kinetic models, with formulation F5 demonstrating zero-order kinetics and anomalous diffusion. Accelerated stability studies conducted at different temperatures showed no significant changes in appearance, drug content, or entrapment efficiency for formulation F5 over 90 days. Overall, formulation F5 containing 0.3% Chitosan concentration emerged as the optimal formulation for achieving controlled drug release.

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