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FORMULATION AND EVALUATION OF FEXOFENADINE HYDROCHLORIDE LOADED CHITOSAN NANOPARTICLES FOR TREATMENT OF SKIN ALLERGY

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ABSTRACT: An attempt was made to formulate and evaluate Fexofenadine HCl loaded chitosan nanoparticles using biodegradable polymers such as chitosan and sodium tripolyphosphate as a crosslinker in different ratio and proportions. In this formulation, Fexofenadine HCl was selected because of wide range of its use in treatment of skin allergy in the form of coated tablet and pediatric suspension. Different formulations of Fexofenadine HCl loaded chitosan nanoparticles were prepared containing 0.5%, 0.75% of chitosan and 0.5% STPP as crosslinker using ionic gelation technique. Nanoparticles were characterized for particle size determination, Polydispersity index, Zeta potential, % Entrapment Efficiency and *in-vitro* release study and Scanning Electron Microscopy. For the formulations F6-F10, no yield was formed which might be due to an insufficient amount of crosslinker to form the nanoparticles. F2 was selected as the best formulation to be incorporated into the gel base using carbopol 934P in different concentrations of 0.5%, 0.75%, and 1%. The formulated gels were evaluated in case of viscosity, spread ability, *in-vitro* release study, kinetic and skin irritation test. G1 was selected as the optimized gel for *in-vivo* study. Skin irritation was not observed from the *in-vivo* study. Thus, study revealed that the developed system has a great appeal for the convenient treatment of dermatological allergy which may overcome in improving the limitations of the existing drug delivery system.

INTRODUCTION: Fexofenadine HCl (FXD) is a non-sedating antihistamine drug indicated for the symptomatic relief of symptoms associated with rhinitis, urticaria and allergic skin conditions [1]. Fexofenadine is used as hydrochloride salt and the probability that cardiotoxic effects occur in connection with fexofenadine is assessed as being extremely low when compared to other anti-histamines.

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Besides, Fexofenadine may improve a safer alternative in the treatment of asthma and atopic dermatitis and is rapidly absorbed with a long duration of action, making it suitable for once-daily administration as its half-life is about 14 h [2]. Nano-sized carriers such as polymeric nanoparticles, solid lipid nanoparticles, liposomes, and nano-emulsions have been widely applied as topical formulations to enhance cutaneous delivery [3, 4].

Among these nano-sized carriers, polymeric nanoparticles with readily-tunable chemical and physical features can effectively protect unstable drugs from degradation/denaturation, decrease the side effects of toxic drugs by producing controlled release, and enhance the cutaneous penetration of the drugs across the skin barrier by increasing the

concentration gradient. Topically applied therapies are promising for the treatment of skin diseases such as psoriasis, contact dermatitis, and skin cancers since the drugs are delivered directly into skin strata [5]. Nano-sized drug carriers have attracted much attention in the past decade as options in formulations for topical therapy. An attempt was made in the present study to formulate and characterize Fexofenadine HCl nanoparticles followed by drug-loaded nanogel.

MATERIAL AND METHOD: Fexofenadine HCl received gift sample from Dr. Reddy Laboratories, Hyderabad, chitosan and sodium tripolyphosphate (STPP) were purchased from Sigma Aldrich Mumbai. Carbopol 934 was purchased from SDFCL, Bengaluru. All other ingredients used in the experiments are of analytical grade.

Preformulation Studies:

Fourier Transformed Infrared Spectroscopic Studies: FTIR spectral studies were carried out for pure drug Fexofenadine hydrochloride, freshly prepared and individual substances to check the compatibility between drug and polymers using Bucker Tensor-27 (Bucker, Germany) FTIR instrument. Interaction between the components, if any, was indicated by either producing additional peaks or absence of the characteristics peaks corresponding to the drug and carrier.

Differential Scanning Calorimetry (DSC): A differential scanning calorimeter (Model DSCQ1000) was used to obtain the DSC curves representing the rates of heat uptake with respect to temperatures (40 °C to 200 °C). About 3 mg of sample was weighed and placed in a standard open aluminum pan.

An empty pan of the same type was utilized as the reference. Samples were heated from 40 °C to 200 °C at a heating rate of 5 °C /min, under a dry nitrogen atmosphere.

Preparation of Fexofenadine Loaded Chitosan Nanoparticles: Chitosan nanoparticles of Fexofenadine HCl were prepared by ionic gelation method [6]. This method involves the ionic interaction between the positively charged amino groups of chitosan and polyanion tripolyphosphate (TPP), which acts as a chitosan cross-linkers.

Chitosan solution was prepared with the use of glacial acetic acid (1% v/v). Sodium tripolyphosphate solution was prepared in distilled water. Chitosan and Sodium tripolyphosphate was used in a different ratio to optimize the best formulation.

The calculated amount of drug (1 mg/ml) was mixed with the required quantity of chitosan. Nanoparticles were prepared with the addition of Sodium tri poly phosphate dropwise to the above solution at room temperature with continuous stirring. Nanoparticles were collected by centrifugation at 8500 rpm using REMI C-24BL centrifuge apparatus, and the supernatant is collected to determine encapsulation efficiency [7].

TABLE 1: FORMULATION CHART OF FEXOFENADINE HCl NANOPARTICLES

Formulation	Acetic Acid	Chitosan	STPP	Drug	Ratio of Chitosan and STPP
F1	1%w/v	0.5% w/v	0.5% w/v	1 mg/ml	1:1
F2					1:1.5
F3					1:2
F4					1.5:1
F5					2:1
F6		0.75% w/v			1:1
F7					1:1.5
F8					1:2
F9					1.5:1
F10					2:1

Preparation of Gel Base: Carbopol gel base was prepared by using carbopol 934 in different concentrations such as 0.5, 0.75 and 1%. A specified quantity of distilled water was placed in a 100 ml beaker. Accurately weighed methylparaben and propylparaben were added to the distilled water and stirred at 50 rpm until it dissolves completely. A specified quantity of carbopol 934 was dispersed in the above solution slowly and mixed for 60 min and kept in the fridge overnight.

TABLE 2: FORMULATION CHART OF GEL BASE FOR FEXOFENADINE HCl NANOPARTICLES

S. no.	Ingredients	Formulation		
		G1	G2	G3
1	Carbopol 934 (gm)	0.5	0.75	1
2	Methyl paraben (gm)	0.02	0.02	0.02
3	Propyl paraben (gm)	0.2	0.2	0.2
4	Drug loaded nanoparticles (gm)	4.3	4.3	4.3
5	Propylene glycol (ml)	5	5	5
6	Triethanolamine (ml)	Q.S	Q.S	Q.S
7	Distilled water (ml)	100	100	100

Preparation of Gel Containing Fexofenadine HCl Nanoparticles: Transfer specified quantity of gel base into the beaker. Drug loaded nanoparticles transferred into another beaker containing a specified quantity of propylene glycol (5 ml) and mixed well. Transfer drug-loaded nanoparticles solution into gel base present in the beaker and mix for 20 min. Add triethanolamine to the above solution till proper consistency of gel obtained.

Determination of Particle Size, Polydispersity Index and Zeta Potential: The particle size, polydispersity index, and zeta potential were measured by using Malvern zeta sizer Nano ZS-90.

Percentage Drug Entrapment Efficiency (%EE): [7] The percentage of incorporated Fexofenadine HCl was determined by using the formula:

% Entrapment Efficiency = (Total drug added – Free drug) × 100/Total drug added

Scanning Electron Microscopy (SEM): A scanning electron microscope is a type of electron microscope that produces images of samples by scanning it with a focused beam of electrons. The electrons interact with atoms in the sample, producing various signals that can be detected and that contain information about the sample's surface topography and composition. SEM photographs were taken for the prepared nanoparticles using a scanning electron microscope (Carl Zeiss fesem model number. Ultra 55 USA) at 100 KX magnifications at room temperature.

***In-vitro* Release Study:** [8, 9, 10] Freshly prepared phosphate buffer pH 5.5 was used as a diffusion medium. *In-vitro* diffusion study was carried out for 6 h. Accurately measured nanosuspension was placed in the donor compartment. The donor compartment was placed above the receptor compartment containing 150 ml of diffusion medium maintained at 37 ± 0.5 °C and clamped. The medium was stirred at 100 rpm using a magnetic stirrer. Aliquots, each 1ml were withdrawn at regular time intervals and replaced with an equal volume of diffusion medium. The aliquots were suitably diluted with diffusion medium and analyzed by using Agilent Technologies Carry-60 UV- visible spectrophotometer at 230 nm.

pH: The pH of the various gel formulations was determined by using a digital pH meter.

Spread Ability: It was determined by a wooden block and glass slide apparatus. The gel is placed in between the glass slides and weights about 15 gm was added to the pan. The time was noted for the upper slide (movable) to separate completely from the fixed slides. Spread ability was then calculated by using the formula:

$$S = M \times L / T$$

Which
S = Spreadability
M = Weight tide to upper slide
L = Length of glass slide
T = Time taken to separate the slide completely from each other

Viscosity: Viscosity of the gel was measured at 25° C ± 2 °C, using Brookfield viscometer (Model-DVII) with spindle LV-4.

Kinetic Modeling of *In-vitro* Drug Diffusion Profile: Data obtained from the *in-vitro* diffusion study of drug was used for kinetic modeling profile. The dissolution profile of all formulations was fitted to zero order, first order, Higuchi and Korsmeyer-Peppas model to ascertain the kinetic modeling of drug release. The methods were adopted to obtain the most appropriate [11, 12, 13].

Skin Irritation Study: [14] The experimental protocol for the skin irritation study was approved by the Institutional Animal Ethics Committee (IAEC/ABMRCP/2017-18/10). Skin irritation study was carried out using 6 rats of either sex weighing between 200-250 gm. The animals were

kept under standard laboratory conditions with a temperature of 25 ± 2 °C and relative humidity of 55 ± 5 °C. The animals were kept in polypropylene cages with free excess to a standard laboratory diet and water. Animals were divided into 2 groups of 3 animals each. Hairs were depleted from the abdominal region using scissors and blade.

After hair depletion, the gel was applied once a day for 7 days, and the site was covered with a cotton bandage. Skin reaction at the site of application was subjectively observed and scored once daily for 7 days after patch removal. The reaction at the site of application was studied and scored according to the following numerical system such as erythema and eschar formation, edema formation, primary skin irritation index.

Stability Studies: Stability studies were carried out on optimized formulation. The optimized formulation was kept in the wide-mouthed bottle and sealed tightly with the cap and kept in the humidity chamber maintained at 40 ± 2 °C/75 ± 5% RH for one month. At the end of one month, samples were analyzed for pH, spreadability, viscosity, and *in-vitro* diffusion studies.

RESULTS AND DISCUSSION:

FTIR Study: In the present study the possible interaction between the drug and polymer is shown in **Fig. 1.** Pure Fexofenadine Hydrochloride showed 1647, 1518, 3073, 2928, 3373 cm^{-1} wavenumber as major peaks. The FTIR spectra of Fexofenadine HCl and the mixture of drug and excipients used in the formulation of nanoparticles reveal that there was no significant interaction between the drug and polymer and other excipients used in the formulation. The result is shown in **Fig. 1.**

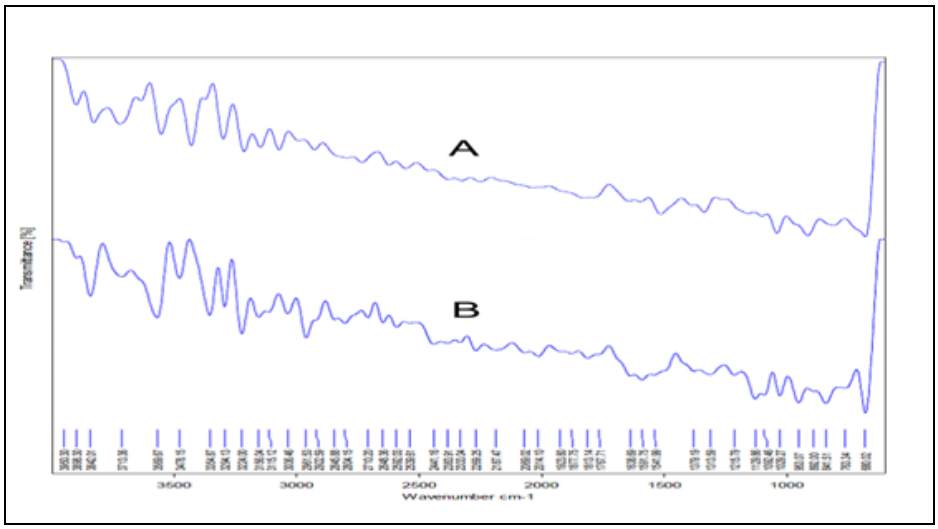

FIG. 1: A. IR SPECTRA OF FEXOFENADINE HCl, B. IR SPECTRA OF THE MIXTURE OF FEXOFENADINE HCl, CHITOSAN AND SODIUM STPP

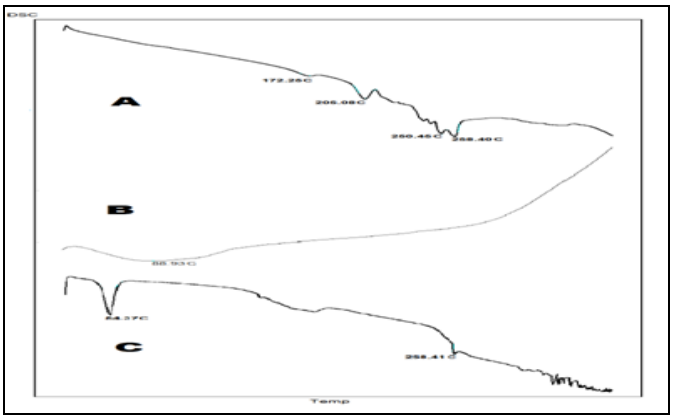

FIG. 2: A. DSC THERMOGRAM OF FEXOFENADINE HCl, B. DSC THERMOGRAM OF CHITOSAN, C. DSC THERMOGRAM OF THE MIXTURE OF FEXOFENADINE, CHITOSAN AND SODIUM STPP

Differential Scanning Calorimetry: DSC thermogram of Fexofenadine HCl and Chitosan and the mixture show that there was no interaction found between the drug and excipients used as shown in **Fig. 2.**

Evaluation of the Prepared Nanoparticles: Mean particle size distribution, PDI and zeta potential value, and % EE of the prepared nanoparticles are shown in **Table 3.** The ratio of chitosan and cross-linker has a significant effect on particle size, zeta potential as well as % EE. It was observed that with an increase in the chitosan volume, the % EE and zeta potential value was increased, which could be

due to the high payload of the drug in the polymeric matrix and the positive charge of the amino group present in the chitosan structure. As the volume of STPP increased, the lowering of zeta potential value was observed which might be due to the presence of more anionic groups present in the STPP structure. All formulation has PDI less than 0.3 indicates all formulations are homogenous in nature. For the formulations F6-F10, no yield was found which could be due to the insufficient concentration of crosslinker to form the nanoparticles.

TABLE 3: EVALUATION PARAMETERS OF FEXOFENADINE HCl LOADED CHITOSAN NANOPARTICLES

Formulations	% EE	Size (nm)	PDI	Zeta Potential (mV)
F1	68.18 ± 1.41	209.50 ± 10.70	0.18 ± 0.01	17.81 ± 0.39
F2	70.91 ± 0.87	211.70 ± 17.20	0.21 ± 0.02	15.00 ± 0.04
F3	73.31± 0.64	231.43 ± 19.49	0.17 ± 0.04	13.26 ± 0.18
F4	53.54 ± 0.56	284.00 ± 27.28	0.27 ± 0.02	18.16 ± 0.29
F5	51.85 ± 0.73	337.06 ± 31.94	0.27 ± 0.03	18.73 ± 0.81
F6	No Yield			
F7				
F8				
F9				
F10				

All values are mean ± SD

***In-vitro* Drug Release of the Nanoparticles:** *In-vitro* drug release carried up to 8 h which is shown in **Fig. 3**. The amount of cumulative drug release at the end of 8 h was found to be highest in F1 formulation (61.35 ± 4.73%) and lowest in F5 formulation (28.24 ± 1.09%). The results were shown in **Table 3** and **Fig. 3**.

It was observed that with an increase in the volume of STPP the amount of drug release was decreased, and it could be due to strong chemical bonding. In the case of F4 and F5, drug release rate was low due to the higher concentration of chitosan which affected the drug release rate.

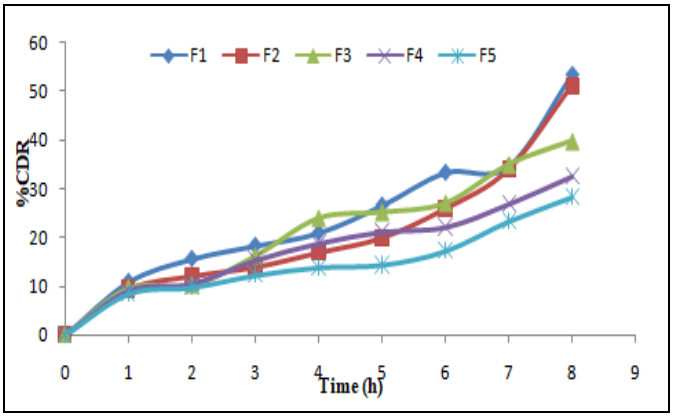

FIG. 3: % CUMULATIVE DRUG RELEASE OF FORMULATION F1-F5

Scanning Electron Microscope: SEM was used to observe the surface topography of the nanoparticles. It was observed that the prepared nanoparticles are spherical in nature. It is shown in **Fig. 4.**

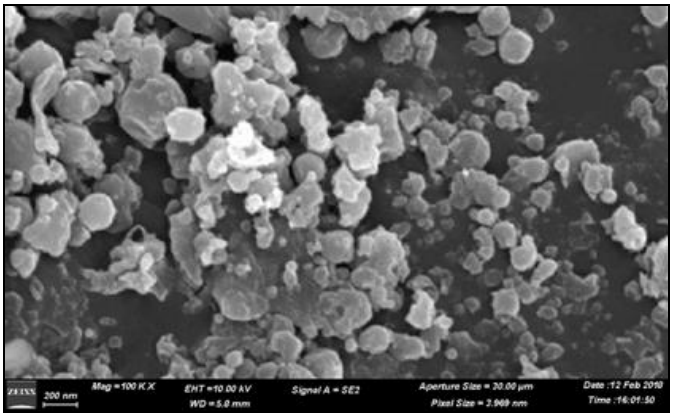

FIG. 4: SEM OF THE FEXOFENADINE HCl LOADED CHITOSAN NANOPARTICLE

Evaluation of the Gel: Spreadability, pH, and viscosity of the prepared gel were observed and shown in **Table 4**. The spreadability of nanogel formulations was found in the range of 0.296 ± 0.59 – 0.428 ± 0.93 gm. cm/sec.

TABLE 4: EVALUATION PARAMETERS OF THE GEL CONTAINING FEXOFENADINE HCl LOADED CHITOSAN NANOPARTICLES

Gel Formulations	Spreadability Coefficient g.cm/sec	pH	Viscosity
G1	0.296 ± 0.59	5.35 ± 031	12865
G2	0.428 ± 0.93	5.97 ± 015	12443
G3	0.382 ± 0.31	5.85 ± 048	12759

All values are mean ± SD

This indicates the spreading of gel on the skin is easy and also found within the range. The pH of gels was found to be 5.35-5.97 and it is found to be near to skin pH. So, that it will not causes damage to skin pH. The viscosity of nano gels was found in the range of 12443 to 12865 cps at 50 rpm by using a T-bar spindle (96 F).

***In-vitro* Diffusion Study of the Gels:** The diffusion studies were carried out in Franz-diffusion cell using phosphate buffer pH 5.5 as a diffusion medium. The diffusion studies were carried for 6 h.

The formulations G1, G2, G3 showed a drug release of 51.38 ± 1.56%, 49.71 ± 0.35% and 46.86 ± 0.81% respectively. G3 formulation showed a minimum amount of drug release up to 6 h. As the concentration of carbopol 934 increases the swelling of the gel is increased so that the drug release rate is also decreased. The result is shown in **Fig. 5.**

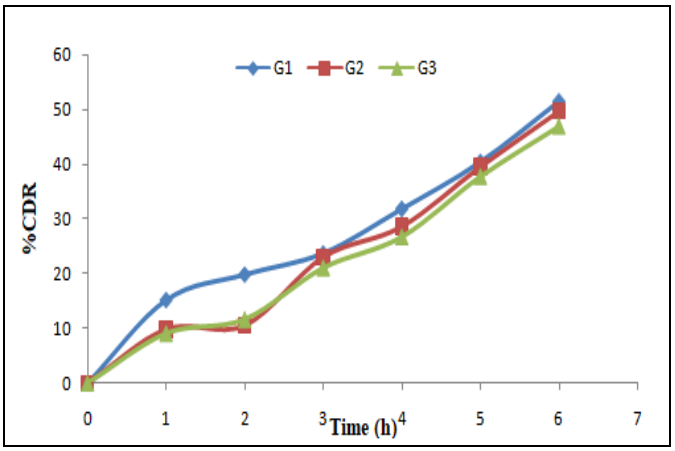

FIG. 5: % CUMULATIVE DRUG RELEASE OF G1-G3

Kinetic Modeling of *In-vitro* Drug Diffusion Profile for G1-G3: The kinetic studies for drug release of all formulations G1, G2 and G3 were done. For this purpose, the regression coefficient of the respective formulation was determined by plotting variables as per model, *i.e.*, zero-order, first-order, Higuchi model and Korsmeyer- Peppas model.

It was concluded that G1 and G2 are following first-order kinetic and G3 follows zero-order. The data of kinetic modeling are shown in **Table 5.** The n value obtained from the Korsmeyer-Peppas graph revealed that all the formulation's release pattern follows non- fickian diffusion. It is shown in **Fig. 5.**

Skin Irritation Study: The primary skin irritation index was found 0.00 for erythema, eschar and edema formation in the rats of the control group, test group and marketed group. From the results of the primary skin irritation index, it was concluded that there is no skin irritation was found in rats.

TABLE 5: KINETIC STUDY OF G1-G3

Formulations	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	R^2	R^2	R^2	n. value
G1	0.962	0.972	0.919	0.67
G2	0.976	0.977	0.854	0.96
G3	0.982	0.979	0.863	0.95

CONCLUSION: The prepared nanoparticles were used to formulate the nanogel using carbopol 934. The nano-drug delivery system developed by the ionic-gelation method has demonstrated their suitability for a topical route for the treatment of skin allergy. Thus the studies revealed that the developed system has a great appeal for the convenient treatment of dermatological allergy that may overcome in improving the limitations of the existing drug delivery system.

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CONFLICTS OF INTEREST: Nil

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