IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
September 2017 Vol.:10, Issue:2

Formulation and Evaluation of In Situ Nasal Gel of Doxylamine Succinate

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Manju Salim S*, Smt. Sheri. P. S, Dr.M.A.Kuriachan

Department of Pharmaceutics, Mar Dioscorus College of Pharmacy, Thiruvananthapuram, Kerala

Submission: 25 August 2017
Accepted: 3 September 2017
Published: 30 September 2017

Keywords: In situ nasal gel, Doxylamine succinate, Xanthan gum, HPMC K100 M, Poloxamer

ABSTRACT

This study aimed to formulate and evaluate in-situ nasal gel containing Doxylamine succinate was prepared for improving the bioavailability & sustaining the drug release. Doxylamine succinate is a first generation histamine H1 receptor antagonist and rapidly absorbed from gastrointestinal tract but it is subjected to first pass metabolism. Thus oral bioavailability is only 24.7%. The main objective of present work is to enhance the bioavailability; reducing the dose. Thermoreversible, bioadhesive polymers such as poloxamer and Hydroxy Propyl Methyl Cellulose (HPMC) K100 M in the form of in situ gel was prepared by hot technique. Xanthan gum was used as the base polymer. The results revealed that as the increase of bioadhesive polymer HPMC K100 M concentration, decrease in gelation temperature. pH of all formulation was found to be within the range between 5.8 to 6.1. The drug content for all formulation was found to be 96.28%-98.42%. The developed formulations had optimum viscosity. The optimized formulation shows the controlled drug release. The accelerated stability studies indicated that the gels were stable over the test period. The FT-IR analysis revealed that there was no drug-polymer interaction. From these findings, it can be concluded that in situ nasal gels may be potential drug delivery systems for Doxylamine succinate to overcome the first-pass metabolism and thereby to improve the bioavailability.

INTRODUCTION

The most desirable and convenient method of drug administration is the oral route because of their ease of administration. However, in many instances, oral administration is not desirable since the drug undergoes significant degradation via first pass effect in liver[1]. In the recent years, considerable attention has been focused on the development of new drug delivery systems[2-3]. The goal of any drug delivery system is to deliver a prescribed therapeutic amount of drug to the proper site in the body. In order to maintain the drug concentration within therapeutically effective range, novel drug delivery system can be employed. NDDS is advanced drug delivery system which improves drug potency, control the drug release to give a sustained therapeutic effect, provide greater safety, finally it target a drug specifically to the desired tissue. The new drug delivery systems that have been developed and developing are the mucoadhesive drug delivery systems, drug patches, transdermal patches etc.

Mucoadhesive drug delivery system shows promising future in enhancing the bioavailability and specific needs by utilizing the physiochemical characters of both the dosage form and the mucosal lining. Various sites for the mucoadhesive drug delivery system are ocular, buccal cavity, GIT, vaginal, rectal, nasal etc.

Due to the anatomy and physiology of the nasal passage, i.e. large surface area, highly vascularized epithelium, porous endothelial membrane and the avoidance of the first-pass metabolism, nasal drug delivery has emerged as a promising drug administration route for the systemic therapy. Administering the drug through nasal mucosa possesses following advantages, circumvents hepatic first-pass metabolism and acidic or enzymatic degradation of the drug in GIT, provides rapid absorption and onset of action, improves bioavailability, easy accessibility, and non-invasive route, direct delivery into the systemic circulation, lower risk of overdose and no need for complex formulations. Through nasal cavity, drugs are administered by different dosage forms like solutions, emulsions, gels etc. But these formulations had certain drawbacks like not easy to administer, low dose accuracy, the irritant to the nasal mucosa and give the gritty feel. To overcome such drawbacks *in situ* nasal gel are an attractive alternative route of administration.

In situ gel is dosage form in which medicament is present in solution form before administration in the body, but once administered, undergo gelation that is *in situ*, to form a gel. In the nasal cavity, nasal in-situ gels are installed as low viscosity solutions then forms a

gel after coming in contact with the nasal mucosa. It also prolongs the contact time between drug and absorptive sites in the nasal cavity and also releases the drug slowly and at a constant rate[4].

Antihistamines are often employed to provide symptomatic relief to allergic symptoms due to histamine release. Intranasal drug delivery is an attractive option for drugs, such as the oral antihistamine. Intranasal antihistamines are the most effective agents in the treatment of AR and nasal blockage owing to their efficacy over oral antihistamines[9]. Doxylamine is a first generation histamine H1 receptor antagonist most commonly used in the treatment of AR. Doxylamine succinate belongs to ethanolamine class of antihistamines and is metabolized by the liver into N-desmethyl doxylamine and N, N-didesmethyl doxylamine. Doxylamine competes with free histamine and exhibits specific, selective peripheral H1- antagonistic activity. On oral administration, bioavailability was only 24.7% but for intranasal administration, it was about 70.8%. Therefore the selected drug will be a suitable candidate for mucoadhesive nasal *In situ* gel drug delivery system in order to circumvent the first-pass metabolism and improve the bioavailability.

EXPERIMENTAL

Doxylamine succinate was supplied from Yarrow Chem Products, Mumbai. All other excipients and solvents used were of an analytical or pharmaceutical grade.

Compatibility studies using FT-IR Spectroscopy

The FT-IR spectrum of the obtained sample of drug and polymer were compared with the standard functional group frequencies of Doxylamine succinate, xanthan gum, HPMC K100M, poloxamer respectively. FT-IR spectroscopy was carried out to check the compatibility between drug and polymer. The compatibility between the drug, polymer was evaluated using FTIR peak matching method and the spectrum was scanned in the wavelength range of 400-4000 cm^{-1}.

Preparation of calibration curve of Doxylamine succinate

- **Preparation of phosphate buffer solution pH 6.4 (PBS pH 6.4)**

Dissolved 1.79 g of disodium hydrogen phosphate and 1.36 g of potassium dihydrogen phosphate and 7.02 g of sodium chloride in sufficient quantity of water to produce 1000 ml of buffer solution.

- **Preparation of calibration curve of Doxylamine succinate**

Accurately weighed quantity of pure drug (10 mg) was transferred into the 100ml volumetric flask, dissolved in distilled water and made the volume to 100ml with the same solvent. The stock solution was sonicated for 2min.

From the above stock solution, 0.5, 1, 1.5, 2, 2.5, 3 ml was taken and further diluted to 10 ml with distilled water to obtain a concentration of 5, 10, 15, 20, 25, 30µg/ml. The absorbance of solutions was measured at 262 nm by using UV-Vis spectrophotometer. A graph of concentration vs absorbance was plotted.

Preparation of Doxylamine succinate in situ nasal gel

The formulations F1-F8 were prepared by the hot method. In this method, the gelling polymer was dispersed at 100^0C with reasonable stirring. Afterwards, the solution was cooled to less than 40^0C.The drug and other ingredients (PEG, mannitol, methyl paraben) are separately dissolved in distilled water and added to the above solution during the cooling process and are mixed well. The final volume was made using distilled water.

Table 1: Formulations of Doxylamine succinate *In situ* nasal gel

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Doxylamine succinate(gm)	0.5	0.5	0.5	0.5	0.5	0.5	05	0.5
Xanthan gum(gm)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
HPMC K 100 M(gm)	0.2	0.4	0.6	0.8	-	-	-	-
Poloxamer(gm)	-	-	-	-	0.2	0.4	0.6	0.8
PEG 6000(gm)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol(gm)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Methylparaben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
PBS(ml)	2	2	2	2	2	2	2	2
Distilled water(ml)	q.s to 25ml							

EVALUATION OF PREPARED FORMULATION

- **Clarity test**[1]

The clarity of formulated solution was determined by visual inspection against the black & white background.

- **pH** [6, 7]

1 ml quantity of each formulation was transferred into a 10 ml volumetric flask and the pH of each formulation was determined by using pH meter which was calibrated using solution of pH 5 and 7 before the measurement.

- **Gelling Temperature**[1]

In this, 2 ml of formulation was transferred to test tube and placed into water bath then the temperature of water bath increased slowly and constantly. The gel was allowed to equilibrate for 5 minutes at each setting, and then formulation was examined for gelation. When the meniscus would no longer move upon tilting to 90^0 angles, this is known as a gelation temperature.

- **Gelling time**[4, 5]

2 ml of prepared formulation was transferred into a test tube and sealed with a parafilm. The tube was kept in a water bath maintained at 37˚C. Then the viscosity was measured as the system was allowed to cool gradually. Gelling time was recorded as the time for the first detection of gelation.

- **Gel strength**[9]

50 ml of formulation was placed in a 100 ml graduated cylinder and allowed to gel by placing the formulation in a thermostat at 37˚C. To the above-gelled solution, a weight of 35gm was positioned and permitted to pierce 5cm in the gel and time taken by weight to sink 5cm was measured.

- **Spreadability**[9]

To determine spreadability, a 10X4cm rectangular glass slide was used. The goat's nasal mucosa from the serosal side was tied on the surface of the slide with thread. The slide was then kept in a hot air oven at 37^0C and one drop of the gel was placed on the mucosa at an angle of 120°. The distance traveled by the drop before it gets gelled will be determined.

- **Viscosity Measurement**[2]

The viscosity of each formulation before and after gelation was measured by using Brookfield Viscometer DV-I Prime LV model coupled with the S-18 spindle. The prepared formulation was placed in small sample adapter, spindle was lowered perpendicularly into the formulation at l0 rpm and the temperature was maintained at 37 ± 0.5°C.

- **Drug Content**[10]

1 ml of formulation was taken in 10 ml volumetric flask. It was diluted with 10 ml of distilled water. 1 ml from this solution again diluted with distilled water up to 10 ml. After this, the absorbance of the prepared solution was measured at the wavelength of 262 nm by using UV visible spectrophotometer.

- **Mucoadhesive strength**[11]

The mucoadhesive strength was determined by using the modified method. The force required to detach the formulation from nasal mucosal tissue was determined to find out the mucoadhesive potential of each formulation. For this purpose, a section of goat nasal mucosa was fixed on each of two glass slides using thread. 50 mg of the gel was placed on the first slide and this slide placed below the height adjustable pan. While another slide with mucosal section was fixed in inverted position to the underside of the same pan. Both the slides with gel formulation between them held in contact with each other, for 2 min to ensure intimate contact between them. Then weight was kept rising in the second pan until slides get detached from each other. The mucoadhesive force expressed as the detachment stress in dynes/cm^2 was determined from the minimal weight that detached the mucosal tissue from the surface of each formulation.

$$\text{Mucoadhesive Strength (dynes/cm}^2\text{)} = mg/A$$

Where, m = weight required for detachment in gram,

g = Acceleration due to gravity,

A = Area of mucosa exposed.

- **In vitro drug release study[6]**

In vitro release study of the formulation was carried out using laboratory designed diffusion cell through egg membrane. Before starting the experiment, these egg membrane was soaked in a phosphate buffer having pH 6.4 for 24 hrs. From the formulation, 2 ml of formulation was placed in donor compartment and freshly prepared phosphate buffer in receptor compartment. Egg membrane was mounted between donor and receptor compartment. The temperature of receptor compartment was maintained at 37 ± 2^{0}C during experiment and content of the receptor compartment was stirred using magnetic stirrer. The position of donor compartment was adjusted so that egg membrane just touches the diffusion fluid. An aliquot of 2 ml was withdrawn from receptor compartment after 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6 hr and the same volume of fresh medium was replaced. Aliquot so withdrawn were suitably diluted and analyzed using UV visible spectrophotometer at 262 nm. The concentration of drug was determined from a previously constructed calibration curve.

- **Kinetics of in vitro drug release[8]**

The results obtained from in-vitro release studies were attempted to fit into various mathematical models as follows:

1) Cumulative percent drug released Vs. Time (Zero order kinetics)

2) Log cumulative percent drug retained Vs. Time (First order kinetics)

3) Cumulative percent released Vs. Square root of Time (Higuchi model)

4) Log cumulative percent drug released Vs. Log Time (Korsmeyer- Peppas model)

➢ **Zero Order**

$$\mathbf{Q = K_0 t}$$

Where Q is the amount of drug release at time t

K_0 is the zero-order release rate constant expressed in units of concentration/time

- **First Order**

$$\textbf{Log Q} = \textbf{K}_1\textbf{t}$$

Where Q is the percent of drug release at time t

K_1 is the release rate constant.

- **Higuchi's classical diffusion equation**

$$\textbf{Q} = \textbf{K}_2\ \textbf{t}_{1/2}$$

Where Q is the percentage of drug release at time t

K_2 is the diffusion rate constant.

- **Korsmeyer-Peppas**

$$\textbf{Q} = \textbf{Kt}_n$$

Where Q is the percent of drug release at time t

K is the diffusion rate constant and n is the diffusional exponent.

Table 2: Diffusion exponent and solute release mechanisms[8]

Diffusion exponent (n)	Overall solute diffusion mechanism
<0.45	Quasi- Fickian diffusion
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-Fickian) diffusion
0.89-1.0	Case- II transport(Zero order release)
>1.0	Super case- II transport

- **Stability studies[3, 6]**

Stability studies were conducted according to ICH guidelines 40^0C ± 2^0C/ 75%± 5% RH to test the physical and chemical stability of the developed formulations. Throughout the study, nasal *in situ* gel formulation was stored in aluminum foil sealed glass bottles. The stored

formulations were evaluated periodically for drug content, pH, viscosity and *in-vitro* drug release at predetermined time interval.

RESULTS AND DISCUSSIONS

Compatibility studies

The FT-IR spectrum of Doxylamine succinate is shown in figure 1, which complies with standard functional group frequencies.

Figure 1: FT-IR spectrum of Doxylamine succinate

Table 3: IR frequencies of Doxylamine succinate

Functional group	Characteristic Wavenumber(cm^{-1})	Doxylamine succinate - observed Wavenumber (cm^{-1})
C_6H_5	650-600	623.81
C-CH_3 bending	1458-1380	1411.89
C-O-C	1300-1000	1303.88
C=N	1650-1550	1583.56

Compatibility between drug and polymer

The FT-IR spectrum of the combination of Doxylamine succinate with excipients is shown in figure 2 and 3.

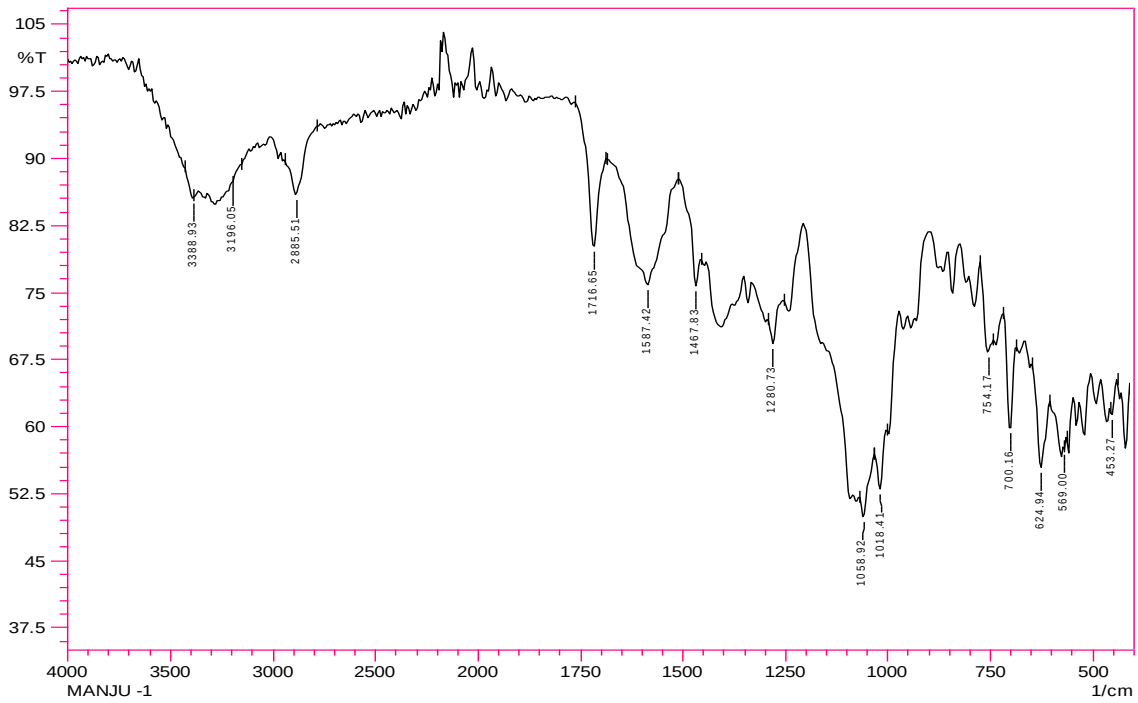

Figure 2: FT-IR spectrum of the physical mixture of Doxylamine succinate + Xanthan gum + Poloxmer.

Table 4: IR frequencies of Doxylamine succinate with xanthan gum & poloxamer.

Functional group	Characteristic Wave number(cm^{-1})	Doxylamine succinate -observed Wave number(cm^{-1})	Doxylamine succinate + Xanthan gum + Poloxmer (cm^{-1})
C_6H_5	650-600	623.81	624.94
C-CH_3 bending	1458-1380	1411.89	1410.81
C-O-C	1300-1000	1303.88	1302.96
C=N	1650-1550	1583.56	1587.42

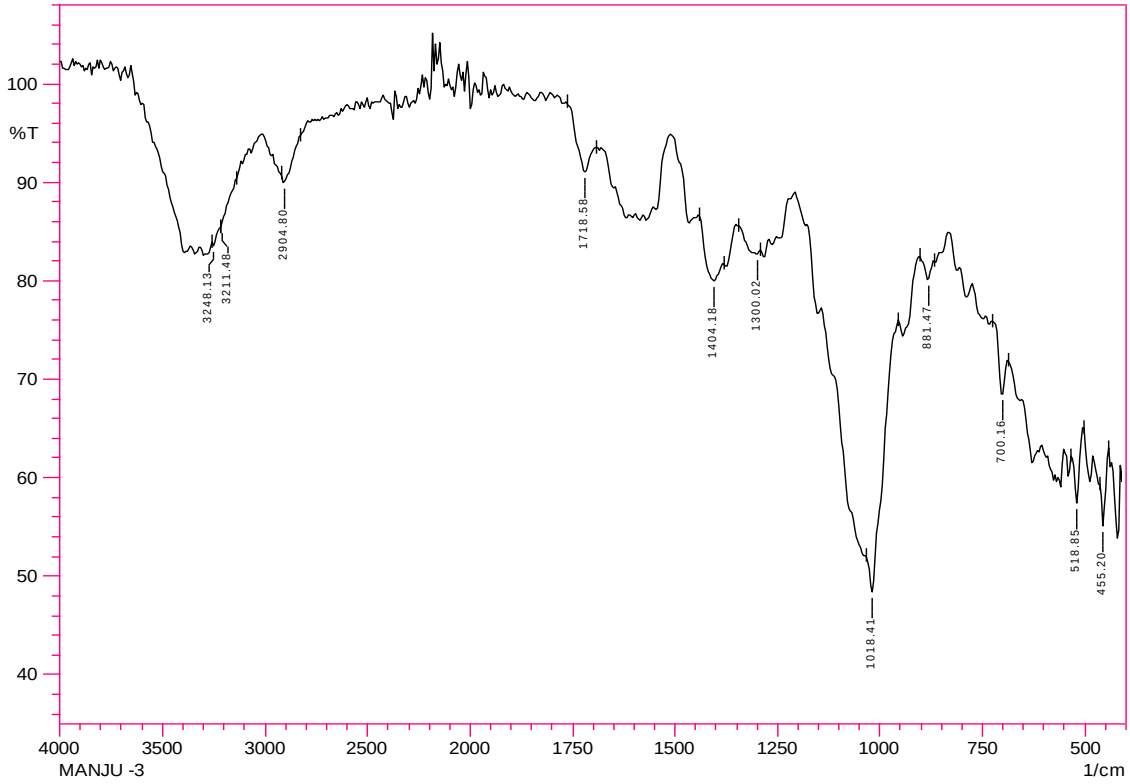

Figure 3: FT-IR spectrum of the physical mixture of Doxylamine succinate + Xanthan gum + HPMC K100M.

Table 5: IR frequencies of Doxylamine succinate with xanthan gum & HPMCK100 M

Functional group	Characteristic Wave number(cm^{-1})	Doxylamine succinate -observed Wave number(cm^{-1})	Doxylamine succinate + Xanthan gum + HPMC K100M(cm^{-1})
C_6H_5	650-600	623.81	625.61
C-CH_3 bending	1458-1380	1411.89	1404.18
C-O-C	1300-1000	1303.88	1303.91
C=N	1650-1550	1583.56	1686.41

.The compatibility between drug-polymer was carried out by using FT-IR peak matching method. All major peaks present in the spectrum of a pure drug were observed in the spectrum of drug-polymer gel. This suggests that the drug remains in its normal structure and hence this confirmed the absence of any chemical interaction or complexation between drug and polymers.

Preparation of calibration curve of Doxylamine succinate

Standard calibration curve of Doxylamine succinate was determined in water by measuring the absorbance of the standard solutions at 262nm using double beam UV spectrophotometer. The calibration curve was found to be linear in the range of 5-30 µg/ml at λmax 262nm.

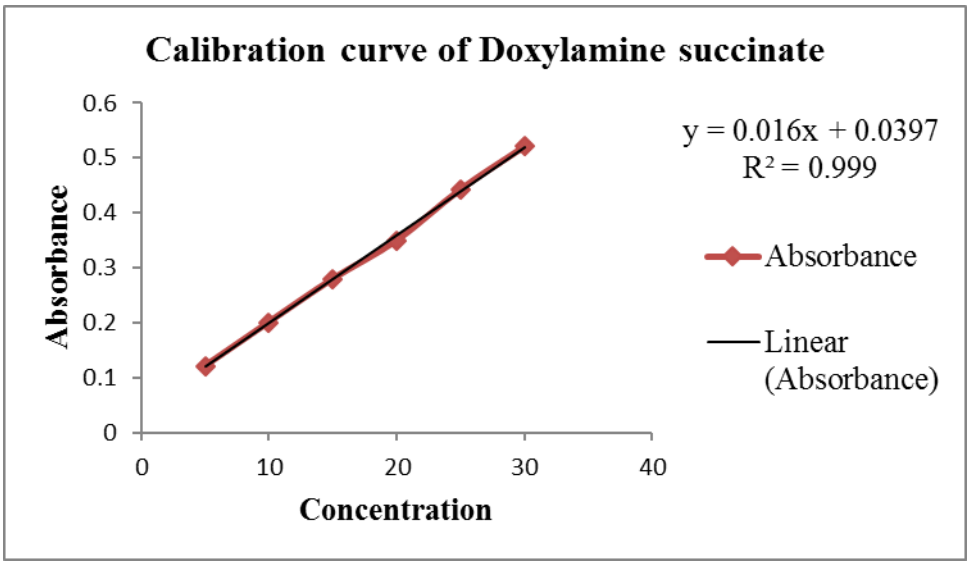

Figure 4: Standard calibration curve of Doxylamine succinate

Evaluation of nasal *in situ* gel

- **p^H**

The p^H of the formulations was found to be satisfactory and did not show any mucosal irritation. P^H of all the formulations is listed in table 6.

- **Gelation temperature**

The data shows the wide range of gelation temperature for different formulations. It indicated that as the concentration of polymer increases the gelation temperature of the formulation decreases. Formulations are having the gelation temperature in the desired range of 35.1-36 ^{0}C which are presented in table 6.

- **Gelling time**

The gelling time of the formulation is shown in table 6.

Table 6: P^H, Gelling temperature (˚C), Gelling time(s)

Formulation code	P^H	Gelation temperature (˚C)	Gelling time(s)
F1	5.9 ± 0.002	35.1 ± 0.41	11.5 ± 0.24
F2	5.8 ± 0.001	34.9 ± 0.28	10.4 ± 0.41
F3	6.1 ± 0.001	34.7 ± 0.44	9.4 ± 0.56
F4	6.1 ± 0.002	34.4 ± 0.34	8.2 ± 0.52
F5	5.8 ± 0.003	36.0 ± 0.21	14.3 ± 0.21
F6	5.9 ± 0.003	35.7 ± 0.29	13.3 ± 0.45
F7	5.9 ± 0.004	35.41 ± 0.32	12.5 ± 0.37
F8	6.0 ± 0.001	35.2 ± 0.22	11.2 ± 0.41

- **Gel strength**

The gel strength is an indication for the viscosity of the nasal gel at physiological temperature. The data obtained indicated, as the polymer concentration increases the gel strength of the formulation also increases. The formulation F4 has the highest gel strength.

- **Spreadability**

The spreadability was found to be in the range of 7.2 to 11.6 cm. The formulations prepared with a high concentration of HPMC K100 M showed less spreadability.

- **Estimation of drug content**

Drug content of all the formulations was carried out by using UV spectrophotometer at 262 nm and was found to be in the range of 96.28% to 98.42%. The maximum % drug content was found to be 98.42% in F4 and 98.16% in F3. The result of above studies is summarized in table 7.

Table 7: Gel strength, Spreadability (cm), Drug content(%)

Formulation code	Gel strength	Spreadability (cm)	Drug content (%)
F1	50 ± 0.54	9.7 ± 0.11	96.64 ± 0.36
F2	53 ± 0.48	8.9 ± 0.14	97.12 ± 0.28
F3	57 ± 0.49	8.4 ± 0.12	98.16 ± 0.56
F4	60 ± 0.56	7.2 ± 0.18	98.42 ± 0.49
F5	46 ± 0.41	11.6 ± 0.17	96.28 ± 0.24
F6	49 ± 0.37	10.4 ± 0.17	96.45 ± 0.41
F7	52 ± 0.52	9.3 ± 0.14	97.09 ± 0.32
F8	55 ± 0.48	8.5 ± 0.13	97.41 ± 0.31

- **Viscosity**

The viscosity was directly dependent on the polymeric content of the formulations. The presence of a combination of polymers significantly increased the viscosity and the values are shown in table 8.

Table 8: Viscosity of formulations F1-F8

Formulation code	Viscosity of sol(cP)	Viscosity of gel(cP)
F1	127 ± 0.25	168 ± 0.52
F2	145 ± 0.38	196 ± 0.44
F3	168 ± 0.21	236 ± 0.27
F4	186 ± 0.44	251 ± 0.56
F5	106 ± 0.46	146 ± 0.39
F6	121 ± 0.29	162 ± 0.54
F7	142 ± 0.31	185 ± 0.48
F8	162 ± 0.26	228 ± 0.32

- **Mucoadhesive strength**

Mucoadhesive strength was directly proportional to the concentration of polymers. Results reveal that increase in HPMC K100 M concentration increases the mucoadhesive strength. This was due to the interaction of polymeric chains with the mucin strands to form weak chemical bonds due to stronger mucoadhesive force. The mucoadhesive strength ranged between 2123.24-6556.45 dyne/cm^2 and shown in table 9.

Table 9: Mucoadhesive strength of formulations F1-F8

Formulation code	Mucoadhesive strength (dyne/cm^2)
F1	3016.41 ± 0.24
F2	4271.56 ± 0.52
F3	5884.78 ± 0.67
F4	6556.45 ± 0.56
F5	2123.24 ± 0.28
F6	3210.42 ± 0.12
F7	4061.89 ± 0.87
F8	5456.62 ± 0.45

- **In-vitro drug release study**

The in-vitro release studies were carried out using Franz diffusion cell for a period of 6 hrs. The percentage of drug released from the formulations F1-F4 were tabulated in table 9 and F5-F8 were tabulated in table 10.

Table 9: Percentage cumulative drug release data for formulations F1-F4

Time (Hrs)	F1 %CDR	F2 %CDR	F3 %CDR	F4 %CDR
0	0	0	0	0
0.25	6.61	6.24	6.11	5.87
0.5	12.96	12.85	12.76	11.7
1	23.2	22.38	21.88	21.18
1.5	32.66	31.25	30.42	29.91
2	37.97	36.88	36.24	34.89
2.5	49.41	48.99	47.64	46.97
3	54.28	53.17	52.89	51.74
3.5	63.83	62.95	61.65	60.04
4	72.85	71.95	70.91	69.12
5	84.11	83.94	82.94	81.86
6	91.75	90.76	89.46	88.05

Table 10: Percentage cumulative drug release data for formulations F5-F8.

F5 %CDR	F6 %CDR	F7 %CDR	F8 %CDR
0	0	0	0
7.89	7.41	6.76	6.35
15.45	14.45	13.96	13.68
29.89	26.08	25.97	24.6
35.22	34.91	34.13	33.52
41.77	38.67	37.95	37.14
51.99	50.65	49.94	49.56
59.96	58.51	57.44	56.67
66.24	65.85	65.07	64.16
76.47	74.64	73.94	72.95
86.48	86.02	85.72	84.89
97.75	96.37	95.07	93.97

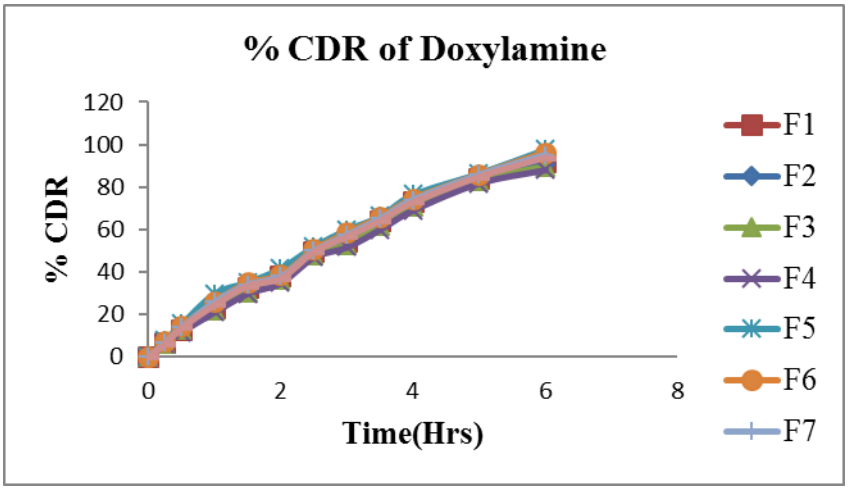

Figure 5: Percentage cumulative drug release profile of Doxylamine formulations F1-F8

- **Kinetics of in vitro drug release**

The results obtained of in vitro release studies were attempted to fit into various mathematical models.

Table 11: Kinetic study of Doxylamine succinate release from formulations F1-F8

Formulation code	Release Kinetics				
	Zero-order R^2	First order R^2	Higuchi R^2	Peppas	
				R^2	n
F1	0.9828	0.9547	0.9652	0.9972	0.8290
F2	0.9838	0.9580	0.9618	0.9966	0.8409
F3	0.9847	0.9629	0.9609	0.9967	0.8420
F4	0.9855	0.9654	0.9588	0.9973	0.8562
F5	0.9791	0.8581	0.9736	0.9929	0.7729
F6	0.9833	0.8953	0.9682	0.9960	0.7974
F7	0.9833	0.9191	0.9668	0.9942	0.8171
F8	0.9840	0.9316	0.9653	0.9940	0.8316

The in-vitro drug release data were subjected to a goodness of fit by linear regression analysis, according to zero order, first-order kinetic equation, Higuchi and Korsmeyer models to ascertain the mechanism of drug release. The result of linear regression analysis of data including regression coefficient is summarized in above table. When the regression coefficient '$R^{2'}$ values of zero order and first order plots were compared, it was observed that

the 'R^2' values of zero order were higher than that of first-order plots. Which indicates that the drug release from the formulation is more likely to follow zero order kinetics.

Based on the values of regression coefficient, it was concluded that the formulation F4 strictly follows zero order kinetics compared to other formulations.

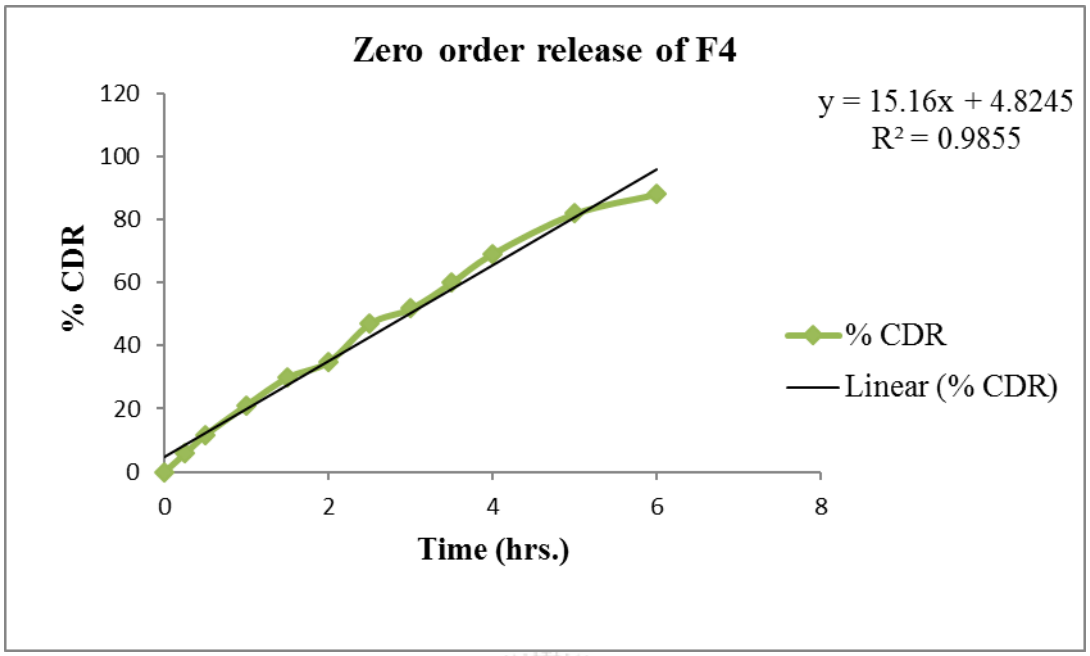

Figure 6: Zero order plot of F4

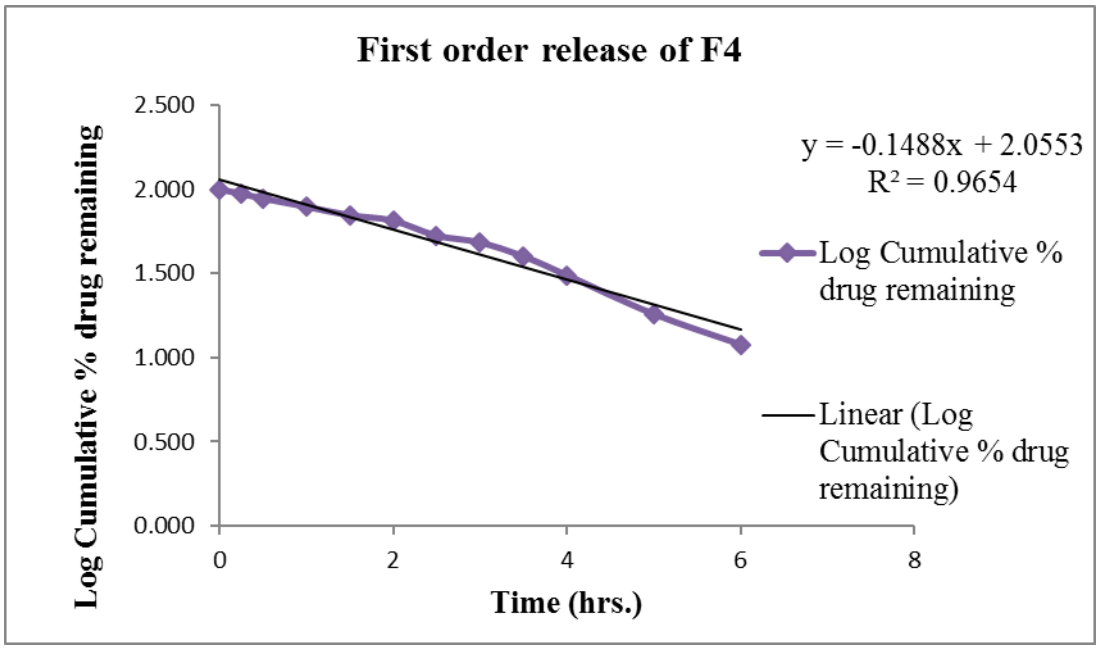

Figure 7: First order plot of F4

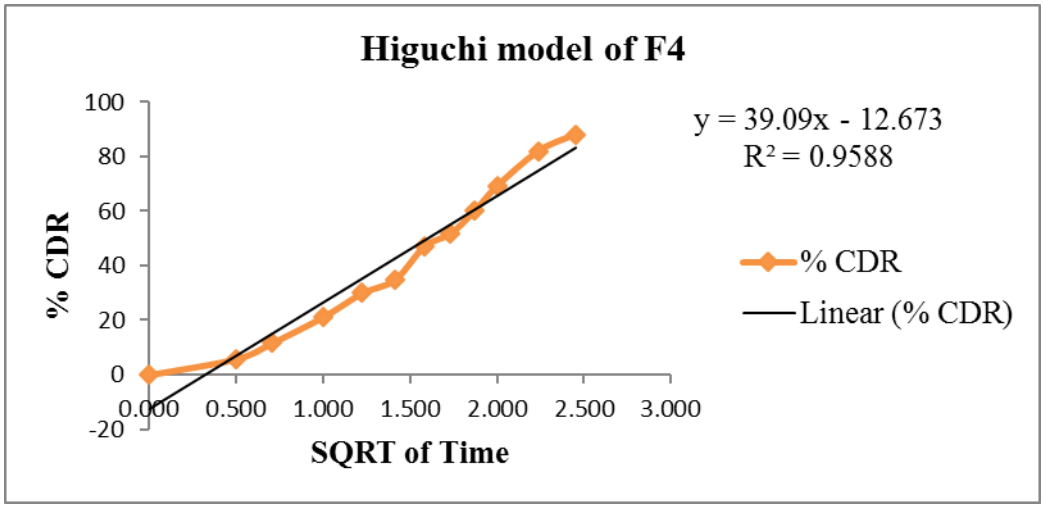

Figure 8: Higuchi plot of F4

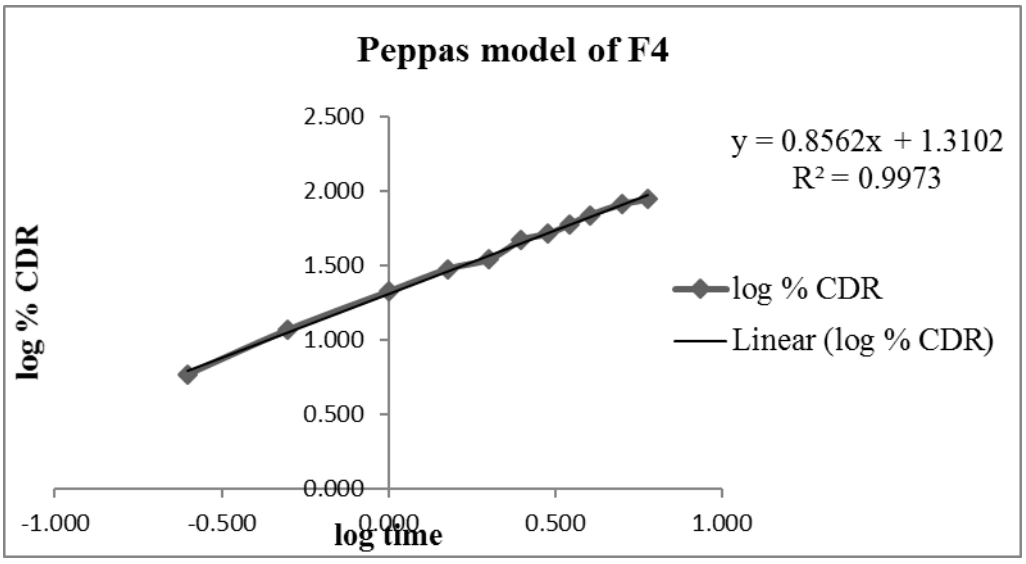

Figure 9: Peppas plot of F4

From the above graphs, it was concluded that the formulation F4 follow zero order kinetics.

The in-vitro drug release data as log % CDR versus time were fitted to Korsmeyer equation in order to understand the mechanism by which Doxylamine was released from this formulation. Value of exponent 'n' was found to be 0.7729-0.8562 indicating that the drug release is by non-fickian mechanism.

- **Stability studies**

Stability studies were carried out on formulation F4 for a period of 1 month and comparison of the parameters before and after stability studies was represented in table 12.

Table 12: Comparison of parameters before and after stability

Parameters	Appearance	P^H	Drug content (%)	% CDR
Before stability	Transparent	6.1	98.42	88.05
After stability	Transparent	5.9	97.91	87.60

The result showed that F4 showed the slight decrease in drug content of Doxylamine at 40˚C after 1 month of storage. The in vitro drug release also slightly decreased after stability period. This may due to relative drug content. From the stability studies, it was confirmed that *in situ* gelling formulation of Doxylamine remained stable at 40˚C and 75% relative humidity. The appearance of the formulation was transparent and observed a slight difference in p^H.

CONCLUSION

The in-situ nasal gels of Doxylamine succinate were prepared using xanthan gum, thermoreversible poloxamer and mucoadhesive polymer HPMC K100 M by varying their concentrations. Among all the formulations, the results indicated that the drug content was uniform, gelling temperature & time are within the range and p^H of the formulations did not show any mucosal irritation. The presence of the combination of polymers significantly increased the viscosity as well as gel strength. The formulation prepared with the high concentration of HPMC K100 M showed less spreadability and exhibited more mucoadhesion strength as compared to other formulations. The formulations prepared with high viscous polymers prolonged the drug release during the study period. Based on the physicochemical, drug release characteristics, the present study concludes that the formulation F4 containing xanthan gum: HPMC K100 M (0.1:0.8 ratio) are suitable to form nasal in situ gel for Doxylamine succinate. The findings of results revealed that a stable and effective *in situ* nasal gel of Doxylamine succinate can be formulated which will bypass the first-pass effect, improve the bioavailability, and give a controlled release of the drug at the site which gave the possibility of lowering the dosing frequency.

ACKNOWLEDGEMENT

We are extremely grateful to Mar Dioscorus College of Pharmacy, Thiruvananthapuram, Kerala for the facilities provided to complete this work successfully.

REFERENCES

1. Baban A. More et al., A Review on In-Situ Nasal Gel Drug Delivery System. Int. J. Pharm. Sci. 2015; 33(1): 199-207.
2. Y.W. Meshram et al., Formulation And Evaluation Of Ph Induced In-Situ Nasal Gel Of Levocetirizine Hydrochloride. Int. J. Drug Res. Tech. 2016; 6 (3): 120-126.
3. Mothukuri Tejaswini and A. Seetha Devi., Formulation and evaluation of nasal in situ gel of phenylephrine hydrochloride. Int. J. Drug Res. Tech. 2016; 6 (2): 64-78.
4. Vinay Pandit et al., Mucoadhesive in situ nasal gel- A novel approach. JADD. 2014; 1(6): 1-8.
5. Ashok Kumar Rajpoot et al., Mucoadhesive, thermosensitive prolonged release in situ nasal gel of Domperidone. IJDFR. 2011; 2(4): 210-224.
6. S. A. Pagar et al., Development and evaluation of in situ nasal mucoadhesive gel of metoprolol succinate by using 3^2 full factorial design. Int J Pharm Pharm Sci. 2014; 6(11): 218-223.
7. Parth Gandhi et al., Research on formulation and evaluation of in-situ mucoadhesive nasal gels of metoclopramide hydrochloride. Innovate Journal of Medical Sciences. 2013; 1(3): 1-3.
8. Suvakanta Dash et al., Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica Drug Research. 2010; 67(3): 217-223.
9. Sheri P S et al., Development and evaluation of in situ nasal gel formulations of loratadine. Research in Pharmaceutical Sciences. 2015; 10 (6): 466-76.
10. Bajpai Vibha et al., In Situ Gel Nasal Drug Delivery System – A Review. Int J Pharm Sci. 2014; 4(3): 577-580.
11. D. V. Gowda et al., Formulation and evaluation of in-situ gel of Bromhexine hydrochloride for nasal delivery. Der Pharmacia Sinica. 2012; 3 (6): 699-707.
12. Parmar Viram, A.N.Lumbhani., Development, and evaluation of ion-dependent in- situ nasal gelling systems of metoclopramide hydrochloride as an antimigraine model drug. International Journal of Latest Research in Science and Technology. 2012; 1(2): 80-89.
13. Ashish Gorle et al., A Possible Way to Improve the Therapeutic Effectiveness of Levetiracetam Via Nose to Brain. RJPBCS. 2017; 8(2): 2258-2269.
14. Yadav DJ et al., Formulation and evaluation of thermosensitive in situ gel of salbutamol sulfate for nasal drug delivery system. International Journal of Pharmacy and Pharmaceutical Sciences. 2012; 4(4): 188-194.
15. Prasad K. More et al., Nasal in-situ gel: a novel approach for nasal drug delivery system. WJPR. 2015; 4(2): 686-708.