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FORMULATION AND EVALUATION OF *IN-SITU* NASAL GEL OF MONTELUKAST SODIUM FOR THE EFFECTIVE TREATMENT OF ASTHMA

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ABSTRACT: In this research work an attempt was made to formulate and evaluate *in-situ* gel for the intranasal delivery of montelukast sodium for the effective treatment of asthma. Thermally gelling *in-situ* gel formulations for nasal administration were prepared by using polymers such as poloxamer 407 and HPMC K4M in varying concentrations by using cold method. The formulated *in-situ* gels were evaluated for clarity, pH, gelation temperature, gel strength, viscosity, drug content and *in-vitro* drug diffusion studies. The drug-polymer compatibility was determined by using FTIR studies. On the basis of clarity studies formulations F3, F4, F5 and F6 were selected for further evaluation testing because all of these formulations were found clear in appearance as compared to formulations F1 and F2 which showed hazy appearance and thus rejected. Further the drug release data obtained from the selected formulations were fitted to various kinetic models such as zero order, first order and Higuchi matrix kinetic models. Finally, based on the results obtained from all the evaluation parameters formulations F5 and F6 were found to be potential candidates for controlled drug delivery as *in-situ* nasal gel.

INTRODUCTION: The nasal route is an important mode of drug delivery, with a growing number of products available for administration through this route for systemic and local action, such as for allergic rhinitis. *In-situ* gel is a new dosage form which has been applied in nasal drug delivery recently.

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Compared with liquid nasal formulations, nasal in situ gels are instilled as low viscosity solutions into the nasal cavity. Upon contact with the nasal mucosa, the polymer changes conformation producing a gel, so that it can not only prolong the contact time between the drug and the absorptive sites in the nasal cavity, but also releases drug slowly and continuously [1, 2, 3]. Hence, it is especially useful for those drugs that are used for long term management of chronic ailments [4, 5, 6]. Montelukast sodium is a leukotriene antagonist, effective in chronic management of asthma. The oral bioavailability of montelukast sodium shows values between 64 and 68% due to extensive first pass metabolism.

The intranasal delivery seems to be an attractive alternative. poloxamer 407 (Pluronics F127) has excellent thermo-sensitive gelling properties, low toxicity, excellent water solubility, good drug release characteristics and compatibility with other excipients [7, 8]. It is an ABA triblock copolymer consisting of the hydrophilic polyethylene oxide (PEO) and the hydrophobic polypropylene oxide (PPO) [9, 10]. The objective of the present study was to develop an optimized montelukast sodium mucoadhesive *in-situ* nasal gel with an accurate phase transition temperature which would enhance nasal residence time and absorption of drug across nasal mucosal membrane.

MATERIALS AND METHODS: Montelukast sodium was obtained from Yarrow chemical products along with Poloxamer 407. HPMC K4M was obtained from Molychem.

Preparation of Nasal *in- situ* gel of Montelukast: Various formulations of *in situ* gels in different drug and polymer ratios as given in **Table 1** were prepared by Cold method. Initially in a very small quantity of water, poloxamer was dissolved separately in a concentration of 20% w/v at cold conditions. Then HPMC was dissolved in the quantity as specified in the composition **Table 1**. Later drug, PEG 400 and methyl paraben were incorporated and stirred until clear solution was obtained. Finally made the volume up to 100 ml with distilled water and kept it overnight at freezing conditions (4 - 10 °C) [11].

TABLE 1: FORMULATION COMPOSITION OF *IN-SITU* GEL OF MONTELUKAST SODIUM

Ingredients	F1	F2	F3	F4	F5	F6
Montelucast (mg)	8	8	8	8	8	8
Polaxmer 407 (%W/V)	20	20	20	20	20	20
HPMC K4M (%W/V)	0.2	0.4	0.6	0.8	1.0	1.2
PEG 400 (ml)	0.5	0.5	0.5	0.	0.5	0.5
Methyl Paraben (ml)	0.05	0.05	0.05	0.05	0.05	0.05
Water(ml)	100ml	100ml	100ml	100ml	100ml	100ml

HPMC = Hydroxy Propyl Methyl Cellulose, PEG = Polyethylene Glycol

Evaluation of *in-situ* Gel: [12, 13, 14]

Drug Polymer Interaction Studies: Fourier Transform Infrared Spectroscopy was used to determine the purity of the drug sample and interaction of the drug with the polymers. Infrared spectra of drug and polymers, alone and in mixture were taken. Then it was investigated for possible interaction between polymer and drug and compared with the standard IR spectra of the pure drug.

Clarity: The developed formulations were inspected visually for clarity, colour in sol and gel form against white background and for any particulate matter if present.

pH of gel: pH of each formulation was measured using pH meter which was previously calibrated using standard buffers of pH 4, pH 7 and pH 9.

Measurement of Gelation Temperature: It was determined by using modified Miller and Donovan technique. A 2 ml aliquot of gel was taken into the test tubes which were placed in water bath at 4 ºC inside an insulating chamber. The temperature of water bath was increased in the increment of 1ºC. The samples were examined for gelation, which was said to have occurred when the meniscus would follow non Newtonian flow upon tilting.

Drug Content Estimation: 1 ml formulation was taken in 10 ml volumetric flask and then diluted using distilled water upto 10 ml. Again 1 ml quantity from this solution was taken and diluted with 10 ml of distilled water.

Finally the absorbance of prepared solution was measured at 286 nm against blank reagent using UV visible spectrophotometer (Shimadzu UV-1800). Finally concentration of the drug present in formulation was computed with the help of calibration curve.

Gel Strength: A sample of 50 g of nasal gel was taken in 100 ml graduated cylinder and gelled in thermostatically controlled water bath at 37 ºC. Weight of 35 g was placed onto the gelled solution. The gel strength, which is an indication for the viscosity of the nasal gel at physiological temperature, was determined as time in sec required by the weight to penetrate 5 cm into gel.

Viscosity: The rheological studies were carried out using the Brookfield viscometer. The gel formulation under study was placed in the sample holder and then suitable spindle was selected and inserted perpendicular into the sample.

The spindle was rotated at constant optimum speed. The viscosity determinations of formulation were carried out at different temperature from 5 ºC to 40ºC.

***In-vitro* Drug Release:** *In-vitro* drug release study of the formulated in situ gel was carried out in two chambered diffusion cell by using dialysis membrane-70 with molecular weight cut off 1200-1400 KDa. Diffusion cell of specifications such as 2.4 cm diameter and 25 ml capacity consisted of upper cylindrical compartment open from above and diffusion membrane at its base. To prepare artificial membrane, pieces of dialysis membrane were soaked in PBS pH 6.4 for h before mounting on diffusion cell. Dialysis membrane was in a two chamber cells.

In-situ gels of HPMC K4M and poloxamer 407 loaded with drug were placed in the donor compartment; 20 ml of PBS 6.4 was placed in the receptor compartment. The temperature of receiver compartment was maintained at the 37 ºC ± 1 ºC during the entire experiment and the content of the receiver compartment was stirred using magnetic stirrer. The position of the donor compartment was adjusted so that dialysis membrane just touches the diffusion medium. An aliquot of 1 ml was withdrawn from receiver compartment initially after 15 and 30 min and then 1 h interval and replaced with same amount of fresh medium. Withdrawn aliquots were suitably diluted and analyzed using UV spectrophotometer at 286nm for drug. *In-vitro* drug release was carried out for 8h.

RESULTS AND DISCUSSION: Recent advances in *in-situ* gelling systems provides multiple opportunities to improve overall therapeutic effectiveness and patient compliance. It is a novel approach to address the limitations of conventional dosage forms which are currently available in market. This system allows rapid achievement of drug plasma concentration *via* various body cavities bypassing the first pass metabolism & thereby reducing the excessive incorporation of drug dose, thereby minimizing the side effects. An attempt was made to formulate several *in-situ* nasal gel formulations of montelukast sodium using varying drug polymers ratios as given in formulation composition **Table 1**. The color, odor and taste of the drug were characterized and recorded. Melting point of montelukast sodium was found to be 135° ± 1.5 °C (n=3). UV absorption spectrum showed λ_{max} to be 286nm.

TABLE 2: CALIBRATION CURVE OF MONTELUKAST SODIUM IN PBS 6.4

Conc. (µg/ml)	Absorbance
10	0.0308
20	0.0571
30	0.0922
40	0.1273
50	0.1650

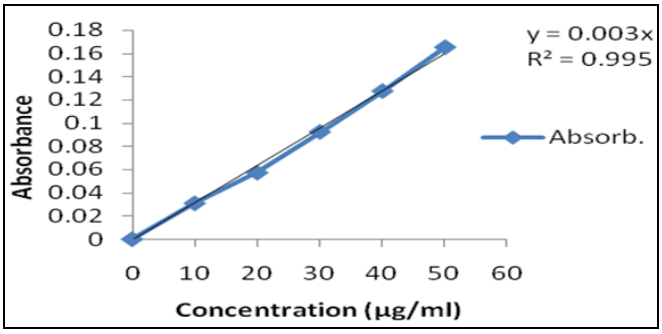

FIG. 1: CALIBRATION CURVE OF MONTELUKAST SODIUM IN PBS 6.4 AT 286 nm

The graph of absorbance *vs*. concentration for pure montelukast sodium was found to be linear; hence the drug obeys Lambert-Beer's law. UV absorption spectrum showed λ_{max} to be 286nm. The graph of absorbance vs. concentration for pure montelukast sodium was found to be linear; hence the drug obeys Lambert-Beer's law. **Table 2** depicts the various absorbance values of standard stock solutions of montelukast sodium containing 10-50 µg/ml of montelukast sodium in PBS 6.4. **Fig. 1** shows the standard calibration curve with slope 0.0032 and regression value of 0.995.

Drug Polymer Interaction Studies: Drug polymer interaction studies were performed by using FTIR spectroscopy in order to know the compatibility aspects of drug and polymers. The characteristic C-H band stretch of carboxylic group was present in the spectrum which is stretching between 2800-3600 cm^{-1}. N-H stretching at 3417.44 cm^{-1}, alkane saturated peak at 2925.59 cm^{-1} and C=C at 1600.98 cm^{-1} were also observed in the obtained spectra. From the FT-IR spectra of pure drug and the combination spectra of drug with the polymers, it was observed that all the characteristics peaks of drug are present in the combination spectra thereby indicating the compatibility of the drug with the polymers used.

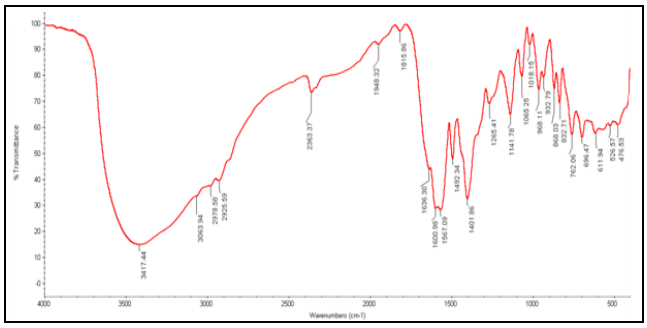

FIG. 2: IR SPECTRA OF PURE MONTELUKAST SODIUM SAMPLE

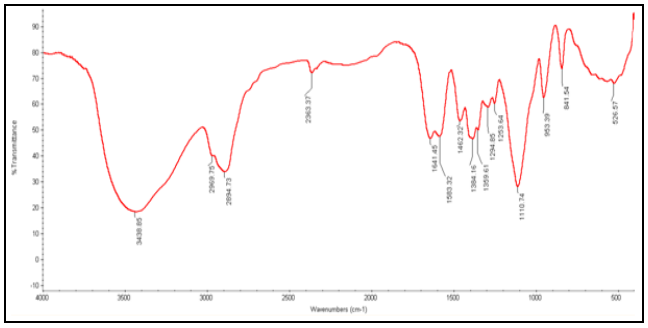

FIG. 3: IR SPECTRA OF MONTELUKAST SODIUM WITH HPMC K4M AND POLOXAMER 407

Clarity: Clarity of the formulation plays an important role not only from the point of view of appearance but is one of the important criteria for pharmaceutical elegance as well. Keeping this fact in mind the clarity of all the formulations was observed under ambient lighting with black and then white background. There were no foreign particles present in the formulation, the observations are shown in **Table 3**. The formulations F3, F4, F5 and F6 were excellent and clear where as F1 and F2 were hazy in appearance. Therefore, formulations F1 and F2 were rejected because of their hazy appearance and further evaluation parameters were performed for rest of the formulations.

TABLE 3: VISUAL CLARITY AND pH OF VARIOUS *IN-SITU* GEL FORMULATIONS

Formulation code	Appearance	Formulation code	pH
F1	Hazy	F3	5.60 ± 0.6
F2	Hazy	F4	5.50 ± 0.7
F3	Clear solution	F5	5.70 ± 0.94
F4	Clear solution	F6	5.72 ± 0.58
F5	Clear solution		
F6	Clear solution		

*Mean ± SD (n=3)

pH Determination: pH of the nasal formulation is one of the most important parameter in which the success of the dosage form depends. It is not only important from the point of view of stability and solubility but it also effects the nasal irritation. The pH of the dosages form should be such that it should remain stable at that pH and at the same time it should not cause any irritation to the nasal mucosa after the administration of the dosage form. All the formulations were diluted suitably with distilled water and then pH was determined using pre-calibrated pH meter; observations are mentioned in **Table 3**. All the formulations are within the pH range of 5.50 - 5.72 which is favorable to the pH range of nasal secretions, *i.e.* 5.5 - 6.5. Lysozyme, an enzyme secreted by nasal secretions plays important role in the destruction of certain bacteria by dissolving them. It has been found that the activity of lysozyme is greatly influenced by the hydrogen ion concentration of the medium and lysozyme activity is optimum at acidic pH. Under alkaline pH the lysozyme gets deactivated and nasal mucosa becomes susceptible to microbial attack. Therefore it is highly required to maintain the pH of the formulations in the physiological pH range for optimum lysozyme activity. In this respect also the prepared dosages form are suitable in maintaining the favorable pH range.

Gelation Temperature: The gelation temperature and the nature of gelation of prepared formulations are depicted in **Table 4**.

TABLE 4: GELATION TEMPERATURE AND GEL MELTING TEMPERATURE OF VARIOUS FORMULATIONS

Code	Gelation Temp. (°C) ± SD*	Gel melting Temp. (°C) ± SD*
F3	28 ± 0.9	80 ± 1.7
F4	25 ± 0.9	84 ± 0.6
F5	23 ± 1.4	87 ± 0.8
F6	21 ± 1.2	91 ± 1.3

*Mean ± SD (n=3)

Gelation temperature is the temperature at which liquid phase gets converted into gel phase at a particular temperature. From the above given table it can be clearly seen that the gelation temperature of prepared formulations decreases as the concentration of mucoadhesive polymer *i.e.* HPMC K4M increases. The reason attributed to this gelation temperature lowering effect of muco-adhesive polymer is increases in the viscosity of formulation with increase in concentration means higher number and volume occupied by the

micelles at low temperature. Gel melting temperature is also very important parameter because the success of the dosages form once after its application in the desired site depends upon its retention time at the applied site. Longer will be the time of contact of the dosages form at the site of absorption greater will be the bioavaibility of the dosages form. Data given in table number IV clearly revealed that as the concentration of polymer increases gel melting temperature also increases.

FIG. 4: PHOTOGRAPHIC EVIDENCE OF SOL TO GEL CONVERSION STUDIES

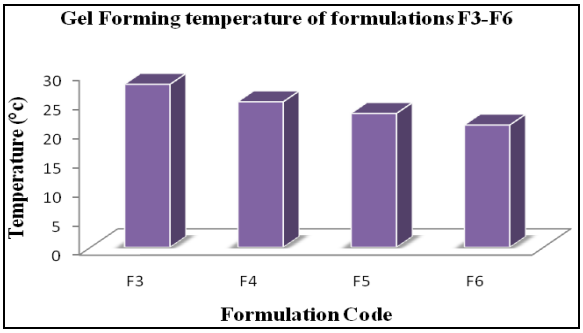

FIG. 5: GEL FORMING TEMPERATURE OF FORMULATIONS F3-F6

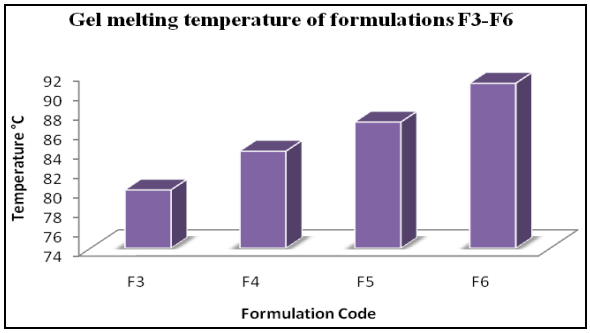

FIG. 6: GEL MELTING TEMPERATURE OF FORMULATIONS F3-F6

Drug Content Studies of Formulations: Drug content is one of the most important attribute of dosage form because it plays prime role in the determination of efficacy of the formulation and batch to batch uniformity thus makes a drug delivery system effective. Therefore, drug must be distributed uniformly throughout the dosage form. Drug content studies of formulations which were selected on the basis of their appearance were done. The results of the study are given in **Table 6**. The drug content in all the formulations was found to be in the range of 83 to 95%. The highest drug content was observed in the formulation F6 *i.e.* 95% followed by 93% in F5 as given in **Table 5.**

TABLE 5: ESTIMATED DRUG CONTENT OF VARIOUS *IN-SITU* GEL FORMULATIONS

Formulation	Drug Content (%) ± SD*
F3	87 ± 1.1
F4	83 ± 1.5
F5	93 ± 0.7
F6	95± 0.5

*Mean ± SD (n=3)

Gel Strength Studies: The gel strength of various formulations is acceptable within the range of 26-35 sec. The observations are shown in the **Table 6**.

TABLE 6: GEL STRENGTH OF VARIOUS *IN-SITU* GEL FORMULATIONS

Formulation	Gel Strength (sec)
F3	29
F4	28
F5	32
F6	35

Viscosity Studies: Optimum viscosity of the formulation plays an important role in the development of successful in situ nasal gel drug delivery system because viscosity is the deciding factor for ease of application of formulation in nasal cavity, in determining the residence time of formulation in nasal cavity and for the maintenance of integrity of the gel without dissolving and eroding quickly. In addition, the sol to gel conversion and drug release also depends in the viscosity.

Viscosity studies which are given in **Table 7** revealed that the formulation F4 had viscosity of 14,600cP and formulation F5 possessed viscosity of 33,300cP. A large increase in the viscosity of F5 and F6 can be seen from the data which is due to the increase in the concentration of polymer HPMC K4M AS given in composition **Table 1** in comparison to formulation F3 and F4 which was prepared by using low concentration of same polymer. Results showed that polymer HPMC K4M has profound effect in increasing the viscosity of the formulations.

TABLE 7: VISCOSITY OF VARIOUS FORMULATIONS MEASURED WITH BROOKFIELD RV DV-E VISCOMETER USING SPINDLE NO. 4 AT RPM = 30

Formulation	Viscosity (Cps) @ 30 RPM
F3	14,600 ± 0.12
F4	26,200 ± 0.17
F5	32,200 ± 0.86
F6	33,300 ± 0.94

*Mean ± SD (n=3)

***In-vitro* Drug Diffusion Studies:** All the formulations were subjected to dissolution studies using KC diffusion cell in PBS 6.4 as diffusion medium. The percentage cumulative drug release after 8 h of study was found to be 98.5005%, 96.608%, 89.772% and 86.530% for formulations F3, F4, F5 and F6 respectively, as shown in **Table 8**. The maximum cumulative drug release after 8 h of drug diffusion studies was shown by formulation F3 followed by F4 because of low concentration of drug release rate controlling polymer *i.e.* HPMC K4M. It can be clearly seen from the given drug release rate data of various formulations that the amount of this polymer play a significant and tremendous role in controlling the release characteristic of drug from the formulations because with the increase in the concentration of this polymer drug release rate decreases in a controlled fashion. Therefore, formulations F5 and F6 were found to release the medicament in a well controlled manner for prolonged period of time.

TABLE 8: *IN-VITRO* ZERO ORDER AND HIGUCHI DRUG RELEASE PROFILE OF VARIOUS *IN-SITU* GEL FORMULATIONS

Time (h)	√t	% Cumulative Release			
		F3	F4	F5	F6
0	0	0	0	0	0
0.25	0.5	12.27916 ± 0.21	9.846 ± 1.22	7.196 ±1.93	6.985 ± 0.42
0.50	0.70	25.2343 ± 0.13	20.338 ± 1.87	15.471 ± 1.23	12.751 ± 0.12
1	1	35.20439 ± 0.11	29.461 ± 1.90	24.384 ± 1.53	21.231 ± 0.22
2	1.414	44.28315± 0.41	38.262 ± 1.46	34.965 ± 1.93	30.435 ± 0.31
3	1.732	49.99003 ± 0.24	47.534 ± 1.33	42.789 ± 1.86	41.926 ± 0.16
4	2	62.22333 ± 0.27	59.599 ± 1.52	55.123 ± 1.21	53.632 ± 0.31
5	2.236	78.03589 ± 0.33	68.375 ± 1.97	63.054 ± 1.11	61.762 ± 0.14
6	2.449	89.41176 ± 0.31	78.367 ± 1.90	72.233 ± 1.36	69.952 ± 0.12
7	2.645	97.23031 ± 0.12	94.941 ± 1.88	86.486 ± 1.39	84.740 ± 0.43
8	2.828	98.5005 ± 0.14	96.608 ± 1.02	89.772 ± 1.14	86.530 ± 0.54

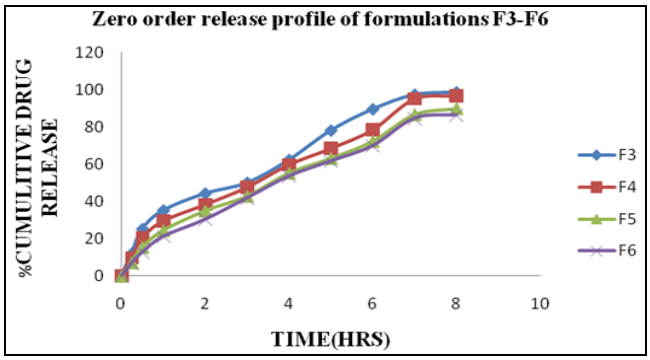

FIG. 7: PLOT OF % CR *vs.* TIME OF VARIOUS FORMULATIONS FOR ZERO ORDER KINETICS

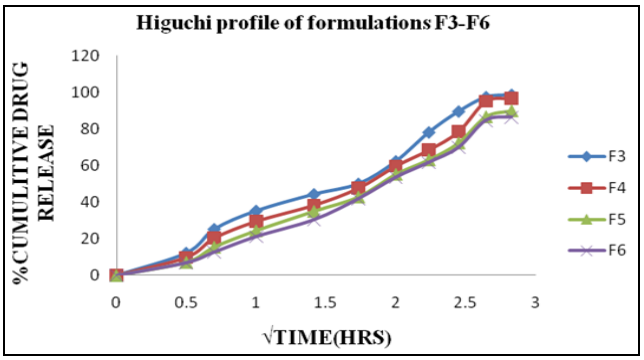

FIG. 8: PLOT OF % CR *vs.* √time OF VARIOUS FORMULATIONS FOR HIGUCHI KINETICS

In order to study the exact mechanism of drug release from the *in-situ* gel formulations the data obtained from various formulations were fitted to the kinetic models such as zero order, first order and Higuchi matrix kinetic models. The regression coefficients (R2) of the various formulations for the

zero order plots, first order plots and Higuchi plots are given in **Table 10**. From the above given table it can be clearly seen that in most of the cases the values of regression coefficient is very close to each other and quite overlapping which indicates the involvement of more than one release mechanism. Korsmeyer-Peppas model is widely used to identify the exact release mechanism when the mechanism is not well known or when more than one type of release phenomenon could be involved.

TABLE 9: *IN-VITRO* DRUG RELEASE PROFILE OF VARIOUS *IN-SITU* GEL FORMULATIONS FOR FIRST ORDER KINETICS

Time (h)	Log (% Amount remaining to be absorbed)			
	F3	F4	F5	F6
0	2	2	2	2
0.25	1.943	1.954	1.967	1.968
0.50	1.873	1.901	1.927	1.940
1	1.811	1.848	1.878	1.896
2	1.745	1.79	1.813	1.842
3	1.699	1.719	1.757	1.763
4	1.577	1.606	1.652	1.666
5	1.341	1.500	1.567	1.582
6	1.024	1.335	1.443	1.477
7	0.442	0.704	1.130	1.183
8	0.1759	0.530	1.009	1.129

Therefore for all the formulations the best fit model on the basis of 'n value' obtained from Korsmeyer and Peppas plots for each formulation was determined. The "n" value could be used to characterize different release mechanisms.

The "n" values for formulation are 0.542, 0.602, 0.645 and 0.708 and when compared with the standards for the diffusion release mechanism, it was found that all the formulations follow non-fickian diffusion release mechanism. This may be due to release from initially dry hydrophilic glassy polymer that swell in contact of water and become rubbery show anomalous diffusion as a result of rearrangement of macromolecular chain.

The thermodynamic state of polymer and the penetrate concentration are responsible for different type of diffusion mechanism. Among the different montelukast sodium *in-situ* gel formulations, the formulations F5 and F6 were selected as the best formulation on the basis of various evaluation parameters such as their clarity, gelation temperature, drug contents and *in-vitro* diffusion studies.

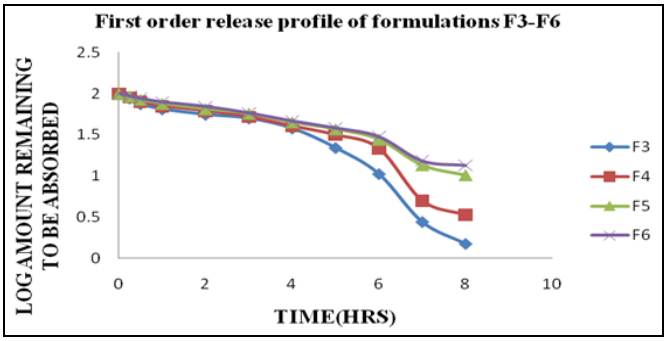

FIG. 9: PLOT OF LOG ARA *vs.* TIME OF VARIOUS FORMULATIONS FOR FIRST ORDER KINETICS

TABLE 10: RESULT OF REGRESSION COEFFICIENTS OF RELEASE DATA BY CURVE FITTING METHOD ON ZERO-ORDER, FIRST-ORDER AND HIGUCHI KINETIC MODEL AND THEIR DIFFUSION EXPONENT (*n*)*

Formulations	regression coefficients (r^2)			n value	Best fit model	Mechanism of release
	Zero Order	First Order	Higuchi			
F3	0.955	0.894	0.981	0.542	Higuchi model	non-fickian
F4	0.974	0.877	0.978	0.602	Higuchi model	non-fickian
F5	0.980	0.946	0.978	0.645	Zero order	non-fickian
F6	0.984	0.958	0.974	0.708	Zero order	non-fickian

CONCLUSION: The present study made an attempt to develop an *in-situ* gelling system for nasal drug delivery of water soluble anti-asthmatic drug montelukast sodium with a view of improving its bioavailability, reducing its dose and increasing patient compliance. Clear, accurately gelling solutions of montelukast sodium were obtained with poloxamer 407 and HPMC K4M polymers. Gelling temperature, drug content and pH of all the formulations remained uniform with low SD values. The *in-vitro* diffusion data of various formulations was analyzed by fitting the release data into various kinetics models **Table 10**. For the *in-situ* nasal gel formulations of montelukast sodium, it was observed that the *in-vitro* permeation profiles of all the different formulations of *in-situ* gels obeys Higuchi model for formulations F3 and F4 and zero order for formulations F5 and F6. The "n" values from the drug release experiment for the formulations F3, F4, F5 and F6 lies in the range of 0.5 to 0.7 which indicates the anomalous non-fickian type diffusion.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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