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Research Article

FORMULATION AND EVALUATION OF THERMOREVERSIBLE *IN-SITU* NASAL GEL OF METOPROLOL SUCCINATE

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ABSTRACT

Metoprolol Succinate undergoes hepatic first pass metabolism and hence it shows poor bioavailability. The objective of present research work is to improve bioavailability by formulating thermo reversible *in-situ* nasal gel. Formulation was developed to reduce the mucociliary clearance by using mucoadhesive polymer in gel, thereby increasing the contact time with nasal mucosa and hence improving the absorption of drug. The *in-situ* gelation was achieved by the use of pluronic F127, which exhibits thermo reversible gelation property and Sodium alginate was used as the mucoadhesive agent. Gels were prepared by cold technique method and characterized by Gelation Temperature, Permeation Studies, Histopathological Evaluation, pH, Drug Content, Rheological studies, Gel strength and drug polymer interaction study. The gelation temperature of all studied gel formulations were found in range of 28-40^{0}c. In in-vitro permeation study drug release was found in between 59.8-94.1% with K-peppas best fit model. pH of gel was in the range of 6.2-7.0 and drug content was found between 92.07-99.53 %. Rheological study of the formulations indicated that gels exhibited pseudoplastic rheology. Gel strength was found in range of 30-52 sec. FTIR study revealed no interaction between drug and polymer. Also histopathological study did not detect any change during *in-vitro* release study. This results indicates that bioadhesive thermo reversible nasal gels could be alternative route to avoid first-pass effect of Metoprolol Succinate and hence improvement in bioavailability.

Keywords: Thermoreversible Nasal gel, PF-127, Metoprolol Succiante, Gelation Temperature.

INTRODUCTION

Metoprolol succinate is a selective beta1-adrenoreceptor blocking agent, used in the treatment of hypertension[1]. Even though oral absorption is greater than 90%, only 40% of the orally administered drug reaches the systemic circulation due to hepatic first pass metabolism [2]. In this perspective, nasal administration of metoprolol succinate as intranasal gel could attribute to escaping the first-pass metabolism attendant with per-oral drug administration. Gel also offers decreased mucociliary clearance. The nasal application is the route of administration, which offer rapid onset of action, high absorption of small molecular weight hydrophobic drugs, relatively high bioavailability, avoidance of first pass effect and ease of administration by the patient.

Despite the many advantages offer by the nasal route, it still posses some drawbacks, most importantly, rapid mucociliary clearance which results into reduced absorption of the drug. To increase the nasal absorption of the drug it is necessary to improve the nasal residence time of the formulation. The problem can be removed by formulating in situ nasal gel. The formulation is in the liquid form at the room temperature but get gel consistency after instilling into the nasal cavity due to the nasal temperature. The nasal residence time can be improved by including the bioadhesive in the formulation. The use of mucoadhesive polymer can improve the nasal absorption of the drug by improving the nasal residence time of the formulation. Sodium alginate is used as the mucoadhesive polymer to improve the nasal residence time of the drug[3].

Poloxamer-407 or Pluronics F-127 is polyoxyethylene-polyoxypropylene triblock copolymer. At low temperature in aqueous solution, a hydration layer surrounds PF-127 molecule. However, when the temperature is increased, the hydrophilic chain of the copolymer becomes desolvated and it results in the breakage of the hydrogen bonding that had been established between the solvent and these chains. This phenomena favours hydrophobic interaction among the polyoxypropylene domain and leads to the gel formation. The concentrated solutions (20 -30%) are transformed from low viscosity transparent solutions at 5-8^{o}C to solid gel on exposing to body temperature [4]. By modulating the gelation temperature of different PF127 solutions, liquid bases for nasal use can be formulated that forms a gel in nasal cavity at body temperature resulting in enhancement of residence time in the nasal cavity. The most prominent advantage of the *insitu* gel over the silent gel is that it is fluid like prior to contact with nasal mucosa; a feature that offers the convenience of administration for patients since it can be easily instilled as a drop allowing accurate drug dosing[5]. The objective of present study is to develop an *insitu* gel of metoprolol succinate, with favorable gelation, rheological and release property. This may give patient friendly, needle free dosage form.

MATERIALS AND METHODS

Materials

Metoprolol succinate and Poloxamer-407 was obtained as a gift samples from M/s. Glenmark Pharmaceutical Pvt. Ltd., Nasik. Sodium Alginate, Propylene Glycol was obtained from M/s. Loba Chemie, Cochine.

Method

Preparation Of *In Situ* Gels[6, 7, 8]

Gel was prepared by the cold technique reported by the Schmolka. To the 10% solution of the drug in distilled water, propylene glycol 0.1% v/v was added. Benzalkonium chloride was added as the preservative in the concentration of the 0.1%. To this, sodium alginate was added in the concentration of 0.2%, 0.4%and 0.6% w/v. These solutions were then stirred until sodium alginate was completely dissolved in it. Further, poloxamer 407 (Pluronic F127) was added in the concentration of the 16%, 18% and 20% w/v with constant stirring. This resulting formulation was then kept overnight at 5^{0}C until clear liquid solution was formed.

Evaluation of formulations

Clarity

The clarity of various formulations was determined by visual inspection under black and white background.

pH of Formulation[9]

One ml quantity of each formulation was transferred to a beaker and diluted by using distilled water to make 25ml. pH of the resulting solution was determined using digital pH meter.

Drug Content

One ml of formulation was taken in 10ml volumetric flask, diluted with distilled water and volume adjusted to 10ml. One ml quantity from this solution was again diluted with 10ml of distilled water. Finally the absorbance of prepared solution was measured at 274nm by using UV visible spectrophotometer.

Measurement of Gelation Temperature[7,8]

Gelation Temperature, defined as the temperature at which the liquid phase makes the transition to a gel**,** determined by using method described by Miller and Donovan technique[11]. A 2ml aliquot of gel was transferred to a test tube, immersed in a water bath. The temperature of water bath was increased slowly and left to equilibrate for 5min at each new setting. The sample was then examined for gelation, which was said to have occurred when the meniscus would no longer move upon tilting the test tube to 90^0.

Viscosity Measurement[9,10]

The viscosity measurements were carried out by using Brookfield DV Pro-II model with spindle No.62.The instrument was equipped with the temperature control unit and the sample were equilibrated for 10 min before the measurement. The viscocity was measured against increasing shear rate. Measurement was taken at 4^0c and 34^0c respectively.

Table 1: Formulation of Insitu nasal gel of Metoprolol succinate

S. No.	Formulation	Conc.of drug in w/v	Conc.of PF127(w/v)	Conc.of Sod.alginate (w/v)	Conc.P.G.in (v/v)	Benzenealkonium chloride
1	F1	10%	16%	0.2%	1%	0.1%
2	F2	10%	18%	0.2%	1%	0.1%
3	F3	10%	20%	0.2%	1%	0.1%
4	F4	10%	16%	0.4%	1%	0.1%
5	F5	10%	18%	0.4%	1%	0.1%
6	F6	10%	20%	0.4%	1%	0.1%
7	F7	10%	16%	0.6%	1%	0.1%
8	F8	10%	18%	0.6%	1%	0.1%
9	F9	10%	20%	0.6%	1%	0.1%

Determination of Mucoadhesive Force[11,12]

The mucoadhesive strength of each formulation was determined by measuring the force required to detach the formulation from goat nasal mucosal tissue by using a modified chemical balance. A section of nasal mucosa was cut from the goat's nasal cavity and mucosal side was instantly fixed into each glass vial using a rubber band. The vials with nasal mucosa were stored at 37°C for 5 minutes. Then next vial with a section of mucosa was connected to the balance in inverted position while first vial was placed on a height adjustable pan. Fixed amount of sample of each formulation were placed onto the nasal mucosa of first vial. Then the height of second vial was adjusted so that mucosal surfaces of both vials come in intimate contact. Two minutes contact time was given to ensure intimate contact between tissues and the sample. Then weight was increased in the pan until vials got detached. The bioadhesive force, expressed as the detachment stress in dyne/cm^2, was determined from the minimal weights that detached the tissues from the surface for each formulation using the following equation.

$$\text{Detachment stress (dyne/cm}^2) = m \times g / A$$

Where, m =Weight required for detachment of two vials in gm

g = Acceleration due to gravity [980cm/s^2]

A = Area of tissue exposed

The nasal mucosa was changed for each measurement. Measurements were repeated six times for each of the gel preparations.

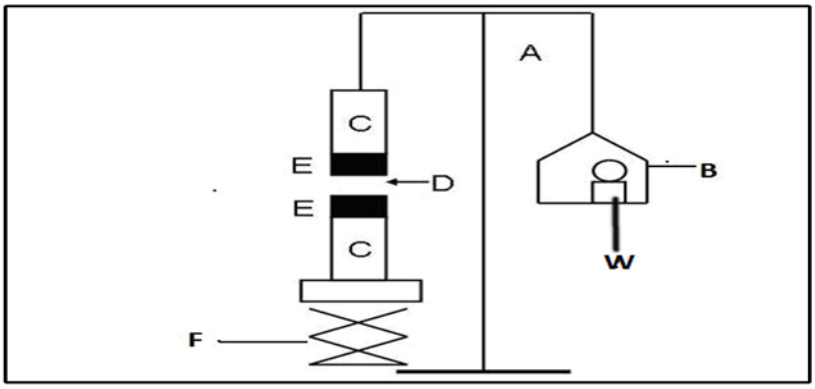


Fig. 1: Modified balance for mucoadhesion study

A: Modified balance, **B**: Weighing pan, **W**: Weight, **C**: Glass Vial, **D**: Poloxamer Gel, **E**: Nasal Mucosa, **F**: Height adjustable Pan.

Gel strength determination[13]

A sample of 50g of the nasal gel was put in a 100 ml graduated cylinder and gelled in a thermostatically controlled water bath at 37°C. A 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 by the time in seconds required by the weight to penetrate 5 cm into the gel.

Ex-vivo Drug Release[14,15]

The use of natural membranes is very important to predict the real drug release characteristic. So in this experimental section of the study goat nasal mucosa was chosen for the following reasons. It is easy to obtain goat nasal mucosa from slaughterhouses. The area of the respiratory mucosa in the snout is relatively large, and this makes it possible to obtain more material from each animal. It also

makes it easier to handle the tissue and increases the chance of getting intact, unstrained pieces of mucosa. Most importantly, it is of ethical advantage as sacrifice of animals for only a small piece of the animal is avoided. Fresh nasal tissue was removed from the nasal cavity of goat obtained from local slaughterhouse. The mucosa was stored in normal saline with few drops of gentamycin sulphate injection to avoid bacterial growth. After the removal of blood and bony cartilage from the mucosal membrane it becomes ready for use. The tissue was inserted in the nasal diffusion cell with permeation area of 0.785 cm^2. Seven ml of the phosphate buffer with pH 6.4 was added to the acceptor chamber. Gel containing drug equivalent to 10mg was placed in donor compartment. At predetermined time, sample was withdrawn from the acceptor compartment and suitably diluted to measure absorbance at 274nm.

Analysis of drug release data[16,17]

The data obtained from the *in vitro* release experiments were analyzed by the following commonly used exponential equation:

$$\frac{Mt}{M} = kt^n$$

$$\log \frac{Mt}{M} = \log k + n \log t$$

Where, *Mt/M* - the fraction of released drug at time t; k - release constant. n - release exponent indicative of the release mechanism.

When n is equal to 0.5, the drug is released from the polymer with a Fickian diffusion mechanism (Higuchi model). If 0.5 < n < 1 this indicates anomalous or non-Fickian release, while if n = 1 this indicates zero-order release.

Drug-Polymer Interaction Study by FTIR[18]

FTIR Spectra was obtained on SHIMADZU – 8400S FTIR Spectrometer. Samples were prepared in KBr disks (2mg sample in 200mg KBr). The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}.

Histopathological study[19]

Fresh nasal tissue was removed from the nasal cavity of goat. The tissue was inserted in the nasal diffusion cell. Phosphate buffer (pH6.4) was then added to the acceptor chamber. Then gel was applied to the mucosa and left for the 12 h. Another control mucosa was also setup without using the drug. After 12h each piece of mucosa was carefully removed from the diffusion chamber, rinsed with phosphate buffer. The mucosa sample was then fixed in the 1% formaldehyde solution for 6h. The samples were then incubated in methyl benzoate for 24 h in order to soften the material. The samples were immersed first into benzene:paraplast (1:1) mixture, and then into pure paraplast for 6 h in a vacuum oven and embedded in paraplast. The blocks were cut in sections of 5-6µm in thickness with a rotary microtom. The section was stained for the light microscope examination.

RESULT AND DISCUSSION

Clarity, pH and Content Uniformity

The visibility of all the formulation was found to be clear. The pH of all formulation was in the range of 6.2 to 7.0 which is the normal pH range of nasal mucosa[20]. The content uniformity was found to be in the range of 92-100% (Table 2).

Gelation Temperature

Gelation temperature range suitable for nasal gel is 32–35°C[21]. As the concentration of the poloxamer-407 (PF-127) and Sodium alginate were increased gelation temperature was decreased. Increasing the concentration of PF-127 to 20 %(w/w) causes gelation in the temperature range of 28–34^{0}C. The temperature-dependent gelation of PF-127 solutions could be explained by configuration change. PF-127 molecules exhibit a well-arranged zigzag configuration. With increasing temperature, the zigzag configuration of poloxamer may be transformed into a close-packed meander configuration, forming a more close-packed and more viscous gel[5]. As the concentration of PF-127 increases, the gel structure becomes more closely packed with the arrangement in the lattice pattern. Gelation temperature lowering effect of mucoadhesive polymer could be explained by its ability to bind to Polyethylene oxide (PEO) chains present in the PF-127 molecules promoting dehydration and causing an increase in entanglement of adjacent molecules with more extensive intermolecular hydrogen bonding[22]. (Table 2).

Bioadhesive force

It is noted that variable sodium alginate and PF-127 both have effect on bioadhesive strength (Table 2). It shows that as the concentration of PF-127 and Sodium alginate increases, the bioadhesive strength increases. The mechanism of bioadhesion can be attributed to hydrogen bonding between gel formulation and oligosaccharide chains of mucosal membrane via carboxyl groups of Sodium alginate. The PF-127 has a bioahdesive force due to binding of the hydrophilic oxide group to oligosaccharide chain[23]. Nasal gel formulation must have the balanced bioadhesive force.

Table 2: Evaluation parameters of formulation

Formulation	pH	Gelation Temp (^{0} c).	Gel Strength (Sec.)	Dug Content	Bioadhesive strength (dy/cm^2)	% release of drug at 6 hr.
F1	6.7±0.37	39.5±3.54	30±2	98.57±3.36	2371.96±35.12	94.1±3.41
F2	6.8±0.12	35±4.21	38±3	95.26±3.05	3495.52±56.23	84.2±4.72
F3	6.5±0.25	32±2.79	45±5	92.07±1.25	4993.60±65.27	75.8±5.78
F4	6.4±0.29	37±4.63	32±4	96.71±3.54	3121.00±46.75	86.3±3.65
F5	6.7±0.45	33.6±3.37	41±5	97.23±4.15	3452.20±51.70	79.1±4.82
F6	7.0±0.78	30±2.68	48±6	99.53±5.24	5243.28±87.01	63.2±4.53
F7	6.2±0.94	36±5.76	35±3	96.42±2.79	3994.88±76.4	78.1±5.41
F8	6.5±0.14	33±3.68	44±6	98.64±3.48	4494.24±47.81	68.7±6.10
F9	6.9±0.34	28±2.49	52±8	97.49±3.98	5617.8±63.72	59.8±6.37

Rheological Studies

The shear rate viscosity was measured at 4^{0}C and 37 ^{0}C.Table 3 and 4 shows viscosity measurement at temperature 4^{0}C and 37 ^{0}C respectively. Results revealed that the viscosity was increased as temperature increased (Table 5). Fig.2 shows as the viscosity of the gels decreased with increasing shear rate as they were pseudoplastic. The viscosity was directly dependent on the polymeric content of the formulations. As the concentration of the polymer increased the viscosity of the formulation increased.

Table 3: Viscosity in cP at 4⁰ C temperature

Shear Rate	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	1185±46.21	1220±39.04	1340±52.97	1198±31.74	1233±47.75	1370±55.74	1212±45.22	1257±34.88	1399±60.93
1	807±23.51	913±35.06	1085±24.16	846±30.15	936±21.56	1118±32.44	827±19.45	974±30.42	1140±24.17
2	648±20.12	708±24.98	860±21.56	685±21.23	727±30.78	922±22.34	673±29.03	753±23.15	942±32.14
2.5	552±19.14	595±18.14	718±22.47	590±16.76	612±19.32	764±25.46	569±15.94	646±22.45	796±31.62
4	489±15.43	500±14.67	637±20.98	505±15.78	509±15.45	668±23.44	493±13.36	519±12.03	703±15.66
5	377±12.11	402±17.46	526±15.67	393±13.44	414±14.76	535±17.47	385±14.38	434±18.67	610±20.97
10	275±10.39	318±14.82	443±17.49	290±11.20	330±13.45	459±18.31	290±10.49	356±12.59	501±14.19
20	179±8.84	205±8.41	329±11.98	201±7.51	225±8.27	340±12.63	193±7.84	242±13.64	389±13.87
50	98±2.54	111±3.94	215±5.72	115±3.29	117±4.13	227±6.81	115±3.89	146±4.70	275±8.57
100	56±1.26	76±1.89	122±3.56	70±1.29	85±2.91	141±4.26	65±1.05	92± 2.17	155±5.01

Table 4: Viscosity in cP at 34⁰C

Shear rate	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	2699±85.59	2781±89.61	2909±91.39	2707±89.71	2795±86.43	2697±83.81	2727±87.53	2811±95.42	3032±97.97
1	1980±75.84	2040±78.93	2122±75.79	1985±71.94	2102±74.96	2166±72.81	2117±79.86	2177±71.91	2264±78.9
2	1650±65.98	1740±63.81	1791±67.48	1691±68.47	1761±69.24	1819±70.99	1743±62.71	1785±55.73	_
2.5	1392±45.34	1170±35.98	1710±51.98	1409±56.49	1735±48.31	_	1417±53.87	1748±57.83	_
4	1215±33.65	1695±53.82	_	1327±36.83	1697±48.83	_	1298±35.72	_	_
5	1044±29.74	_	_	1105±35.12	1595±48.52	_	1155±32.81	_	_
10	740±15.79	_	_	791±7.31	_	_	805±8.38	_	_
20	562±4.72	_	_	601±6.91	_	_	617±8.44	_	_
50	416±3.73	_	_	487±5.82	_	_	505±6.38	_	_
100	_	_	_	391±3.61	_	_	_	_	_

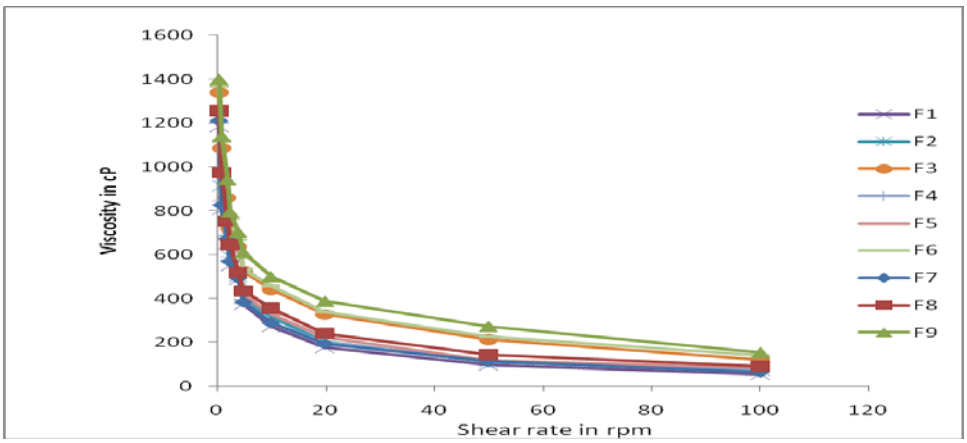


Fig. 2: viscosity of gel at different shear rate at 4⁰C temperature

Table 5: Comparison of viscosities at two temperature (shear rate 0.5rpm)

Formulation	Viscosities at 4⁰C	Viscosities at 34⁰C
F1	1185±46.21	2699±85.59
F2	1220±39.04	2781±89.61
F3	1340±52.97	2909±91.39
F4	1198±31.74	2707±89.71
F5	1233±47.75	2795±86.43
F6	1370±55.74	2697±83.81
F7	1212±45.22	2727±87.53
F8	1257±34.88	2811±95.42
F9	1351±60.93	3032±97.97

Gel strength

The gel strength was found to be affected by concentrations of PF-127 and the level of sodium alginte (Table2). The gel strength value between 25 to 50 seconds is considered sufficient[24]. An increase in gel strength was observed with all gel formulations, the level of sodium alginate have little increasing effect on the gel strength while the level of the PF-127 have promising effect on the gel strength. The gel strength of all formulation was found in the suitable range of 30-50 sec except formulation F9 which showed at 52 sec.

***Ex-vivo* Drug Release**

The release profile of formulation F1, F2 and F3 is shown in (Fig. 3). In these formulations the level of Sod. Alginate is similar while that of PF-127 level is increasing. Since the rate of drug release decreased as the concentration of PF-127 increased, it is apparent

that the gel structure functions as an increasingly resistant barrier to drug diffusion. The mechanism for such enhanced resistant could be because of reduction in the number and dimension of water channels and also to increased drug solubility[25]. The same release profiles were observed with the formulation F4, F5, F6 and formulation F7, F8 and F9. The lower release rate with higher PF-127 concentration was in agreement with the Lauffer's diffusion theory in gels[26]. When we compare formulation F1 with the formulations F4 and F7 (Fig. 4) or F2 with F5and F8 or F3 with F6 andF9, we notice that there is decrease in drug release pattern and which can be concluded to increasing level of the sodium alginate having retarding effect on release.

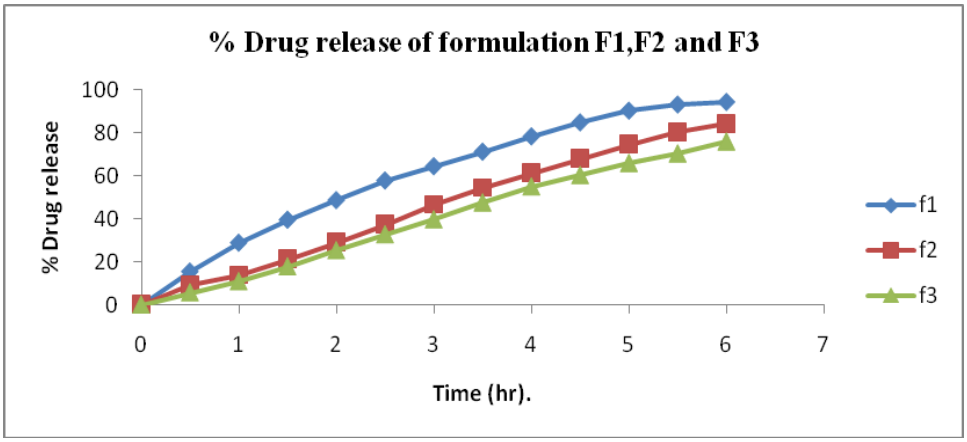


Fig. 3: Plot of % Drug release of formulation F1,F2 and F3.

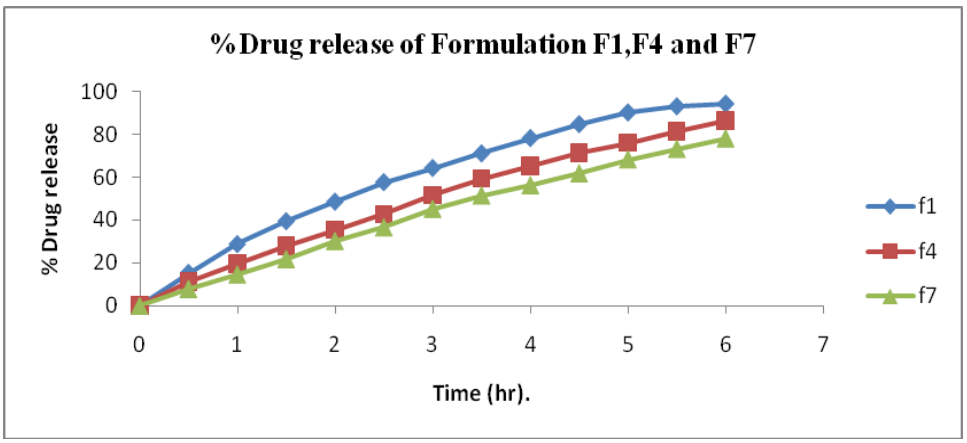


Fig. 4: Plot of % drug release of formulation F1,F4 and F7.

Analysis of drug release

Study of the release kinetics shows that the formulations F3 to F9 follow the korsemeyer peppas equation while F1 follows higuchi model and F2 follows the zero order equation. All formulations follow nonfickian equation as their value of release exponent more than 0.5. The F1, F2, F4, F5, F7 and F8 have values in between 0.5 to 1.0 while the F3, F6 and F9 have the value of n more than 1.0. This indicates that as the concentration of the PF-127 increases it starts to follow nonfickian anomalous. (Table 6)

Drug Polymer Interaction Study

FTIR Studies were done which suggest incompatibility between the drug and different polymers (Fig.5) The studies suggest that the drug and different polymers are compatible to each other.

Table 6: Kinetic values obtained from different plots of the formulations

Formulation	Zero Order plots (r)	First order plots(r)	Higuchi plots(r)	Hixon Crowell	Kores-Meyer peppas	
					R	n
F1	0.965	0.971	0.996	0.891	0.991	0.7
F2	0.994	0.969	0.976	0.953	0.990	0.9
F3	0.995	0.983	0.963	0.940	0.997	1.0
F4	0.990	0.976	0.992	0.935	0.998	0.8
F5	0.985	0.991	0.993	0.915	0.994	0.9
F6	0.995	0.983	0.968	0.956	0.998	1.1
F7	0.993	0.984	0.990	0.934	0.997	0.9
F8	0.988	0.995	0.987	0.922	0.991	1.0
F9	0.996	0.963	0.968	0.956	0.997	1.1

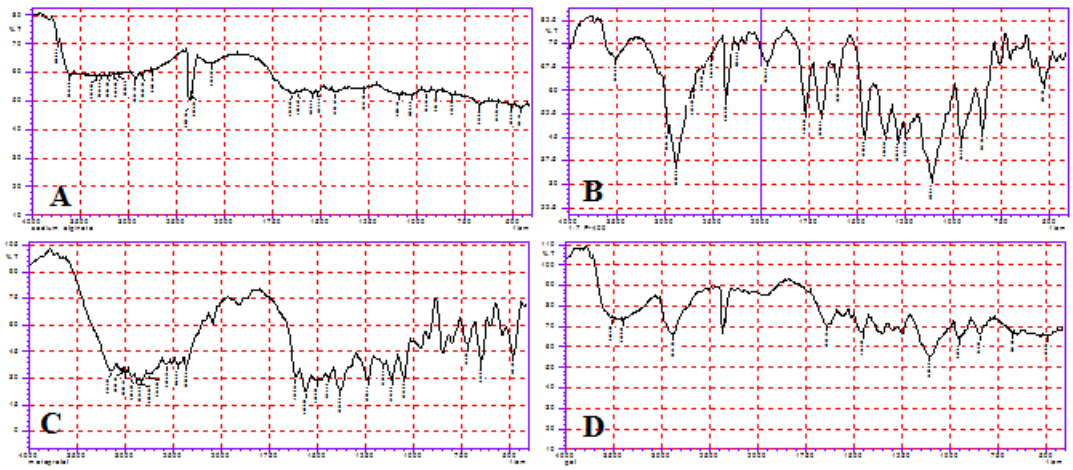
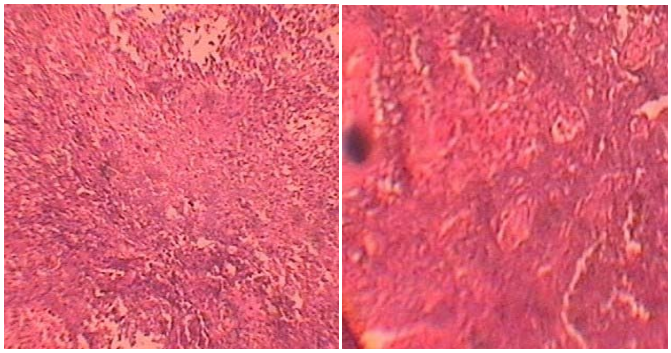


Fig. 5: FTIR Spectra of (A) Sodium Alginate, (B) PF-127, (C) Metoprolol Succinate, (D) Mixture



Untreated **Treated**

Fig. 6: Light photomicrograph of the cross-section of the goat nasal Mucosa treated with nasal *in situ* gel.

Histopathological study

Photomicrographs of nasal mucosa after the permeation studies were observed for histopathological study with the phosphate buffer treated mucosa (Fig 6). The section of mucosa treated with optimized formulation showed no degeneration of nasal epithelium along with no signs of erosion.

CONCLUSION

It is concluded that the developed PF-127 and sodium alginate based bioadhesive gelling systems of Metoprolol Succinate were able to provide longer residence properties and hence better bioavailability of the drug. Formulation in the nasal cavity exhibited prolonged drug release characteristics with almost negligible toxic effects to nasal mucosa. Thus, bioadhesive gelling systems can be considered as a viable alternative for systemic medication of drugs through nasal route. Among all formulation prepared F2 is the best optimized formulation with respect to its evaluation parameters like gelation temperature, mucoadhesive strength and the drug release.

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