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Formulation Development and Evaluation of *In-Situ* Nasal Gel of Glimepiride

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Abstract
To developed In-situ nasal gel of Glimepiride for sustained release and avoid metabolism by first pass effect in the treatment of diabetic mellitus type II. The In-situ nasal gel of Glimepiride was prepared by using HPMC K-100 M, Poloxamer 188 as a gelling agent and xanthan gum as a sustained relesed agent. The formulation was examined for clarity, pH, gelling temperature, Gelling time, gel strength, spreadability, viscosity, rheological study, drug content, mucoadhesive study and In vitro drug diffusion kinetics. All the prepared formulation was clear solution. Prepared formulations were shown pH between 5.5±0.81 to 6.1±0.97. The nasal mucosa can tolerate the above mention pH of the formulation. Gelling temperature was found between 33.06±1.27 to 37.06±0.54 °C. The gelling time was found between 6.6±1.11 to 24.6±0.82 Sec. Gel strength was found between 17.3±1.28 to 58.6±1.53 Sec. Glimepiride content was obtained in the range between 98.10±10.07 to 98.83±0.92%. The drug release of the all of formulation was found between 43.78±0.21 to 61.42±0.24 %. The F4 formualtion showed a drug diffusion 43.78±0.21% in 6 hrs.,indicated sustained release formulation. The higher concentration of HPMC K-100 M increased the mucoadhesive fraction on goat nasal mucosa. The best formulation F4 provide sustained In-vitro release of the drug over extended period of 6 hrs. The In-situ nasal gel of glimepiride was developed to overcome the first pass metabolism, reduce the dosing frequency and improve patient compliance.

Keywords
Glimepiride, Goat nasal mucosa, *In-situ* nasal gel.

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INTRODUCTION
Gels are defined as a substantially dilute cross-linked system, which exhibit no flow in the steady- state [1]. In-situ gel formation is a liquid formulation that generates a solid or semisolid depot after administration and shifts to a gel phase when exposed to physiological conditions. Both natural and synthetic polymers can be used for the production of In-situ gels [2, 3]. After administration of In-situ nasal gel formulation are sol form converts to gel form [4]. The factors regulating of the In situ nasal gel formation process include micro-environmental temperature, changes in pH, presence of ions, ultraviolet irradiation and polymers [5]. The nasal mucosa is one of the major routes of

administration to achieve a rapidly and higher level of drug absorption [6, 7].

Diabetes's mellitus continues to increase in term of the number affected and insignificance worldwide and is a growing burden with regard to public health. It is reported the 285 million people are worldwide with a diabetic in 2010 and this run is to is predicted to raise by 439 million by 2030 [8]. Glimepiride a third-generation sulfonylurea drug is helpful for the cure of type II diabetic mellitus [9]. Glimepiride under the class II as per the biopharmacecutical classification [10]. Glimepiride have several side effect for the oral dosage form such as severe skin infection, hypersensitivity reaction, low blood cells, low sodium level, headache, dizziness, weakness, nausea and flu symptoms [11]. The nasal route has been selected because nasal mucosa has a rich supply of blood, large surface area and porous endothelial membrane. Nasal delivery of drugs offers many advantages over other delivery route [12].

The objective of present work to dvelop In-situ nasal gel of Glimepiride as a sustained released as well to avoid first pass metabolism in treatment of diabetics mellitus type II.

MATERIALS AND METHODS

Materials

The gift sample of glimepiride was obtained from Ajanta pharma, Auranagabad, India. Hydroxypropyl methylcellulose K-100 M (HPMC K-100 M) was obtained from was pallav chemicals, poloxamer 188 was obtained from pallav chemicals, xanthan gum was obtained from vishal chemicals, Polyethylene glycol 400 was obtained from vishal chemicals, benzoalkonium chloride was obtained from pallav chemicals, mannitol was obtained from vishal chemicals and methanol was obtained from pallav chemicals.

Methods-

Drug excipients compatibility study-

FTIR spectrum of Glimepiride and physical mixture-I were studies by using FTIR spectrophotometer (Alginate technology) over the wave number range 4000-500 cm^{-1}. Physical mixture-I containing Glimepiride, HPMC K-100 M, mannitol, xanthan gum benzalkonium chloride. Physical mixture was prepared by mixing drug and excipient in 1:1 ratio. Similar study was carried out for physical mixture-II containing Glimepiride, poloxamer 188, xanthan gum, mannitol and benzalkonium chloride [13]. The study was performed to interpret drug excipients compatibility.

Preparation of In-situ nasal gel of Glimepiride – The Glimepiride was dissolved 10 ml of methanolic PBS pH 6.8. The solution was mixed by constant stirring. The mannitol, PEG 400 and benzalkonium chloride were added in above solution. The polymeric solution was prepared separately The HPMC K 100 M or poloxamer 188 and xanthan gum was dissolved in fresh prepared distilled water and mixed with the above mixture solution. The final solution was stirred for 60 min. Using magnetic stirrer and Phosphate buffer pH 6.8 as added to above solution. The final volume of solution was making up to the 25 ml with distilled water [14]. Developed formulation are show in Table No. 1.

Table No.1 Compositions of different *In-situ* nasal gels of Glimepiride.

Composition	F1	F2	F3	F4	F5	F6	F7	F8
Glimepiride (%w/v)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Hydroxypropyl methyl cellulose K-100 M (%w/v)	0.2	0.4	0.6	0.8	-	-	-	-
Poloxamer 188 (%w/v)	-	-	-	-	12	14	16	18
Xanthan gum (%w/v)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Polyethylene glycol 400 (%w/v)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Mannitol (%w/v)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Methanol (%w/v)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Phosphate buffer solution pH 6.8 (%w/v)	5	5	5	5	5	5	5	5
Distilled water (ml;QS)	25	25	25	25	25	25	25	25

Evaluation of In-situ nasal gels-

Clarity- All the prepared formulations were determining, and it was graded as turbid +, clear ++ and very clear +++ under the black and white background by visual inspection [15].

pH measurement – The prepared formulation was determined by using digital pH meter. 1 gm prepared In-situ nasal gel was dissolved in 100 ml of fresh prepared distilled water and store for 2 hr. pH measurement of each prepared formulations were done in triplicate value were calculated [16].

Gelling temperature- The gelling temperature was determined by the insertion of test tube, containing the enough quantity of the prepared solutions, in a water bath at 4 °C. The temperature of the water bath was increase gradually at a stable value of 1 °C for every 2 min [17].

Gelling time- The 2 ml of sample was transfer in 10 ml of test tube. Tube was sealed with aluminum foil. The sealed test tube was kept in water bath at 37 °C. Then the test tube was placed horizontally to determine the gelling time of prepared formulations [18].

Determination gel strength- The 50 gm of sample were placed in 100.0 ml measuring cylinder. Gelation was obtained by placing the formulation in a water bath at 37 °C. The of strength of the formulations were determined by the weight of 35 gm sample were placed in surface of gel and measure the how many time are taken to sink 5 cm in the gel [19].

Viscosity- The viscosity study was performed by using Brookfield viscometer Model-DV + pro. Spindle no.6 was used and rotated at 0.5 rpm. at 37±1 ºC [20].

Rheological study- The rheological study of In-situ nasal gel formulation was determined using Brookfield viscometer Model-DV-II + pro. The spindle no.6 was rotated at 0.5-100 rpm and readings in triplicate noted [20].

Spreadability Method-I Parallel plate method- wooden block and glass slide apparatus apparatus was used for determination of spredability. By this method, spreadability was measured on the basis of 'Slip' and 'Drag' characteristics of gels. A ground slide was fixed on this block and 1gm of gel sample was placed on this ground slides.gel was sandwiched between ground and upper placing glass slides with the provide hook. 1 kg weight was place in upper glass slide for 5 mi. To remove the air and make uniform layer in between both slides. The excess gel was discarding from the edges of both slides. expel air and provide a uniform film of the gel between the slide. The top plate was then subjected to pull of 5 gm. With the help of string attached to top slide to cover a distance of 7.5 cm be noted and calculated the spreadability by using the following equation. Measured the spreadability of formulations was done in the triplicate and average value was calculated [21]

$$S = \frac{WL}{T}$$

Where,

S= Spreadability, W= weight, L= length and T= time

Spredability method-II Arvout-Grand et. al. method- Spreadability of the various gel was determined by pressing 1g of the sample in between horizontal plates 20×20 cm and 125 gm of weight was place in uppper side of glass slide. Then measured the diameter of spread after 1 min. The spared diameter was show less than 50 mm of diameter it was indicate semi-stiff type of gel. The spredability diameter was show between 50-70 mm it was indicated semi-fluild type of gel [22].

Drug content- 100 mg prepared In-situ nasal gel was dissolved in 100.0 ml of ethanolic PBS pH 6.8 solution. The gel solution was shaken for 2 hr by using mechanical shaker for drug are completely dissolved. The gel solution was filtered and determine the drug content by using UV- Visible spectrophotometer at 224 nm methanolic PBS pH 6.8 was used as blank [23].

Determination of Mucoadhesive Study-

Tissue preparation: - The fresh goat nasal mucosa was obtained from local slinter house after the goat was sacrificed. Nasal mucosa was carefully removed using forceps, scale and surgical seizure and kept in cold phosphate buffer pH 6.8 The mucosal tissue was immediately immersed in Ringer's solution. The freshly excised nasal mucosa was then used for mucoadhesion study [24]

Mucoadhesive study- The fresh goat nasal mucosa was tide on glass slide with thread and the glass slide was attached with clamp at 30° angle. 100 ml beaker put below the glass slide. Then continuously washing with the blank solution (80% of phosphate buffer pH 6.8 and 20% of methanol) 1ml per min. dropwise on the goat nasal mucosa, the time interval was taken 30 min, 1, 1.5, 2 and 3 hr. Then the collected solution was scanned using UV-Visible spectrophotometer. (Lab India UV 3000+) and UV- Visible spectrum was reported. Presence of drug in the collected samples was noted as mucoadhesion time of gel preparation.

***In-vitro* diffusion by using goat nasal mucosa –** In-vitro diffusion studies of the formulation was determined by using Franz- diffusion cell. The biological part used as a goat nasal mucosa was mounted in between the donor and receptor compartments. The methanolic phosphate buffer

solution pH 6.8 was transferred in receptor compartment at 37 °C ± 1° C. The solution was continuously stirred. The 0.1 gm of prepared nasal gel was applied on goat nasal mucosa. The 1 ml sample are withdrawn at determine time interval (0, 0.5, 1, 1.5,2 and 3 hr. Then fulfill the receptor compartment by using methanolic phosphate buffer pH 6.8. And dilution was prepared by using methanolic phosphate buffer pH 6.8 and absorbance are taken at 224 nm [25] by using UV-Visible spectrophotometer (Lab India UV 3000+) The zero order, first order, higuchi and Korsmeyer's-Pappas was plots [26, 27].

Results-

Compatibility study-

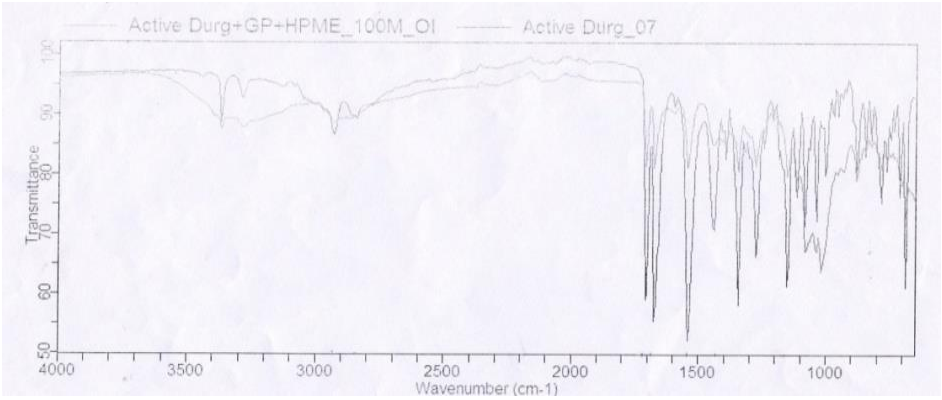

Fig. No. 1 FTIR spectrum of pure Glimepiride and physical mixture I

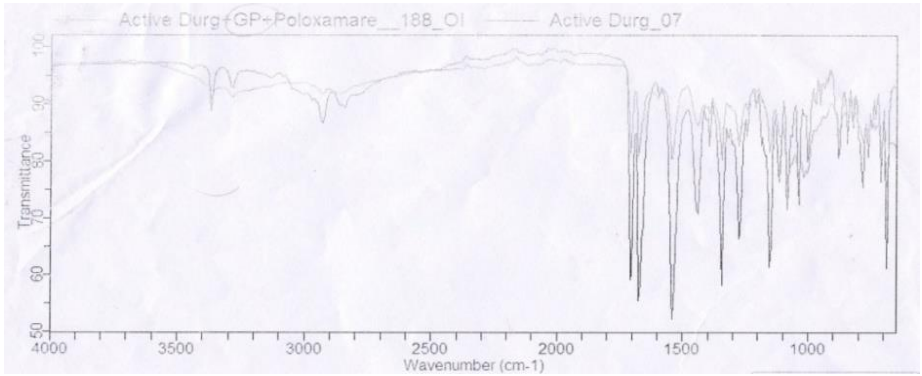

Fig. No. 2 FTIR spectrum of pure Glimepiride and physical mixture-II

Table No. 2 Evaluation of *In-situ* nasal gel of Glimepiriide for clarity, pH, gelling temperature and gelling time.

Formulation Code	Clarity	pH	Gelling temperature (°C)	Gelling Time (S)
F1	++	5.8 ± 0.39	34.3 ± 1.26	15.3 ± 1.34
F2	++	5.8 ± 0.90	34.0 ± 1.34	12.3 ± 1.22
F3	++	5.5 ± 0.81	34.6 ± 0.83	08.6 ± 1.65
F4	++	5.5 ± 0.87	33.6 ± 1.27	06.6 ± 1.11
F5	++	5.9 ± 0.97	36.3 ± 1.34	24.6 ± 0.82
F6	++	6.0 ± 0.75	37.6 ± 0.54	22.0 ± 1.64
F7	++	6.1 ± 0.95	36.6 ± 1.21	17.6 ± 1.34
F8	++	6.1 ± 0.47	36.0 ± 1.45	15.6 ± 1.24

Table No. 3 Evaluation of *In-situ* nasal gel of Glimepiride for gel strength, viscosity, spreadability and drug content

Formulation code	Gel strength (S)	Viscosity (cp) At 0.5 Rpm	Spreadability		Drug content (%)
			Method 1 (gm.cm/s)	Method II (mm)	
F1	51.3 ± 1.23	107 ± 54.12	9.1 ± 1.11	63 ± 1.29	98.33 ± 0.87
F2	52.2 ± 1.64	120 ± 64.17	8.4 ± 1.82	59 ± 1.07	98.55 ± 0.74
F3	55.8 ± 1.17	142 ± 48.89	7.6 ± 1.64	54 ± 0.98	98.22 ±0.72
F4	58.6 ± 1.53	200 ± 62.88	7.3 ± 0.91	52 ± 0.91	99.83 ± 0.92
F5	17.3 ± 1.28	87 ± 54.72	9.6 ± 0.97	68 ± 1.11	98.99 ± 0.45
F6	22.8 ± 1.60	100 ± 48.88	9.2 ± 1.48	66 ± 1.20	98.10 ± 1.07
F7	29.3 ± 1.11	124 ± 68.11	8.9 ± 1.74	63 ± 0.98	98.16 ± 0.67
F8	33.6 ± 1.21	160 ± 34.60	8.7 ± 1.45	61 ± 0.89	98.89 ± 0.89

Rheological study-

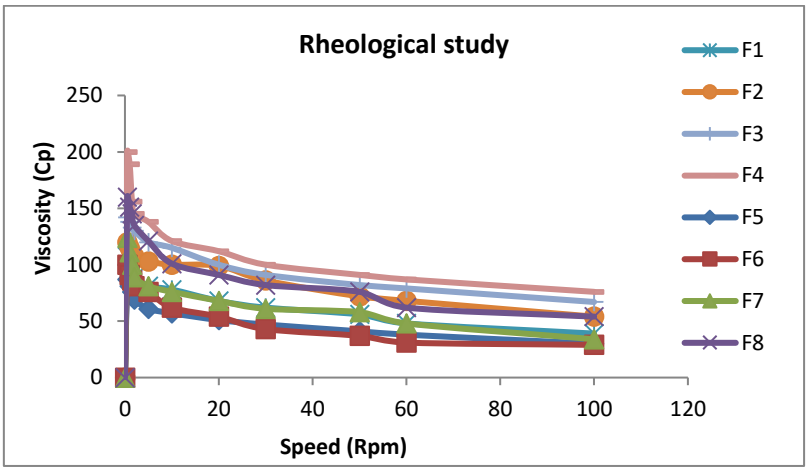

Fig. No.3 Rheological profile of F1 to F8 formulation.

Table No.4 Mucoadhesive study of F4 Formulation by using Goat Nasal Mucosa.

Sr. No.	Time (hrs)	Absorbance (nm)
1	0.5	0.628
2	1	0.516
3	1.5	0.209
4	2	0.107
5	3	0.007

UV Spectra's of F4 Formulation for mucoadhesive study.

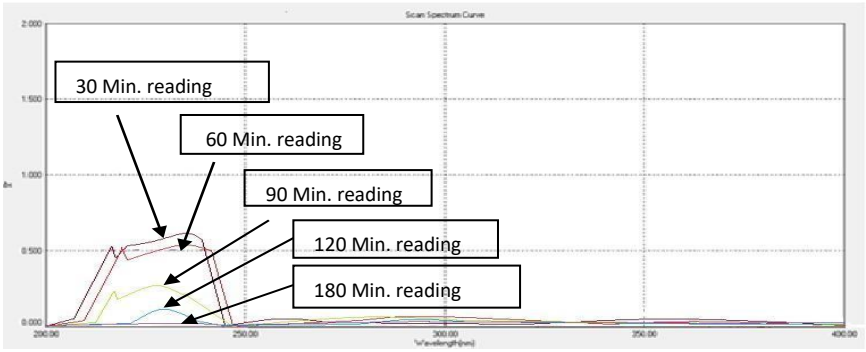

Fig. No.4 UV Spectra's of F4 Formulation for mucoadhesive study.

In-vitro drug diffusion kinetics study-

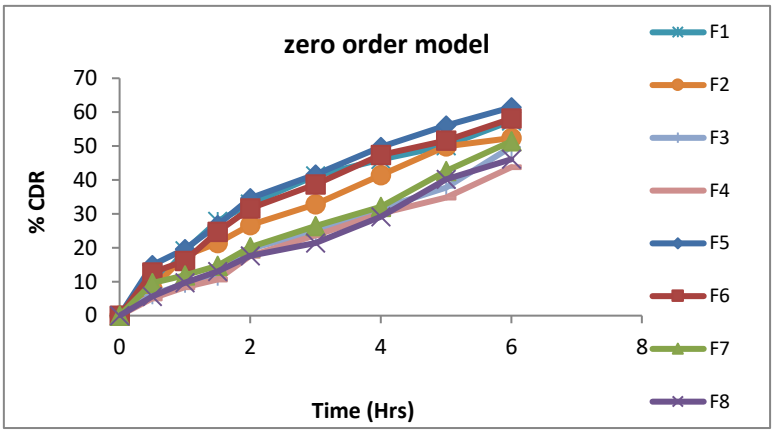

Fig.No.5 Zero order drug release kinetics

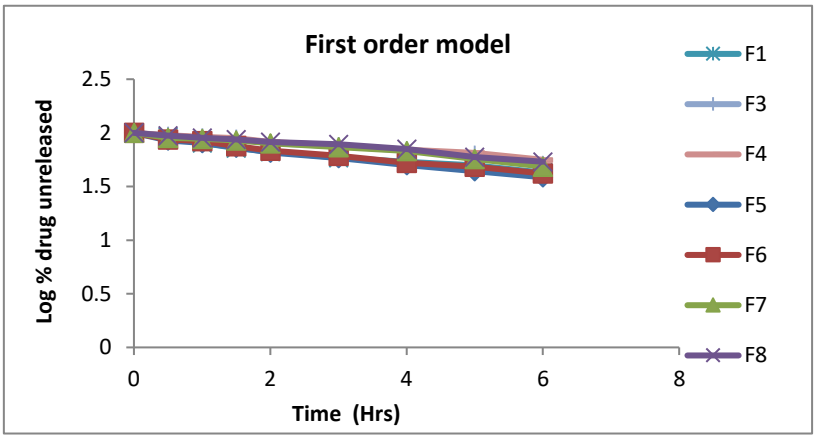

Fig. No. First order drug release kinetics

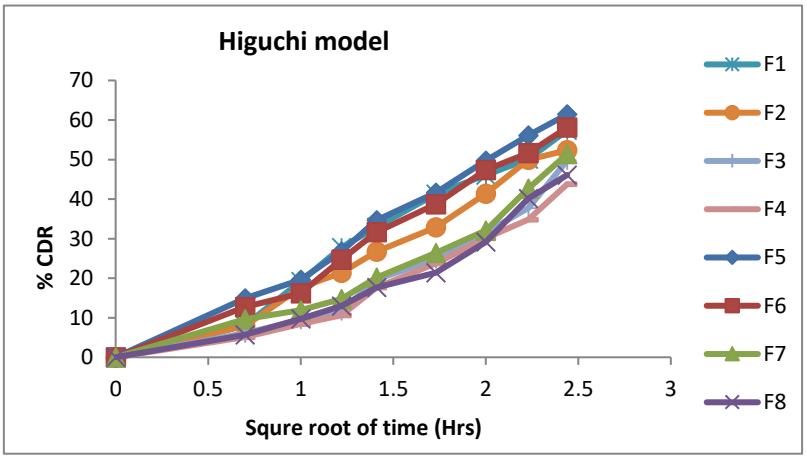

Fig.No.7 Higuchi drug release kinetic.

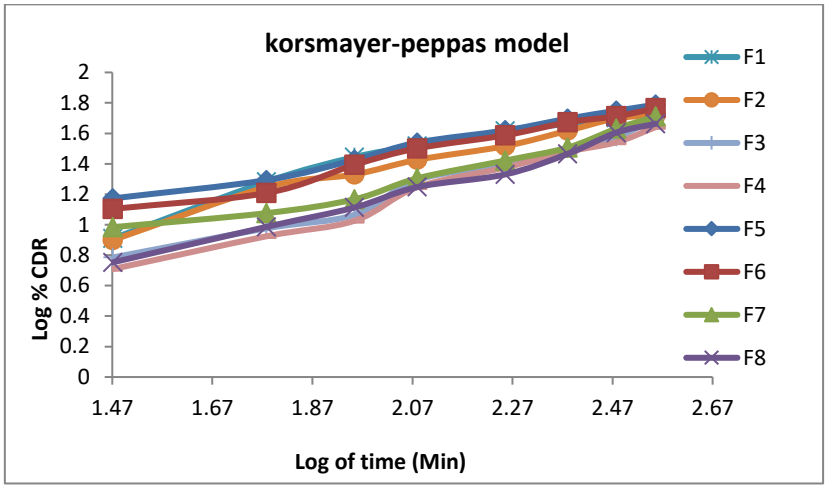

Fig. No. 8 Korsmeyers-Peppas drug rlease kinetic

Table No. 5 *In-vitro* Drug diffusion kinetic study

Formulation code	Zero order		First order		Higuchi		Kormayer-peppas		
	R2	K0	R2	K1	R2	KH	R2	Kp	n
F1	0.9620	8.061	0.984	0.058	0.981	25.03	0.566	0.866	0.2132
F2	0.9863	7.877	0.985	0.949	0.996	25.67	0.728	0.990	0.2252
F3	0.9937	7.629	9.988	0.045	0.979	24.25	0.846	0.990	0.3040
F4	0.9958	6.928	0.995	0.040	0.988	22.18	0.726	0.919	0.3241
F5	0.9871	6.928	0.994	0.066	0.997	27.95	0.598	0.997	0.1733
F6	0.984	8.300	0.993	0.060	0.998	26.30	0.621	0.998	0.1929
F7	0.995	7.582	0.988	0.048	0.970	23.76	0.691	0.979	0.2392
F8	0.995	7.306	0.996	0.043	0.977	23.15	0.889	0.984	0.3029

DISCUSSION

Result of FTIR studies was shown in fig. no. 1 and 2. FTIR spectrum of Glimepiride and physical mixture-I was obtained. Glimepiride was shown frequency at 3368.33 cm-1 due to N-H stretching, 3288.86 cm-1 due to O-H stretching, 2930.63 cm-1 due to C-H stretching, 1707.07 cm-1 due to C=O stretching, 1542.71 cm-1 due to N-O Stretching, 1392.04 cm-1 due S=O Stretching and 1154.02 cm-1 due to C-N Stretching which are match with its physical mixture at 3369.87 cm-1 due to N-H stretching, 3289.78 cm-1 due to O-H stretching, 2987.87 cm-1 due to C-H stretching, 1748.87 cm-1 due to C=O stretching, 1598.12 cm-1 due to N-O Stretching, 1300.78 cm-1 due to S=O Stretching and 1276.56 cm-1 due to C-N Stretching.

FTIR spectrum of Glimepiride, and physical mixture-II was obtained. Physical mixture-II was shows similar frequency. At 3369.45 cm-1 due to N-H stretching, 3254.56 cm-1 due to O-H stretching, 2859.89 cm-1 due to C-H stretching, 1667.98 cm-1 due to C=O stretching, 1500.78 cm-1 due to N-O Stretching, 1298.76 cm-1 due to S=O Stretching and 1298.76 cm-1 due to C-N Stretching. After FTIR studies of Glimepiride and physical mixture, the peaks were obtained in physical mixture in the range between of main principle peaks were found to be very near to previously performed FTIR of pure glimepiride. From all the observed peaks there no major deviation in peaks it was obtained in IR spectra, this is indicated glimepiride was compatible with ingredients used in the formulation.

Result of clarity, pH, gelling temperature and gelling time are shown in table no. 2. The clarity of prepared formulation was clear (++) solution. The pH of prepared formulation was found between 5.5 ±0.81 to 6.1 ± 0.95 which is tolerable range in contact with nasal tissue. The gelling temperature was found to be in between 33.6 ± 1.27 -37.7 ± 0.54 °C. The gelling time was found to be in between 6.6 ± 1.11 to 24.66 ± 0.82 Sec. Gelling temperature range suggest that In-situ gel get retained at mucosal site and produced sustain release of drug from its gel matrix. Gelling time suggest that In-situ gel get formed within very short time indicated gel get formed immediately after installation of solution in nostrils.

Result of gel strength, spreadability, drug content are shown in table no.3 and viscosity was shown fig. no.3. Gel strength In-situ gel was found increase with increase in concentration of HPMC K-100 M and

Poloxamer 188. It was observed that gel containing poloxamer 188 showed better gel strength than HPMC K-100 M containing formulations. This infers that HPMC K-100 M In-situ gel solution has less resistance to flow than its formulations containing poloxamer 188.

The F4 formulation was more viscous solution than other prepared formulation and F5 is very less viscous solution than other prepared formulations. The spreadability by parallel method was found between 7.3 ± 0.91 to 9.6 ±0.97 gm.cm/s. spreadability by Harcourt-grand method was found between 52 ± 0.91 to 68 ± 1.11 mm depicted semi fluid gel. The drug content was found between 98.10 ± 1.07 to 99.83 ± 0.92 %. Result of mucoadhesive study was shown in table no. 4 mucoadhesive study was performed for 4 hours indicated that up to 3 hours drug was available at the site of administration. The mucoadhesive results were depicted in table no. 4 and figure no. 4 as spectrum obtained for Glimepiride for time period 30 min, 1 hr, 1.5 hr, 2 hr and 3 hr.

Drug diffusion study was performed on prepared In-situ gel formulations. Drug diffusion kinetics result are shown in table no.5. Prepared In-situ gel formulation were exhibited zero order kinetic drug diffusion as R^2 value were closed to 0.99. Formulations were exhibited flicking type of diffusion as 'n' value of Korsmeyer's Peppas model was not greater than 0.45.

CONCLUSION

The formulation of In-situ nasal was developed successfully as a temperature-induced In-situ nasal gelling system using HPMC K-100 M, Poloxamer 188 as a gelling agent and xanthan gum as a sustain release agent. The optimized formulation F4 provide sustained In-vitro release of the drug over an extended period of 6 hrs. The In-situ nasal gel of Glimepiride was developed to overcome the first pass metabolism, reduce the dosing frequency, improve patient compliance and travel friendly.

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