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Research Article

FORMULATION, DEVELOPMENT AND EVALUATION OF ANTI-DIABETIC ORAL INSITU GEL

L. Lahari *, E. Hima bindu , Dr. Sowjanya battu, Dr. Abbulu

Department of Pharmaceutics, CMR College of pharmacy, Kandlakoya, Medchal, Hyderabad,501401, Telangana, INDIA.

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ABSTRACT

The present research was focused to develop the formulation to release the drug Repaglinide for an extended period of time, thus prolong the residence time of formulation in the intestine. The in-situ gel formulations were developed to improve patient compliance. HPMC 50 cps, Carbopol 934 is used as polymers. Based on the concentration of polymer, the drug release was varied. Totally 12 formulations were prepared with HPMC 50cps and Carbopol 934P in various combinations. An in-vitro evaluation study was conducted in Franz diffusion cell apparatus. The viscosities of the samples were measured by Brookfield Viscometer. The drug-polymer interactions were evaluated by using FTIR spectroscopy. In all the formulations, F9 is considered as an optimized formulation. From the research it was observed that F9 formulation has high residence time and reduction in the frequency of administration. The mechanism of drug release follows Anomalous non-Fickian diffusion.

KEYWORDS: *Repaglinide, HPMC 50cps, Carbopol 934, Simple mixing method, Oral insitu gel, Controlled release drug delivery system etc.,*

INTRODUCTION

Controlled drug delivery system is one that delivers the drug at a predetermined rate for locally or systemically, for a predefined time [1]. ORAL CRDDS is a system involves the delivery of drug at predictable and reproducible kinetics for predetermined period throughout the span of GIT [3]. An ideal oral drug delivery system should relentlessly convey a measurable and reproducible amount of drug to the target site over a prolonged period.

1. Insitu Gels:

The term insitu is a latin word which means "In position". Insitu gels are the drug delivery system that are initially in solution form before administration into the body, but when administered it undergoes gelation in situ, forming the gel [4].

Advantages:

- They increases contact time,
- Improvcs local bioavailability,
- Patient compliance and comfort,
- Reduces dosing frequency,
- Reduces dose concentration,
- Production is less complex and thus lowers the investment and manufacturing cost.

2. Diabetes Mellitus:

Diabetes mellitus is a group of metabolic diseases in which a person has high blood sugar over prolonged period of time. It is either because the body does not produce enough insulin or because cells do not respond to the insulin that is produced [7].

This high blood sugar shows symptoms such as polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) [7].

There are three main types of diabetes:

- ***Type 1 diabetes:*** results from the body's failure to produce insulin, and there the person requires to inject insulin. (Referred as insulin-dependent diabetes mellitus or juvenile diabetes.)
- ***Type 2 diabetes:*** results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. (Referred as non-insulin-dependent diabetes mellitus or adult-onset diabetes.)
- ***Gestational diabetes:*** is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. It may precede development of type 2 diabetes mellitus.

*** Corresponding author:**

L. Lahari

M Pharmacy,

Department of Pharmaceutics,

CMR College of pharmacy, Kandlakoya, Medchal,

Hyderabad,501401, Telangana, INDIA.

** E-Mail: laxmishettylahari1996@gmail.com*

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3. Repaglinide:

Repaglinide is an anti-diabetic drug which is included under treating type 2 diabetes mellitus [8].

- It is classified under metglinides/phenylalanine analogues.
- It is an oral medication utilized in addition to diet and exercise for blood sugar control in type 2 diabetes mellitus.

MATERIALS AND METHODS

Profiles of materials used:

Repaglinide was obtained as a gift sample from chromo labs (Miyapur, Hyderabad). Carbopol 934, HPMC 50cps were used as polymers. The remaining chemicals are of analytical grade.

Methodology:

Preparation of Oral Insitu Gel:

Simple mixing method: Different formulations were prepared with varies ratio of (HPMC50cps, Carbopol 934), many experiments were conducted varying the concentration of those polymer in order to identify the optimum concentration required for polymer solution. Varied concentrations of HPMC50cps and carbopol 934 were taken, 10ml of deionised water was added to the mixture,The polymer solutions were mixed with magnetic stir, until uniform solution obtained. 2mg of Repaglinide was solubilized in deionised water with continuous stirring until uniform solution obtained. To the polymer solution, drug solution was added. To the above prepared solution, 6.8pH buffer was added there we can observe sol to gel transformation**.** The formulations prepared were shown in table 1.

The twelve formulations were prepared and are shown in the figure 1 given below respectively.

Evalution Studies:

1. Drug – excipient compatability studies by FTIR:

FTIR analysis: The FTIR instrument sends infrared radiation of about 10,000 to 100 cm^{-1} through a sample, with some radiation absorbed and some passed through. The absorbed radiation is converted into rotational and/or vibrational energy by the sample molecules. The resulting signal at the detector presents as a spectrum, typically from 4000 cm^{-1} to 400cm^{-1}, representing a molecular fingerprint of the sample. Each molecule or chemical structure will produce a unique spectral fingerprint, making FTIR analysis a great tool for chemical identification

Principles of IR Spectroscopy: The different regions of the electromagnetic spectrum will be used in this section to find out about the structure and reactions of organic molecules. For each spectroscopic method, it is useful to see how much energy corresponds to each wavelength and how this identifies to the physical procedure after absorption of radiation. Organic molecules can ingest IR radiation between 4000 $cm^{-1}$and 400 cm^{-1} which corresponds to absorption of energy between 11 kcal/mole and 1 kcal/mole. This measure of energy initiates transitions between vibrational states of bonds contained inside the molecule.

2. Physical appearance:

All the formulation which was prepared were evaluated for clearness by visual inspection against a black and white background.

3. pH:

The pH of prepared formulations was determined using a calibrated pH meter at room temperature. The measurement is carried out in triplicate and average values are taken.

4. Gelation time:

The gelation time is the time taken by sol to get converted in to gel in favorable conditions and was determined by adding the polymeric solution containing the drug into the 6.8 pH buffer, it was observed that within part of seconds the solution transformed into a gel when it comes in contact with the buffer. As the formulation came in contact with 6.8 pH buffer, it changed from sol to gel and the time was noted.

5. Drug content:

1 mg of the formulation was taken dissolved in 10ml of 6.8pH phosphate buffer and the solution was stirred for some time until the gel gets dissolved, the solution is filtered from that filtrate 1 ml is taken diluted with 5 ml buffer and analyzed in UV spectrophotometer at 237 nm against a suitable blank solution.

6. Rheological behaviour:

The viscosities of the different formulations were determined by use of Brook field viscometer (LV DVIII Model pr (UCP) having T-bar spindle). The samples were sheared at a rate of 100 rpm using spindle no 64 at room temperature. Viscosity estimation for each sample was performed in triplicate, and average was choosen.

7. Swelling index:

10 ml formulation was prepared and weighed precisely (W1). It was reserved in a beaker and 10 ml of 6.8pH phosphate buffer was added. The beaker was set aside for 24 hrs. The weight of swollen matrix gel (W2) was found and swelling index was calculated by following formulae:

$$\text{Swelling Index} = (W2 - W1/W1) \times 100$$

Where, W1 = initial weight of gel (100 mg),

W2 = weight of bloated matrix after 24 hrs.

8. Mucoadhesive strength:

A modified balance was used for measuring the ex vivo mucoadhesive strength. Fresh sheep intestinal mucosa was obtained from a local slaughterhouse (Small intestine mucosa was used as model membrane since the intestine provides flat and uniform surface, and used within 2 hours of slaughter. The mucosal membrane was isolated by removing underlying fat and loose tissues. The membrane was washed several times with distilled water and then with phosphate buffer 6.8 solutions. The sheep intestinal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of intestinal mucosa was tied to a glass vial; the vial was tightly fitted into a glass beaker filled with phosphate buffer pH 6.8 so that it just touched the mucosal surface. The formulated gel stuck to the lower side of a glass stopper. Both sides of the balance were made equal before examining, by keeping a 5g weight on the right-hand pan. A weight of 5g was taken off from the right-hand pan, including the gel over the mucosa. The balance was kept in this position for 2 minutes contact time; a force was applied to the left pan of balance by pouring water dropwise to the beaker till of gel achieved. The mucoadhesive strength shows the amount of water added minus the weight of the

preload, and the mucoadhesive force was calculated from the following equation:

Mucoadhesive Force = mucoadhesive strength x 0.0098

Figure 2 indicates mucoadhesive strength determination.

9. In-vitro diffusion studies:

Franz diffusion cell consists of two compartments. Upper donor compartment and lower receptor compartment. The receptor compartment consists of 6.8pH Phosphate buffer and to the donor compartment, the formulated gel which contains drug is placed. In between the upper and lower compartments egg membrane is placed. The diffusion of the drug from the semisolid product across the membrane is monitored by assay of sequentially collected samples of the receptor medium. At predetermined time points, an aliquot of the medium is taken from the receptor compartment for drug content analysis. The receptor compartment is replaced with a fresh medium after each sampling. Figure 3 indicates franz cell diffusion.

10. In-vitro drug release kinetic studies:

To know the mechanism of drug release, kinetic models are used. In order to study the definite mechanism of drug release from the formulation, drug release data was analyzed by Zero order, first order, korsmeyer peppas and Higuchi square root. The obtained data were processed for regression analysis by MS EXCEL statistical function.

It is known that the peppas model is broadly used to affirm whether the release mechanism is Fickian diffusion and non-Fickian diffusion. The 'n' (release exponent of korsmeyer-peppas model) value could be used to explain different release mechanisms. The interpretation of n value was done in the following manner.

n <0.5 (0.45) - quasi-Fickian Diffusion
n=0.5 (0.45) - Diffusion mechanism
0.5<n<1 - Anomalous (non Fickian) Diffusion – both diffusion and relaxation (erosion)
n=1 (0.89) - Case 2 transport (Zero order release)
n>1 (0.89) - Super case 2 transport (relaxation).

RESULTS AND DISCUSSIONS

1. Fourier Transformed Infrared (FTIR) Spectroscopy:

Fourier-transform infrared (FTIR) spectroscopy was performed on each of the samples to determine the structure of the organic compounds and to identify the presence of specific functional groups within a sample. Furthermore, drug-polymer interactions were determined using the resulting spectra. Spectra are obtained by passing infrared radiation through a sample and determining what fraction of incident radiation is absorbed at a particular energy. In the drug-excipient interaction study, it was found that Repaglinide was compatible with all the excipient used in the formulation .As there are no extra peaks and no shifting of peaks of the functional groups of Repaglinide (all peaks are within the ± 5 cm^{-1}) in the spectra of binary mixtures of drug and excipients. Figures 5, 6, 7, 8, 10 indicates FTIR SPECTRUM of Repaglinide, Carbopol 934, HPMC 50cps, Methyl paraben, F9 optimized formulation respectively.,

2. Physical appearance:

All the formulations (F1-F12) were found to have clear appearance.

3. pH:

The pH of the gel was determined by using a calibrated pH meter. The readings were taken for average of 3 samples**.** Table 2 indicates pHvalues of 12 formulations.

Discussion: The pH of all the formulations were in the range of 4.74 to 5.13. since the carbopol 934 and HPMC 50cps was formulated with pH 4.7 to 5.2 because this pH is necessary to maintain good viscosity and clarity of the gel.

4. Drug content:

The percent drug content of all formulations was present in the range of 95.0-98.8%. The drug content for 12 formulations can be shown in the table 3,

Discussion: The drug content of all the formulations was stable as we can observe in the above table, It was clear that the drug is stable throughout its shelf-life.

5. Rheology studies:

The viscosity for twelve formulations varies from 192-1083 pa.s. As the rpm increases viscosity of the formulation decreases. This can be observed in the below given table 4.,

Discussion: As the carbopol 934 concentration increases viscosity of the formulation also increases because of its bioadhesive nature. In the F9 formulation, carbopol 934 and HPMC50cps is in equal concentration, it shows greater effect in viscosity of gel.

6. Mucoadhesive strength:

The mucoadhesive strength for all formulations varies from 13.34-20.84 (g). This can be observed in Table 5 given below.

Discussion: As the carbopol 934 concentration increases mucoadhesive strength also increases because carbopol is having bioadhesive property.

7. Gelation time:

The Gelation time for twelve formulations varies from 30-60 sec and this can be observed in the below given table 6.

Discussion: The results of gelation time indicate that gelation time of the formulations was decreased with increased concentration of Carbopol 934 proportion.

8. Swelling index:

The results indicate that the formulation with greater polymer concentration shows effective swelling index. This can be observed in the given table 7.

Discussion: The swelling index of F9 formulation shows greater swelling as the polymer concentration is greatly influenced in F9(HPMC 50cps and carbopol 934 are in higher concentrations) HPMC acts as thickening agent and carbopol as gelling agent.

9. Invitro drug release:

The invitro drug release of insitu gel was carried in 6.8pH phosphate buffer from 0.5 to 10 hrs by franz diffusion cell. The plot of percent cummulative drug release v/s time (min) was plotted. Initially the drug was released more rapidly due to burst effect. The drug release from the gel was at a slower rate in the second phase due to swelling behavior of gelation polymer, which results in moderate release rate. The initial burst release was significantly decreased with increase in polymer concentration. Drug releases for 12 formulations were shown in the table 8.

Discussion: In the above table, it was observed that of all the formulations, F9 is showing the release of drug at around 98.65% for 10 hrs. This is due to more polymer concentration in

F9 formulation, as the drug is entrapped in the gel, it will release slowly and its residence time will increase.

10. Kinetics of drug release:

The r2 values of zero order of all the formulations have shown higher value which indicates the drug release is directly proportional to the time. But n values range from 0.984 which indicate Anomalous non-Fickian diffusion mechanism. However, an n value of Korsmeyer-Peppas strongly indicates that mechanism is Anomalous (non Fickian) Diffusion – both diffusion and relaxation (erosion) of drug from polymer. Table 10 shows kinetic models and their slope and R^2 values and figures 11,12,13,14 indicates kinetic models.

Stability Studies:

Finally, Optimized F9 formulation was subjected to stability studies according to ICH guidelines and results of various evaluation parameters were shown in the table given below. After stability studies, formulation F9 was more stable at accelerated conditions.

Discussion: From the stability studies, it was concluded that the F9 formulation was stable throughout its shelf-life.

Table No. 1: Formulation table

Formulation code	Amount of drug(mg)	HPMC50cps (mg)	CARBOPOL 934 (mg)	Amt of solvent added (ml)
F1	2	0.25	1	10
F2	2	0.25	0.75	10
F3	2	0.25	0.5	10
F4	2	0.25	0.25	10
F5	2	0.5	1	10
F6	2	0.5	0.75	10
F7	2	0.5	0.5	10
F8	2	0.5	0.25	10
F9	2	0.75	1	10
F10	2	0.75	0.75	10
F11	2	0.75	0.5	10
F12	2	0.75	0.25	10

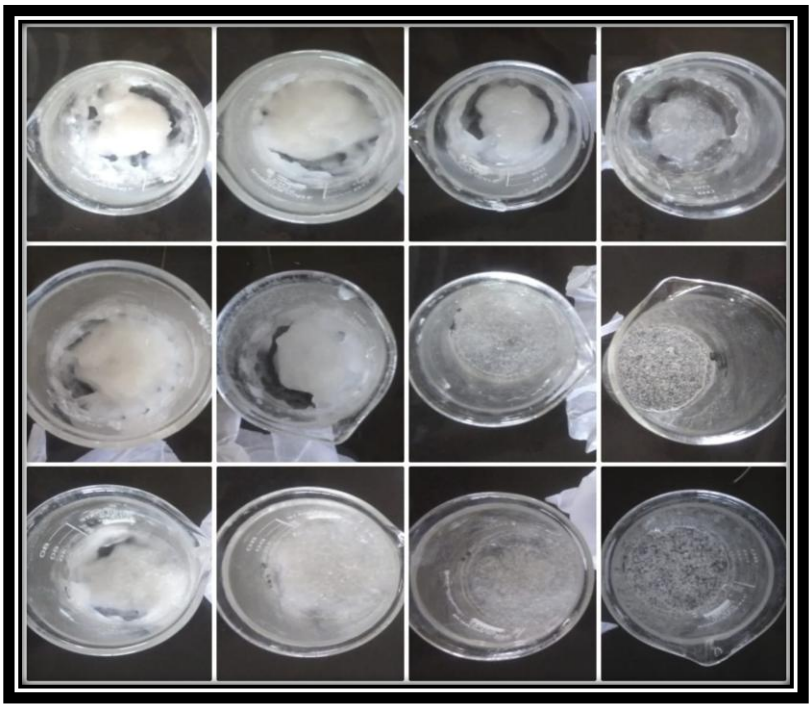
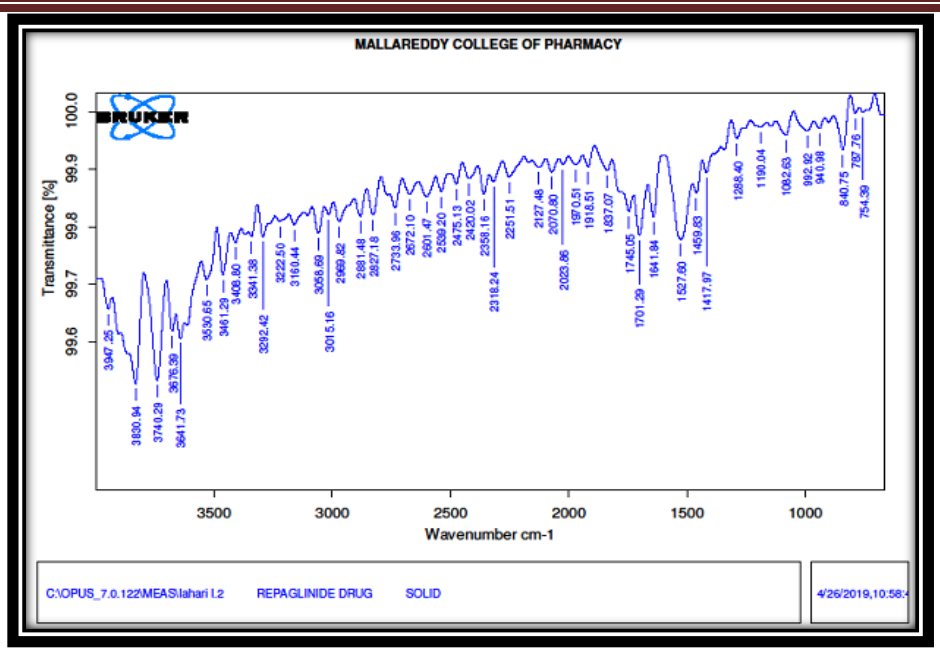
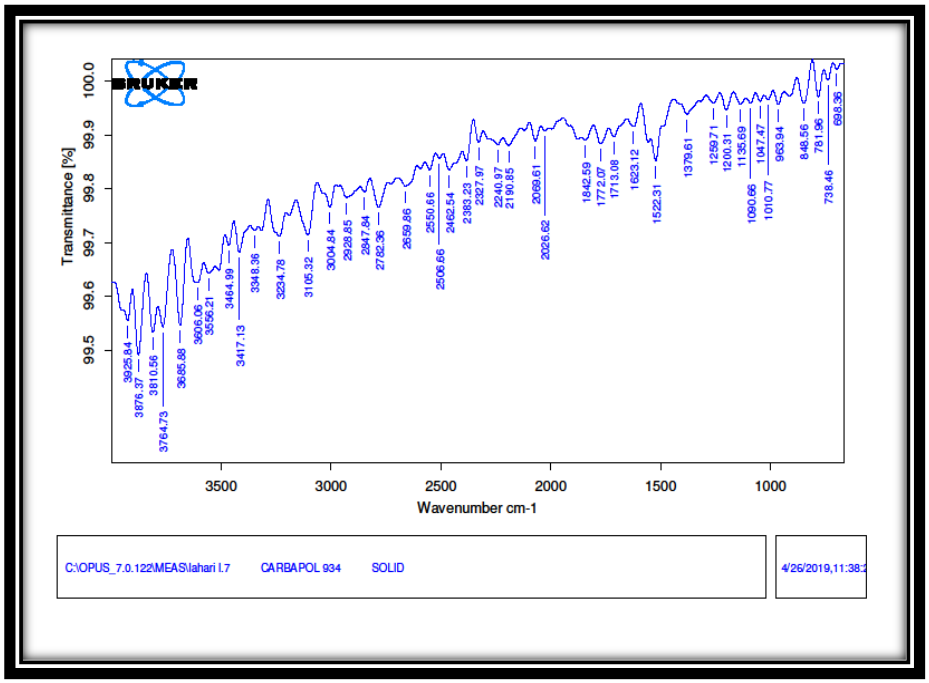


Fig. 1: Formulation from F1-F12 respectively



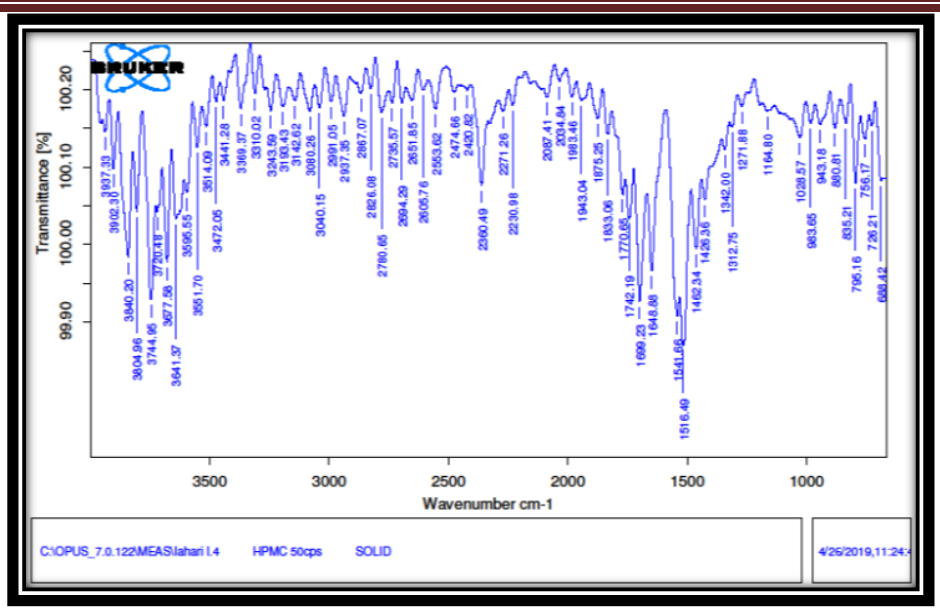
Functional groups	Wavelength range
C-N stretching	1444.02 cm^{-1}
C=O vibration	1682.16 cm^{-1}
C-O-C	1085.35 cm^{-1}
N-H	3301.77 cm^{-1}
C=C group vibration	1630.68 cm^{-1}
O-H vibration	2799.45 cm^{-1}

Fig. 2: FTIR Spectrum of Repaglinide (pure drug)



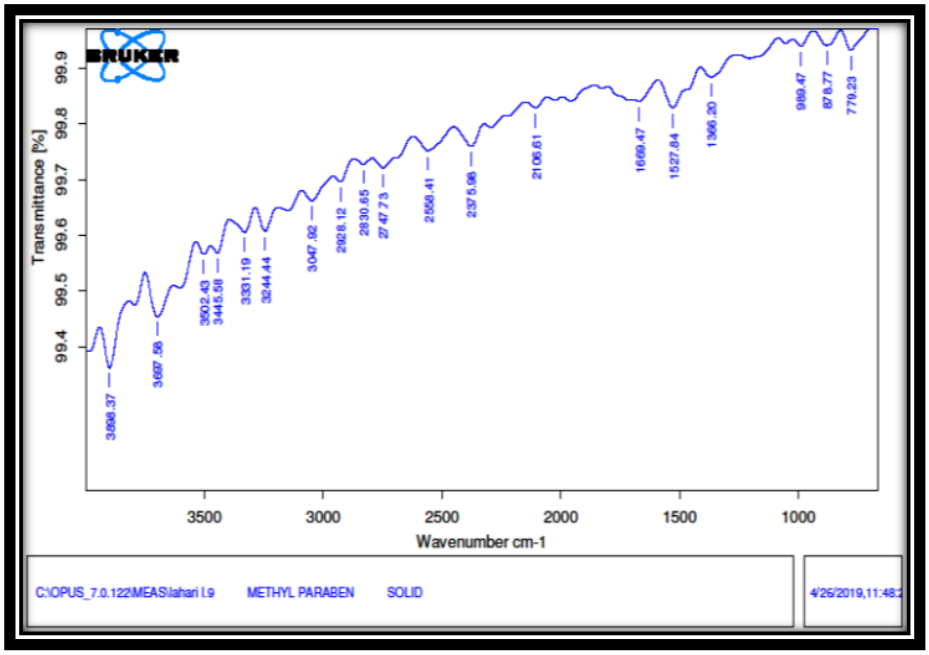
Functional groups	Wavelength range
O-H stretching	3089.75 cm^{-1}
carboxyl group	1706.88 cm^{-1}

Fig. 3: FTIR Spectrum of Carbopol 934



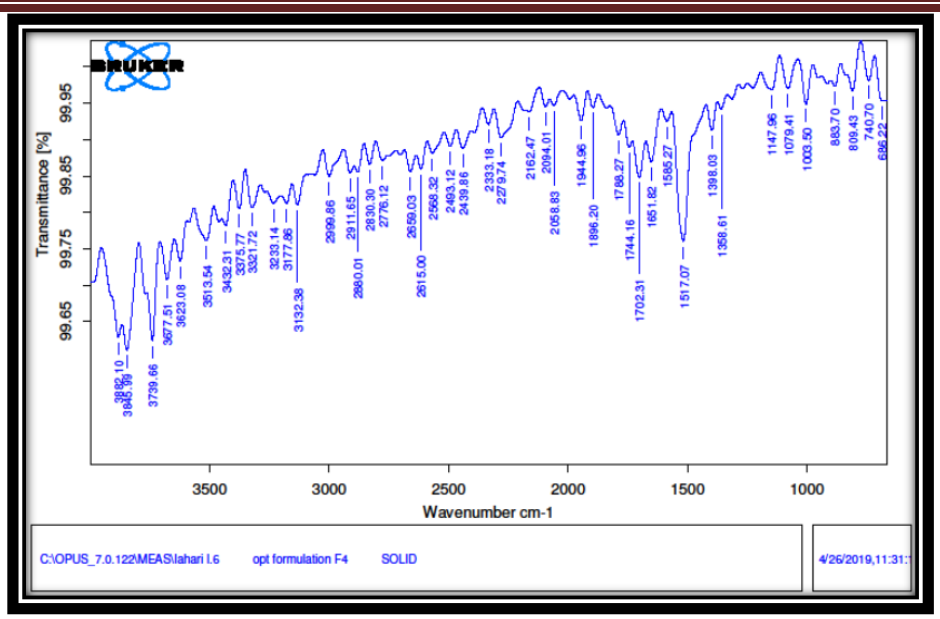
Functional groups	Wavelength range
Methyl and hydroxypropyl group	2900 cm^{-1}
Hydroxyl group	2500 cm^{-1}
Six membered cyclic	1650-1600 cm^{-1}
δCH, δOCH, δCCH	1500-1450 cm^{-1}
Cyclic anhydrides	1400-1350 cm^{-1}
Epoxides	1300-1250 cm^{-1}
Ethereal C-O-C group	1100-1000 cm^{-1}
Pyranose ring	1000-950 cm^{-1}
CH2 group	850-800 cm^{-1}

Fig. 4: FTIR Spectrum of HPMC 50cps



Functional groups	Wavelength range
C=O stretching	1663 cm^{-1}
Phenolic-OH stretching	1588 cm^{-1}
carboxylic acid peak	3449 cm^{-1}

Fig. 5: FTIR Spectrum of Methyl paraben



Functional groups	Wavelength range
C-N stretching	1444.02 cm^{-1}
O-H stretching	3089.75 cm^{-1}
C-O-C	1085.35 cm^{-1}
carboxylic acid peak	3449 cm^{-1}
Hydroxyl group	2500 cm^{-1}

Fig. 6: FTIR Spectrum of Optimized formulation F9

Table No. 2: pH values of F11-F12 Formulations

FORMULATIONS	pH VALUES
F1	4.84 ± 0
F2	4.85 ± 0
F3	4.87 ±0
F4	4.74 ± 0
F5	4.80 ± 0
F6	4.82 ± 0
F7	5.01 ±0
F8	5.02 ± 0
F9	5.10 ± 0
F10	5.13 ± 0
F11	5.12 ± 0
F12	5.13± 0

Table No. 3: Drug content values of F1-F12 Formulations

FORMULATION CODE	DRUG CONTENT
F1	96.8±0.21%
F2	95.0±0.12%
F3	95.9±0.22%
F4	97.6±0.01%
F5	98.2±0.21%
F6	96.5±0.15%
F7	96.8±0.84%
F8	97.2±0.55%
F9	**98.8±0.39%**
F10	97.4±0.46%
F11	96.3±0.33%
F12	98.1±0.17%

Table No. 4 : Viscosity values of F1-F12 Formulations

Formulation code	Viscosity (pa.s)
F1	883.04±0.15
F2	757.13±0.23
F3	964.09±0.45
F4	759.01±0.10
F5	192.97±0.53
F6	347.82±0.34
F7	581.39±0.51
F8	235.66±0.39
F9	**1083.34±0.71**
F10	463.07±0.28
F11	636.45±0.43
F12	1062.21±0.16

Table No. 5: Mucoadhesive strength values of F1-F12 Formulations

Formulation code	Mucoadhesive strength
F1	16.34±0.51
F2	15.49±0.74
F3	13.34±0.44
F4	18.95±0.11
F5	17.64±0.54
F6	15.32±0.63
F7	14.21±0.69
F8	18.46±0.56
F9	**20.84±0.32**
F10	19.88±0.11
F11	18.46±0.24
F12	17.64±0.12

Table No. 6: Gelation time of F1-F12 Formulations

Formulations	Gelation time(sec)
F1	45 ± 1.15
F2	50 ± 1.00
F3	52 ± 0.57
F4	39± 0.10
F5	38 ± 1.22
F6	42 ± 1.00
F7	35 ± 1.15
F8	40 ± 0.52
F9	**31 ± 1.00**
F10	32 ± 0.57
F11	45 ± 0.51
F12	57 ± 1.51

Table No. 7: Swelling index values of F1-F12 Formulations

Formulation code	Swelling index
F1	30.26%±0.1%
F2	30.38%±0.13%
F3	42.68%±0.3%
F4	27.58%±0.2%
F5	42.44%±0.15%
F6	43.79%±0.11%
F7	32.36%±0.13%
F8	38.52%±0.24%
F9	**45.65%±0.15%**
F10	25.87%±0.22%

F11	28.71%±0.14%
F12	30.94%±0.12%

Table No. 8: %drug release values of F1-F12 Formulations

Formulation Code	% Drug Release after 10 hrs
F1	96.2%±0.12
F2	96.5%±0.17
F3	91.15%±0.21
F4	92.49%±0.10
F5	94.5%±0.04
F6	95.5%±0.09
F7	92.7%±0.13
F8	94.75%±0.04
F9	**98.65%±0.02**
F10	91.7%±0.01
F11	95.6%±0.07
F12	96.3%±0.12

Table No. 9: Comparative diffusion studies of F1-F12 formulations

Time (hrs)	% Cummulative drug release of 12 formulations (F1-F12)											
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	12.4	7.5	16.5	17	15.5	14.5	17.5	19.1	15.5	19	12	6.5
1	21.7	11.5	27.7	25	24	22	25.5	27	19.5	20.95	20.5	12
2	27.5	22.5	34.25	29	31	29.1	30	31.5	20.8	27.15	31	24.9
3	43.2	30.5	37.1	36	43.5	37.2	39.5	41.05	30.7	37.3	41.5	32.65
4	58.7	41	42.1	42.5	51.05	47.1	42.5	46.15	39.3	42.15	49.6	42.45
5	81.9	54.2	51.7	61.05	59.1	62.05	48.5	53.55	45.8	45.8	57.3	64.45
6	92.7	61.5	57.6	69.35	62.3	69.8	59.5	59.65	60.8	60.95	67.3	71.6
7	95	68.2	66.1	76.05	73.3	79.1	64.15	62.8	68.25	71.05	72.65	78.2
8	95.6	77.05	77.2	83.5	77.5	82.95	73.75	71.6	77.1	78.15	82.1	84.7
9	96.1	88.3	83.1	91.6	88.5	91.6	84.65	84.2	89.2	89.5	89.8	86.8
10	96.2	96.5	91.15	94.1	94.5	95.5	92.7	94.75	98.65	91.7	95.6	96.3

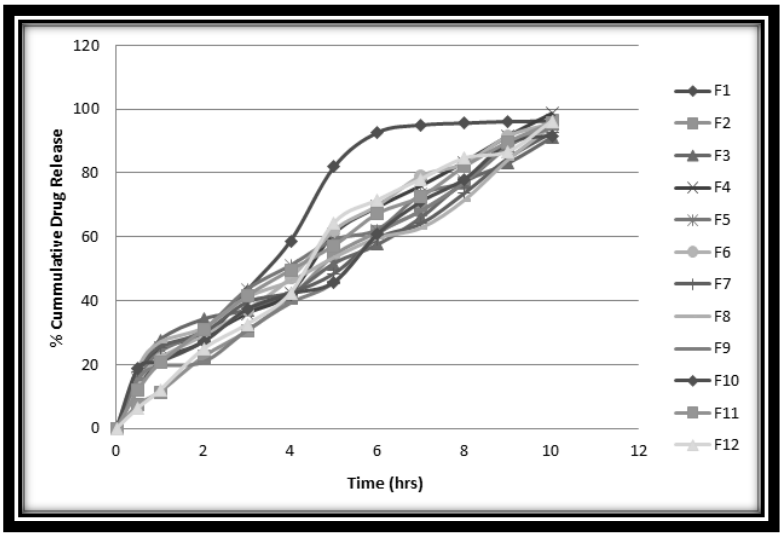


Fig. 7: Comparative diffusion studies graph of F1-F12 formulations

Table No. 10: Kinetic models and their slope values and R^2 values

S.no	Kinectic models	Slope value and R^2value
1	**Zero order kinetic model**	Y = 9.2521x + 9.68 R^2 = 0.9805
2	**First order kinetic model**	y = -0.1407x + 2.1455

		R^2 = 0.8054
3	**Higuchi kinetic model**	y = 4.0841x - 8.6104 R^2 = 0.9573
4	**Korsmeyer peppas kinetic model**	y = 0.6907x + 0.0692 R^2 = 0.9848

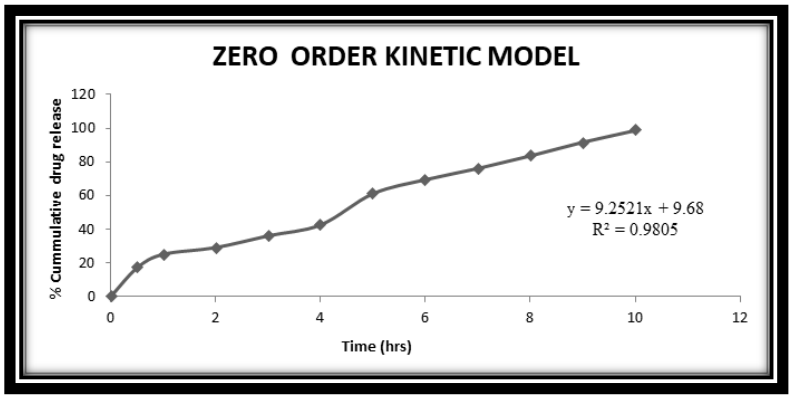


Fig. 8: Zero order kinectic model graph

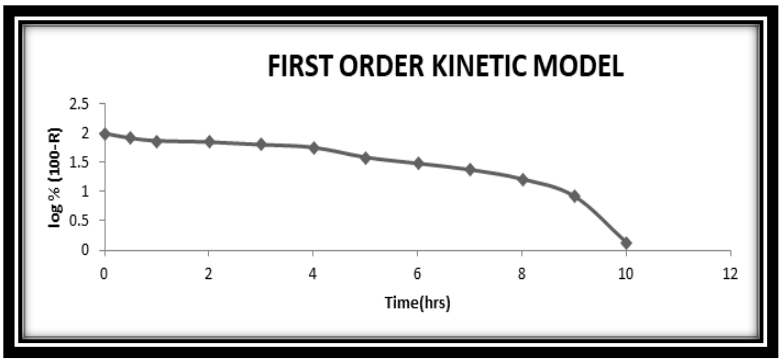


Fig. 9: First order kinectic model graph

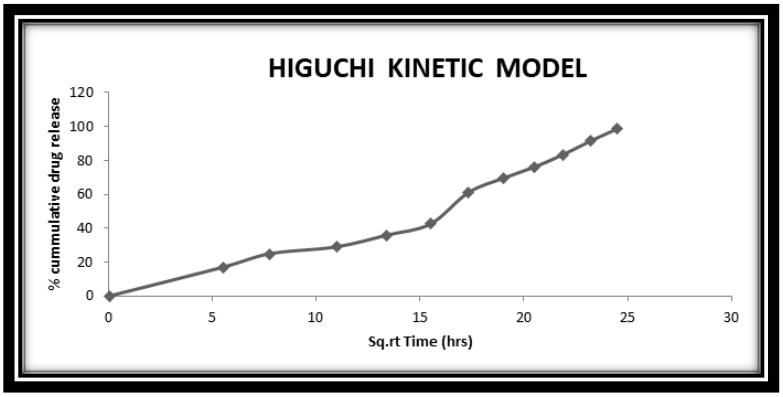


Fig. 10: Higuchi kinectic model graph

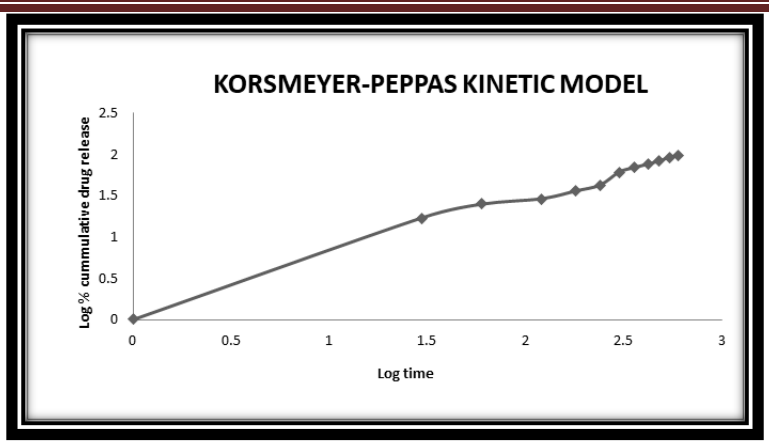


Fig. 11: Korsmeyer- peppas kinectic model graph

Table No. 11: Stability studies of F9 optimized formulation

S. No.	Evaluation parameters	Initial	1 month	2 month	3 month
1	pH	4.74±0	4.74±0.23	4.74±0.24	4.74±0.26
2	Mucoadhesive adhesive strength (g)	20.84±0.11	20.84±0.13	20.84±0.15	20.84±0.12
3	Swelling index (%)	45.65±0.13	46.69±0.15	48.5±0.05	48.7±0.01
4	Viscosity (centipoise)	1083±0.15	1085±0.13	1086±0.11	1086±0.05
5	Drug content (%)	98.8±0.01	98.8±0.012	98.8±0.015	98.8±0.015

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