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Formulation, Optimization, and Evaluation of Buccal Gel Loaded Polymeric Microspheres of Anti-Hypertensive Drug Cilnidipine

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ABSTRACT

The buccal drug delivery system is gaining high importance due to its faster absorption, no first-pass metabolism, and patient compliance. Cilnidipine is a 4th generation calcium channel blocker belonging to dihydropyridine class which is indicated in the treatment of hypertension. Due to the low aqueous solubility of cilnidipine, an attempt was made to develop an optimized polymeric microsphere of cilnidipine. In the present study, polymeric microspheres of cilnidipine were prepared by ionic gelation technique. Polymeric microspheres were then loaded in gellan gum gel for its application on the buccal cavity. Optimization of drug-loaded polymeric microspheres was carried out to check the influence of various parameters on particle size, % drug entrapment, and drug release. Cilnidipine loaded polymeric microspheres were then characterized for micromeritics properties, particle size, surface morphology characteristics, % drug entrapment efficiency, in-vitro drug release, and permeation studies and its comparative in-vitro drug release study was carried with marketed formulations Cilacar and Dilnip tablets. Gellan gum was also characterized for its appearance, pH, viscosity, refractive index, and spreadability.

1. INTRODUCTION:

Sustained release drug delivery is designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period with maximum therapeutic efficacy and minimum side effects. Sustained release drug delivery system (SRDDS) provides optimal therapy in terms of efficiency, reduces the frequency of dosing, targets the drug at the site of action thus increasing the effectiveness of the drug, provide uniform drug delivery, safety as well as patient compliance (1).

Microspheres are characteristically free-flowing powders with particle size in the range of 1-1000 µm consisting of proteins or synthetic polymers which are biodegradable (2). Microencapsulation is a process by which biologically active substance is encapsulated with a continuous film of polymeric material generally to enhance its shelf life and improve its performance (3).

Cilnidipine is chemically known as 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine carboxylic acid 2-methoxyethl(2E)-3-phenyl-2-propenyl ester (Figure no: 1), is the fourth-generation calcium channel blocker belonging to the dihydropyridine class which is indicated in the treatment and management of hypertension, Cilnidipine acts on the L-type calcium channel of blood vessels by blocking the influx of calcium and suppressing the contraction of blood vessels, thereby reducing blood pressure. As per the BCS, cilnidipine belongs to the class II drug which has low aqueous solubility and high permeability. Due to the low aqueous solubility of cilnidipine, it has poor oral bioavailability. Therefore, in the present study, an attempt was made to develop and characterize an optimized polymeric microsphere using sodium alginate as a polymer and calcium chloride as a cross-linking agent to improve oral bioavailability of the poorly soluble drug (4).

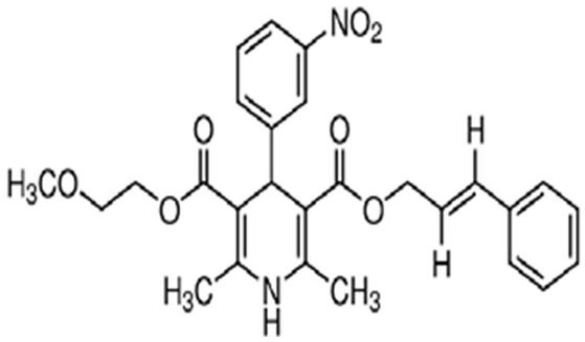


Figure No. 1: Chemical Structure of Cilnidipine

2. MATERIALS AND METHODS:

Cilnidipine gift sample available from Purechem Pvt. Ltd. Ankleshwar and J.B. Chemicals, Pvt. Ltd. Mumbai while Sodium alginate, Calcium chloride, Castor oil was purchased from Vishal Chem, Mumbai. Gellan gum for gel preparation was brought from CP Kelco.

2.1. Saturation solubility of cilnidipine:

Saturation solubility of cilnidipine was carried out in different oils (castor oil, groundnut oil, mustard oil, sesame oil, almond oil, and linseed oil) by using Microcontroller benchtop shaking incubator (LABTOP) (5). The saturation solubility data is given in Table no: 1.

Table No. 1: Saturation solubility data of cilnidipine.

Oils	Amount of API solubilized (mg) / 2ml
Castor oil	17.5 mg
Groundnut oil	14.6 mg
Mustard oil	6.32 mg
Sesame oil	3.9 mg
Almond oil	7.6 mg
Linseed oil	0.9 mg

2.1.Preparation method of microspheres:

2.1.1. Preparation of calcium alginate microspheres:

The calcium alginate microspheres were prepared by ionotropic gelation method. Calcium alginate microspheres formed as a result of the reaction between sodium alginate and calcium chloride.

2.1.2. Preparation of drug solution:

6 mg of Cilnidipine was dissolved in 0.5 ml of castor oil (6).

2.1.3. Preparation of Sodium alginate solution:

2.5% w/v sodium alginate solution was prepared by dissolving 2.5 gm of sodium alginate in 100 ml of distilled water. The polymeric solution was then allowed to stand in a sonicator for the removal of entrapped air bubbles (6).

2.1.4. Preparation of primary emulsion:

The drug solution was added to the sodium alginate solution and stirred vigorously to obtain primary emulsion (o/w) (6).

2.1.5. Preparation of Calcium chloride solution:

40% w/v calcium chloride solution was prepared by dissolving 40 gm of calcium chloride in 100 ml of distilled water (6).

2.1.6. Preparation of polymeric microspheres:

The resulting primary emulsion (o/w) containing drug was added dropwise from the distance of 5 cm using a 22G syringe needle to the calcium chloride solution at temperature 37±0.5°C and speed at 2100 rpm set on a magnetic stirrer (REMI MS-500). Formed microspheres were left for a specified time for curing. After curing, polymeric microspheres were collected by filtration and washed with formaldehyde to harden the microspheres. Collected microspheres were allowed to dry at room temperature until the microspheres are completely dried. The dried microspheres were weighed and stored for further evaluation (7-13).

2.1.7. Preparation of Gellan gum gel:

1.5 gm of gellan gum gel was dissolved in 100 ml of distilled water (1.5%). Gellan gum gel was prepared by using a magnetic stirrer (REMI MS-500) operated at 520 rpm. Polymeric microspheres were then incorporated in gellan gum gel (14).

2.1.8. Optimization parameters:

a. The concentration of sodium alginate

b. The concentration of calcium chloride

c. Stirring speed

d. Needle size

The above-mentioned parameters influence the microsphere's size, % drug entrapment efficiency, and drug release. So, there is a need to optimize the above parameters to obtain

the optimized polymeric microspheres in terms of microspheres size, % drug entrapment efficiency, and drug release (15).

2.2.EVALUATION OF POLYMERIC MICROSPHERES:

2.2.1. Micromeritics properties: (16,17).

2.2.2. Bulk density:

Polymeric microspheres are transferred to a graduated measuring cylinder. The volume filled is bulk and it includes the true volume of the microspheres and the void space among the polymeric microspheres. The bulk density is calculated by the formula (1).

$$\text{Bulk density} = \frac{Mass\ of\ polymeric\ microspheres}{Bulk\ volume}$$

2.2.3. Tapped density:

Polymeric microspheres in graduated measuring cylinder were tapped for 100 times. After completion of tapping, the volume of polymeric microspheres was visually examined. The tapped density is calculated by the formula (2).

$$\text{Tapped density} = \frac{Mass\ of\ polymeric\ microspheres}{Tapped\ volume}$$

2.2.4. % of Carr's index:

$$\%\ \text{of Carr's index} = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

2.2.5. Hausner's ratio:

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density}$$

2.2.6. The angle of repose (Ɵ):

The angle of repose measures the resistance to particle flow which was determined by the fixed funnel method. Accurately weighed polymeric microspheres were allowed to pass freely through the funnel on to the surface. The radius and height of the cone of powder were measured and the angle of repose was calculated using the formula:

$$\Theta = \tan^{-1} \frac{h}{r}$$

2.2.7. Particle Size and Shape:

Polymeric microsphere's size was measured using the Optical stage micrometer (Micro lab). About 100 polymeric microspheres were randomly picked and evaluated for its size. The shape of the polymeric microspheres was visually examined (18).

2.2.8. Surface morphology of the microspheres:

The morphological characteristics of the polymeric microspheres were obtained by Scanning Electron Microscope (SEM) (JEOL JSM-7600F) under vacuum. The mounting of dried microspheres was carried out by the gold sputter technique. The sample was then loaded in the SEM chamber. The samples were then randomly scanned, and the photomicrographs were recorded (19,20).

2.2.9. Fourier Transform Infrared Spectroscopy:

The FTIR spectrum for drug cilnidipine, sodium alginate, and calcium chloride was recorded using the potassium bromide technique. FTIR spectrophotometer (LAB INDIA) was operated from wave number 400-2000 cm^{-1} (21).

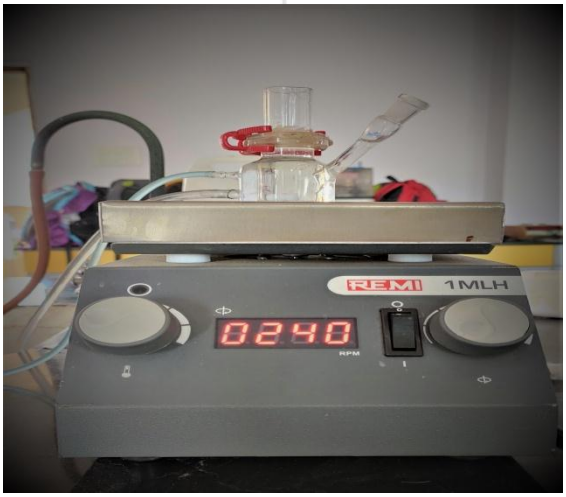
2.2.10. % drug entrapment efficiency:

10 mg accurately weighed polymeric microspheres were taken and crushed in a mortar with pestle. The crushed polymeric microspheres were then dissolved in 10 ml of ethanol. The solution was sonicated using an Ultrasonic sonicator for 5 mins. The resultant dispersion was then filtered through Whatman's filter paper (no.1) and the filtrate was analyzed at 240 nm using UV-Visible spectrophotometry (SHIMADZU, UV-1800). The experiments were performed in triplicate and results were calculated (22). The % drug entrapment efficiency was calculated by the following formula (6).

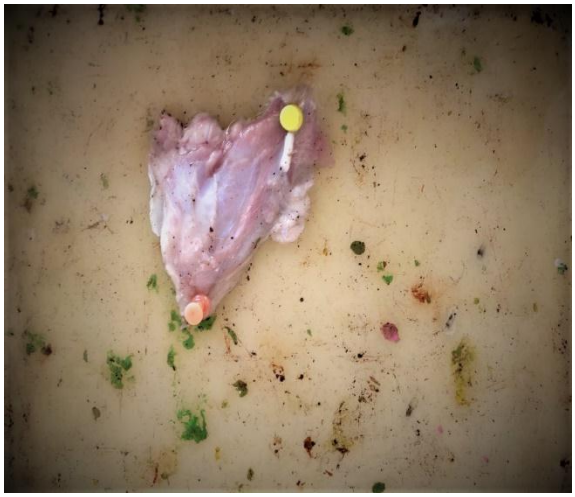
$$\% \text{ drug entrapment efficiency} = \frac{actual\ drug\ content}{therotical\ drug\ content} \times 100$$

2.2.11. *In-vitro* drug release and permeation study:

In-vitro diffusion of gel loaded polymeric microspheres of the drug was carried out using Franz Diffusion Apparatus (Figure no: 2). The donor compartment consists of an accurately weighed quantity of 1 gm gel containing drug on the nylon membrane (semi-permeable membrane) whereas the receptor compartment consists of 22 ml of simulated saliva of pH 7.4 (as the formulation is meant for buccal route). The temperature of the receptor compartment was maintained at 37 ± 0.5°C and the speed was adjusted to 240 nm on the magnetic stirrer (REMI MS-500). At different time intervals, a 1 ml aliquot of the sample was withdrawn, and the volume was replaced with fresh medium to maintain the sink conditions. The collected samples were filtered using Whatman's filter paper (no.1) and analyzed by UV-Visible spectrophotometer (SHIMADZU UV-1800) at 240 nm. The experiments were carried out in triplicates (7,8). In vitro permeation studies were carried out in similar fashion using buccal mucosa of goat bought from the animal slaughterhouse. In vitro drug release and permeation details and descriptions have been mentioned in Table no: 2.



(a)



(b)

Figure No. 2: Franz diffusion apparatus (a) for in vitro drug release (b) for in vitro permeation studies using goat buccal mucosa

Table No. 2: *In-vitro* drug release and permeation study details and descriptions

Details	**Descriptions**
Apparatus used	Franz Diffusion Cell
Release medium	Simulated saliva
pH	6.5
Semipermeable membrane used	Nylon membrane (for in-vitro study)
Tissue used	Buccal mucosa of goat (for ex-vivo study)
Temperature	37±0.5°C
RPM	240
Sampling volume	1 ml
Sampling intervals	0,15,30,45,60,120,180,240,300,360,420,480 mins
Spectroscopy used	UV-Visible Spectroscopy
Wavelength	240

2.2.12. Stability studies:

Stability studies as per ICH guidelines (ICH Q1A, R2, 2.1.7).

Three samples of the same batch of polymeric microspheres were subjected to these studies. The sample were subjected to 40 ± 2°C / 75 ± 5% RH and 25 ± 2°C / 60 ± 5% RH. At the end of 0, 30, 60, and 90 days, sample aliquots were withdrawn, diluted with ethanol, and analyzed using a UV spectrophotometer. A graph was plotted between log percent drug remaining v/s Time. The slope of the straight line from the graph was determined and the degradation rate constant (K) was calculated by using the equation (23). The slope was calculated by the given formula:

$$\text{Slope} = \frac{-K}{2.303}$$

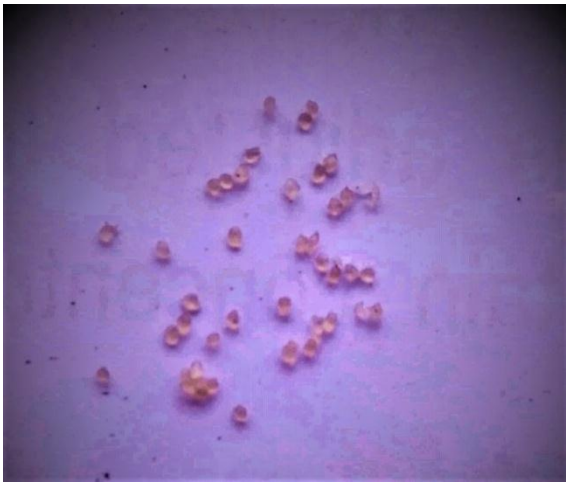
2.3.Evaluation of Gellan gum gel:

The prepared gellan gum gel was evaluated visually for their appearance and consistency. The pH of the gellan gum gel was measured by pH meter. The viscosity of the gellan gum gel was measured by Brookfield viscometer. The refractive index of the gellan gum gel was measured by Abbe's refractometer (24). The spreadability of the gel was evaluated by a wooden box glass slide apparatus.

3. RESULTS AND DISCUSSION:

The purpose of research work was to prepare buccal calcium alginate polymeric microspheres containing cilnidipine by ionotropic gelation method and the images of polymeric microspheres before and after drying were captured (Figure no: 3a and 3b) and examine the effects of various parameters such as the concentration of sodium alginate, concentration of calcium chloride and stirring speed on particle size, % entrapment efficiency, % drug release.

(a)



(b)

Figure No. 3: Polymeric microsphere images (a) before drying (b) after drying

3.1.Micromeritics properties:

The micromeritics properties of cilnidipine loaded polymeric microspheres are given in Table no: 3.

Table No. 3: Micromeritics properties of polymeric microspheres

Parameters	Observation	Inference
Angle of repose	29°	Excellent
Bulk density	1.044 g/ml	-
Tapped density	1.175 g/ml	-
% of Carr's index	1.12	Good
Hausner's ratio	11.14	Good

3.2.Particle Size Analysis:

The mean particle size of optimized polymeric microspheres containing cilnidipine was found to be 77 µm by optical stage micrometer. From Table no: 4, it was found that as the concentration of sodium alginate decreases from 8% to 2.5% w/v, the particle size gets decreased. As the concentration of calcium chloride increases from 20% to 40 % w/v, the particle size gets decreased. As the RPM speed increases from 990 to 2100 rpm, the particle size of polymeric microspheres gets decreased (25).

Table No. 4: Optimization of cilnidipine loaded polymeric microspheres concerning particle size (in µm).

Formulation code (F)	Conc. of sodium alginate (%w/v)	Conc. of Calcium chloride (%w/v)	Speed (rpm)	Particle size (µm)
F1	8	20	990	254
F2	5	25	1620	174
F3	4	40	1980	102
F4	2.5	40	2100	77

3.3.Scanning Electron Microscopy:

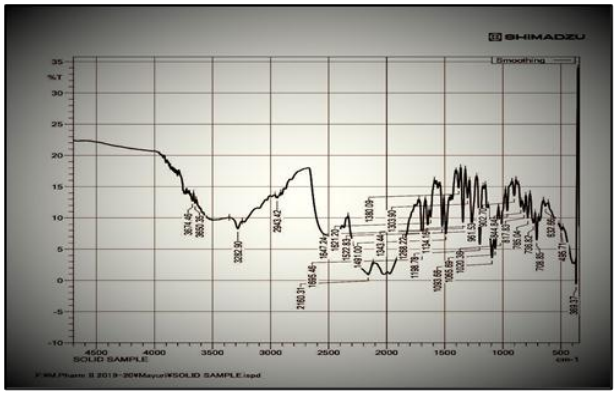
The morphological characteristics of the optimized F4 polymeric microspheres were carried out by scanning electron microscope (JEOL JSM-7600F) as shown in the figure. SEM study revealed that the polymeric microspheres were spherical (Figure no: 4).

Figure No. 4: SEM image of polymeric microspheres containing cilnidipine

3.4.Fourier Transform Infrared Spectroscopy:

FTIR absorption spectrum of cilnidipine was recorded by the potassium bromide pellet technique. FTIR spectrophotometer showed characteristic peak N-H stretch (aromatic 2° C amine)-3458 cm^{-1} C-N stretch (aromatic 2° C amine) -1376 cm^{-1} N-O (Nitro)- 1349 cm^{-1} methoxy(-OCH3)-2801 cm^{-1}. FTIR mixture of the physical structure of cilnidipine along with sodium alginate and calcium chloride showed a characteristic peak at 3349.50 cm^{-1}, 2928.10 cm^{-1}, 1630 cm^{-1}, 1432.16 cm^{-1}, 1080.14 cm^{-1}, 1025.44 cm^{-1} typical of N-H symmetrical stretching vibration C-H stretching, C=O stretching, C=C (Aromatic) stretching and C-N

stretching vibration respectively. These peaks are the characteristic peak of cilnidipine. The result showed that the characteristic peak of cilnidipine was not affected as it was observed in the FTIR spectrum of physical mixture. The result of this observation was concluded that there is no interaction between the cilnidipine (Figure 5a), sodium alginate (Figure 5b), and calcium chloride (Figure 5c).



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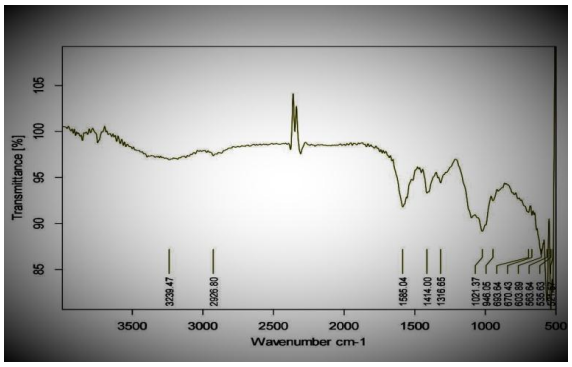

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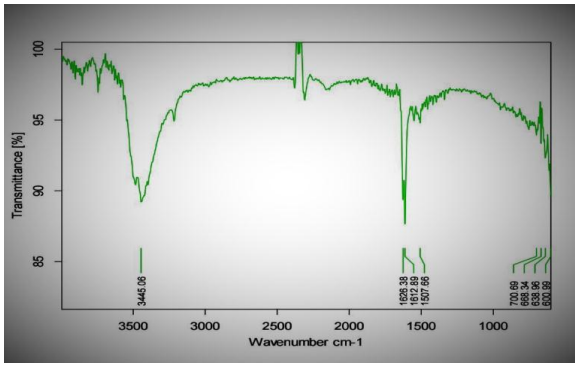

(c)

Figure No. 5: FTIR spectrum of (a) Cilnidipine (b) Sodium alginate (polymer) (c) Calcium chloride (cross-linking agent).

3.5.% drug entrapment efficiency:

Table No. 5: % drug entrapment efficiency study

Formulation code (F)	Conc. of sodium alginate (%w/v)	Conc. of Calcium chloride (%w/v)	% entrapment efficiency
F1	8	20	22
F2	5	25	42
F3	4	40	54
F4	2.5	40	95

From Table no: 5, it can be concluded that conc. of sodium alginate (%w/v) and calcium chloride (%w/v) also influences % drug entrapment efficiency. It was found that as the concentration of sodium alginate decreases from 8% w/v to 2.5% w/v, the entrapment efficiency of the drug gets increased whereas as the concentration of the calcium chloride increases from 20% w/v to 40 % w/v, the entrapment efficiency also gets increased from 22% to 95%.

3.6.Evaluation of Gellan gum gel:

The gellan gum gel was evaluated for appearance, consistency, pH, viscosity, and refractive index (Table no: 6). The cilnidipine loaded polymeric microspheres were then incorporated in gellan gum gel (Figure no: 6).

Table No. 6: Gellan gum evaluation

Parameters	Observation
Appearance	Transparent
Consistency	Thick
pH	7.1
Viscosity	31.66 cps
Refractive index	0.33

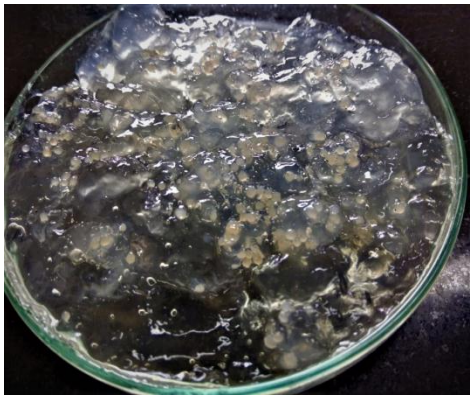

Figure No. 6: Cilnidipine loaded polymeric microspheres incorporated in gellan gum gel.

3.7.*In-vitro* drug release and permeation study:

The *In-vitro* study revealed that the release of the drug from the polymeric microspheres was found to be in the order of F4>F3>F2>F1. The amount of drug released from polymeric microspheres after 8 hrs. was found to be 60.78%, 72.46%, 78.09% & 84.13% for formulations F1, F2, F3 & F4 respectively (Table no: 7 & Figure no: 7). The results obtained through study for optimized F4 polymeric microspheres and marketed formulations of Cilacar and Dilnip tablets were fitted in various kinetic models like zero order, first order, Korsemeyer Peppa's and Higuchi to analyze drug release mechanism and its pattern. From table no:8, it is clear that the Higuchi (matrix) is the best fit model for the polymeric microspheres loaded gel as the plot obtained was of higher linearity (R^2 = 0.93-0.97) which confers that through a diffusion process drug is released from the optimized polymeric microspheres. Korsmeyer Peppa's plot was further analyzed to confirm the release mechanism of optimized polymeric microspheres. The drug release was found to be nonfiction or anomalous type ($0.5<n<1$) as the slope value ranged from 0.61-0.63. Therefore, it can be concluded that the drug release was dependent on both drug diffusion and polymer relaxation, indicating diffusion and erosion mechanisms-anomalous release. Kinetic modeling data of pure drug cilnidipine was also carried out to illustrate drug release mechanism and its pattern as given in table no: 9 (26).

Table No. 7: Data for *In-vitro* cumulative % drug release data of formulations F1-F4

Time (min)	F1	F2	F3	F4
0	0	0	0	0
15	12.24	14.64	16.24	18.65
30	16.24	16.78	23.20	23.45
45	23.46	23.73	29.41	33.09
60	29.76	30.21	32.21	44.20
120	33.85	34.00	40.23	47.54
180	41.19	45.24	49.85	51.98
240	45.43	46.23	56.23	54.32
300	47.14	50.14	58.74	58.04
360	50.17	52.34	61.35	62.13
480	53.28	58.65	64.28	70.12

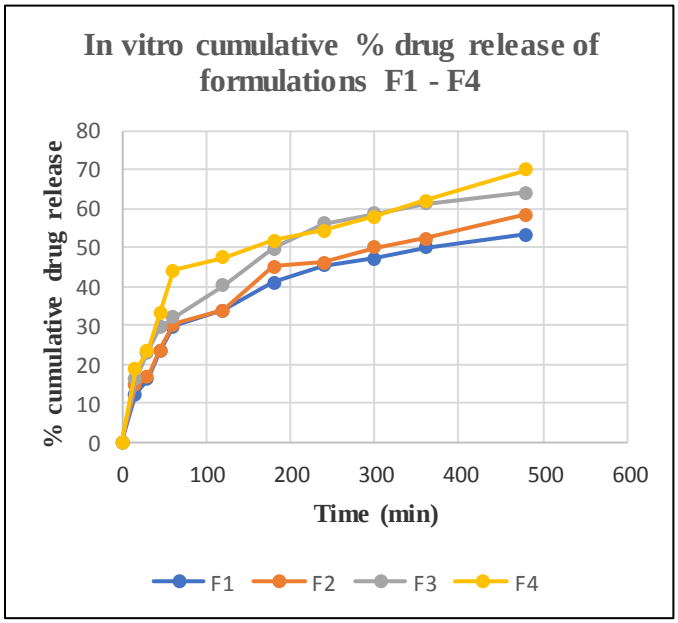

Figure No. 7: In vitro cumulative % drug release of formulation F1 – F4

Table No. 8: In vitro kinetic modeling data of formulation F1-F4

Release type	Formulation code	R^2	Slope
Zero-order	F1	0.82	0.19
	F2	0.85	0.213
	F3	0.83	0.2319
	F4	0.73	0.2483
First-order	F1	0.811	-0.00121
	F2	0.91	-0.0013
	F3	0.90	-0.0015
	F4	0.80	-0.0016
Higuchi	F1	0.97	3.115
	F2	0.97	3.2791
	F3	0.98	3.637
	F4	0.92	4.0237
Korsmeyer Peppas	F1	0.93	0.6168
	F2	0.93	0.6205
	F3	0.92	0.6353
	F4	0.89	0.6321

Table No. 9: In vitro kinetic modeling data of pure drug cilnidipine

Drug	Release	R^2	Slope
Pure cilnidipine	Zero-order	0.6987	0.2189
	First order	0.9271	3.6353
	Higuchi	0.7748	-0.0014
	Korsemeyer Peppa's	0.8814	0.6195

Table No. 10: Comparative studies of in-vitro permeation studies of optimized polymeric microspheres (F4) and marketed formulation Cilacar and Dilnip tablets

Time (min)	F4	Cilacar	Dilnip
0	0	0	0
15	18.65	25.87	22.65
30	23.45	35.17	33.13
45	33.09	42.16	40.09
60	44.20I	51.18	47.15
120	47.54	59.98	57.23
180	51.98	54.23	59.98
240	54.32	53.18	61.24
300	58.04	56.18	56.34
360	62.13	51.67	53.21
480	70.12	49.90	51.17

In vitro permeation study for optimized F4 polymeric microspheres was also carried out to evaluate the drug release mechanism and its pattern. From table no:10 it can be concluded that the Higuchi (matrix) is the best fit model considered for in vitro permeation as it has the highest linearity plot of R^2 = 0.90. Further, Korsemeyer Peppa's plot was analyzed to determine the drug release mechanism. As the slope value was found to be within the range of 0.5-1, the drug release mechanism was found to be of the non-fickian or anomalous type as given in table no:11. From figure no: 8, it is clear that optimized F4 polymeric microspheres provide sustained effect and prolonged the retention time of drugs at the site of action in comparison to marketed formulations Cilacar and Dilnip tablets (26).

3.8.*In vitro* permeation study:

Table No. 11: *In vitro* permeation studies of F4 optimized polymeric microspheres

Formulation	Release type	R^2	Slope
F4 optimized polymeric microspheres	Zero-order	0.6719	0.1852
	First order	0.7341	-0.0011
	Higuchi	0.9057	3.100
	Korsemeyer Peppa's	0.9035	0.6149

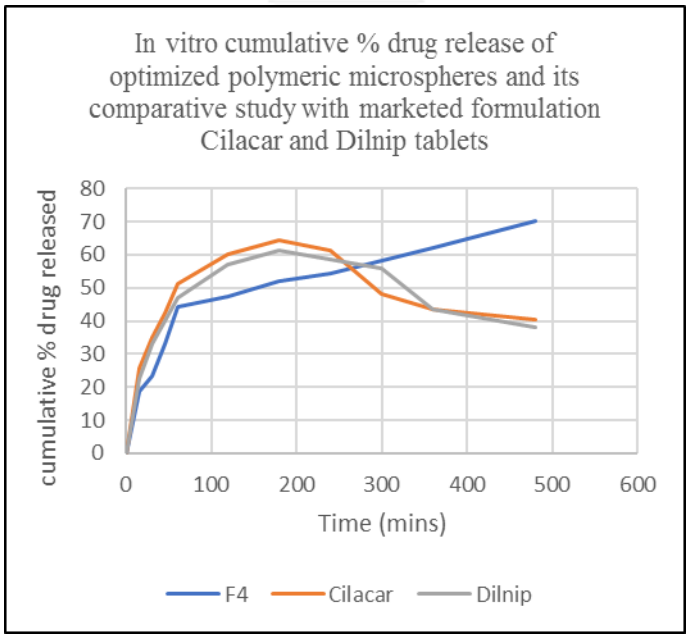

Figure No. 8: In-vitro permeation studies of optimized polymeric microspheres and its comparative study with marketed formulations Cilacar and Dilnip tablets using goat buccal mucosa

3.9.Stability studies:

Table No. 12: Degradation of Cilnidipine in polymeric microspheres at 40°C ± 2°C / 75 ± 5% RH

Time (days)	40°C ± 2°C / 75 ± 5% RH		
	Drug content (mg)	% drug remaining	Log % drug remaining
0	6	100	2
30	5.91	98.5	1.9934
60	5.82	97	1.9867
90	5.78	96.3	1.9836

Table No. 13: Degradation of Cilnidipine in polymeric microspheres at 25ºC ± 2ºC / 60 ± 5 % RH

Time (days)	25 ± 2°C / 60 ± 5% RH		
	Drug content	% of drug content	Log% drug remaining
0	6	100	2
30	5.93	99.33	1.9970
60	5.89	98.16	1.9919
90	5.82	97	1.9897

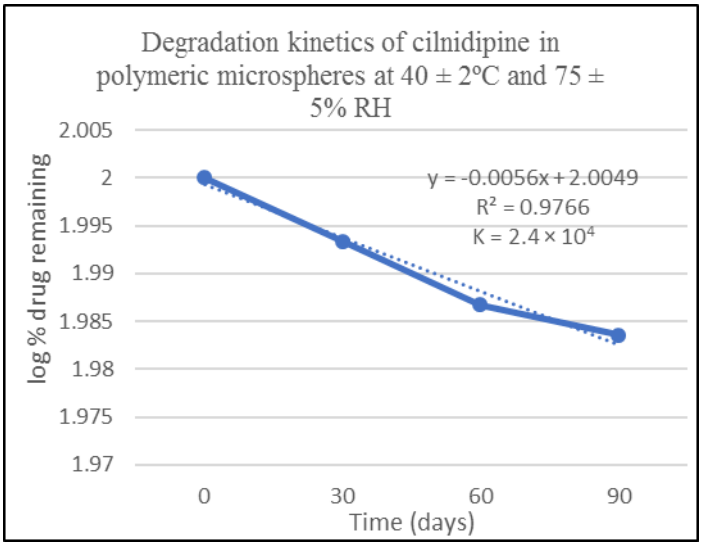

Figure No. 9: Degradation kinetics of Cilnidipine in polymeric microspheres at 40°C ± 2°C / 75 ± 5% RH

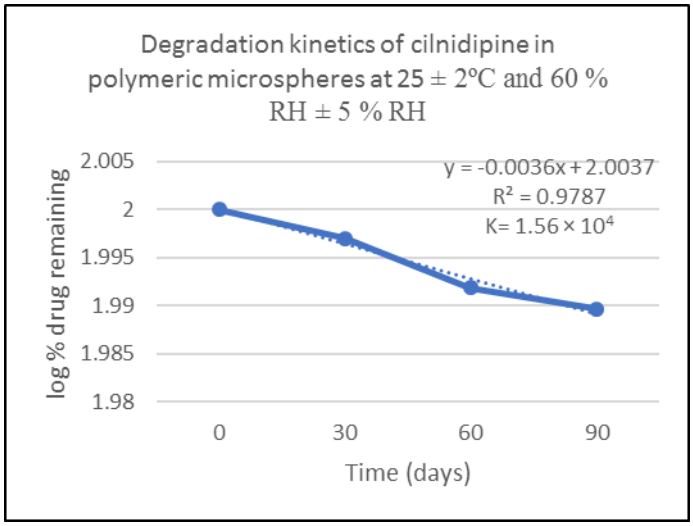

Figure No. 10: Degradation kinetics of Cilnidipine in polymeric microspheres at 25ºC ± 2ºC / 60 ± 5 % RH

Table No. 14: Assay of sample kept for stability studies and rate constant.

Stability studies	Drug content	Rate constant
40°C ± 2°C / 75 ± 5% RH	93.11 ± 0.49 %	2.4×10^4
25ºC ± 2ºC / 60 ± 5 % RH	97.98 ± 1.34 %	1.56×10^4

The stability studies were conducted at two different conditions at accelerated stability conditions and real-time stability conditions and the results were found to be satisfactory. The degradation kinetics of cilnidipine in polymeric microspheres at two different conditions has been illustrated (Table no: 12 and 13) and plotted (Figure no: 9 & 10). The rate constant (K) for accelerated conditions 40°C ± 2°C / 75 ± 5% RH were found to be 2.4×10^4 and real-time stability conditions 25ºC ± 2ºC / 60 ± 5 % RH were found to be 1.56×10^4. Assay of sample kept at two different conditions 40°C ± 2°C / 75 ± 5% RH and 25ºC ± 2ºC / 60 ± 5 % RH was performed and found satisfactory (Table no: 14).

4. CONCLUSION:

It can be concluded that the ionic gelation technique is a simple and reproducible method for the preparation of cilnidipine polymeric microspheres. With the above results, it states that various formulation parameters have a direct effect on the release rate of drug, entrapment efficiency, and particle size. Polymeric microspheres of cilnidipine were evaluated for particle size, surface morphology, FTIR spectrum. In vitro drug release of polymeric

microspheres containing cilnidipine was also carried out to determine drug release from polymeric microspheres. From the in vitro studies, formulation F4 showed a maximum drug release of 70.12 % in 480 min (8hrs.) in comparison to formulations F1, F2, and F3. The in vitro drug release and permeation studies results revealed that the diffusion process and non-fickian or anomalous type of release mechanism is responsible for drug release from optimized polymeric nanoparticles. The stability study for polymeric microspheres containing cilnidipine was carried out at 40°C ± 2°C / 75 ± 5% RH and 25 ± 2°C / 60 ± 5% RH as per ICH guidelines. Optimized polymeric microsphere formulation F4, Cilacar and Dilnip tablets showed a drug release of 70.12%, 49.90% and 51.17% respectively. This indicates that the optimized formulation F4 showed an improved permeability with sustained release of drug in comparison to marketed formulations Cilacar and Dilnip. Thus, buccal gel loaded cilnidipine polymeric microspheres was developed as a novel approach to provide a sustained effect and prolong the retention of drug at the site of action.

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