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Formulation and Evaluation of Candesartan Niosomal Floating Gel Formulation

Dr M Sunitha Reddy*,
Nazari Sai Bhavana Centre for pharmaceutical sciences, Institute of science and technology, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad-500085, Telangana State, India.

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ABSTRACT
Niosomes are lamellar structures that are microscopic in size. Niosomes constitute a non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous medium.
Candesartan is an angiotensin receptor blocker used mainly for the treatment of blood pressure and congestive heart failure. Candesartan has a low maintenance dose. To increase the bioavailability candesartan niosomal formulation was formulated. The candesartan niosomal formulation was formulated using handshaking method. Cholesterol and surfactantslike Span 60 are used in formulating the candesartan niosomal formulation. To overcome the problem of short gastro residence time novel approach to increase the gastro residence have made. Gelling agents like Xanthan gum, guar gum, sodium alginate and Carbopol are used in formulating candesartan niosomal floating gel formulation. In this research we have discussed a novel approach to gastro retentive drug delivery system. This achieves increased residence as well as sustained release. This system is useful for systemic as well as local effect of drugs administered. In this research we have discussed a novel approach to gastro retentive drug delivery system.
keywords: niosomes, surfactants

I. INTRODUCTION

Niosomes are promising drug carriers that have bilayer structure and are self-associating structures of non-ionic surfactants and cholesterol in aqueous phase. They are biocompatible, nonimmunogenic and biodegradable. They are stable, have long shelf life, and enable to deliver the drug to targeted site of action, and also deliver the drug in controlled or sustained released pattern. Over the time various studies have been conducted on niosomes and various types of niosomes have been reported to niosomes and enable the entrapment of a large number of drugs with wide range of solubility.

STRUCTURE OF NIOSOMES

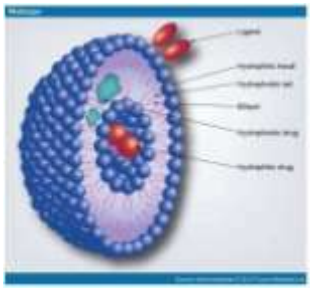

Fig1: structure of niosome

MATERIALS

All the materials and equipment used in the formulation, evaluation and other experiments are given below.

Table 1 List of materials used with supplier

Category	Chemical Name
Drug	Candesartan

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Lipid	Cholesterol
Surfactants	Span-60
Volatile solvents	Ethanol and Methanol
Gelling Agents	Sodium alginate, Xanthane gum, Guar gum, Carbapol.

INSTRUMENTS USED

Table 2 List of equipment's used with manufacturers

S.No.	Instruments	Supplier
1	Analytical Balance	Sartorius, India
2	UV- Spectrophotometer	Shimadzu, Japan
3	Milli-Q Water Purifier	Millipore (India) Pvt.Ltd
4	Electronic Balance	Shimadzu
5	FTIR Spectrophotometer	Bruker-Alpha
6	Light Microscope	Bio Techniques, Mumbai
7	pH Meter	Systronics
8	Diffusion Apparatus	Locally Fabricated
9	Micro pipette	Pfact
10	Zeta sizer	Malvern zeta sizer

Formulation design for Candesartan noisome preparation:

Candesartan niosome were prepared by hand shaking method.

This method was prepared niosomes by dissolving the ingredients like surfactant, Cholesterol dissolved in volatile organic solvent in RBF. The organic solvent is expelled at room temperature using rotary evaporator leaving the thin layer of solid mix deposited on the walls of the flask. The dried surfactant film is rehydrated with aqueous phase at 0-60^{0}C with gentle agitation. This procedure forms typical MLN.

Table 3 Formulation of candesartan niosomal formulation

Formulation codes	Drug: cholesterol: surfactants (Span-60)
CANDIF1	1:1:1
CANDIF2	1:1:2
CANDIF3	1:1:3
CANDIF4	1:1:4
CANDIF5	1:1:5
CANDIF6	1:1:6
CANDIF7	1:1:7
CANDIF8	1:1:8
CANDIF9	1:1:9
CANDIF10	1:1:10

Preparation of niosomal floating gel preparation:

The optimal niosomal formulation is selected which acts as a lipid phase and to it aqueous gelling agents like sodium alginate, guar gum, xanthane gum and Carbopol were added in optimal formulations to form candesartan niosomal floating gel formulation.

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Table 4 Floating gel formulation

Formulation	Sodim Alginate	Guar Gum	Xanthan Gum	Carbapol	Total polymer concentration (w/v)
CANDIFSG1	0.2	0.4			0.6
CANDIFSG2	0.4	0.2			0.6
CANDIFSX1	0.2		0.4		0.6
CANDIFSX2	0.4		0.2		0.6
CANDIFSC1	0.2			0.4	0.6
CANDIFSC2	0.4			0.2	0.6
CANDIFGX1		0.2	0.4		0.6
CANDIFGX2		0.4	0.2		0.6
CANDIFGC1		0.2		0.4	0.6
CANDIFGC2		0.4		0.2	0.6
CANDIFXC1			0.2	0.4	0.6
CANDIFXC2			0.4	0.2	0.6
CANDIFSGX	0.2	0.2	0.2		0.6
CANDIFSGXC	0.2	0.2	0.2	0.2	0.8

II. RESULTS

Physical appearance: Physical appearance of the drug was examined by organoleptic properties and results were obtained as follows.
Color: White

Solubility studies:

Table 5 Candesartan solubility studies

Solvents	Solubility
Water	Insoluble
Methanol	Soluble
Ethanol	Soluble
Chloroform	soluble

Calibration curve

Table 6 Concentration v/s Absorbance

Sr No.	Conc.(u g/ml)	Absorbance
1	2.5	0.127
2	5	0.228
3	10	0.423
4	15	0.634
5	20	0.912

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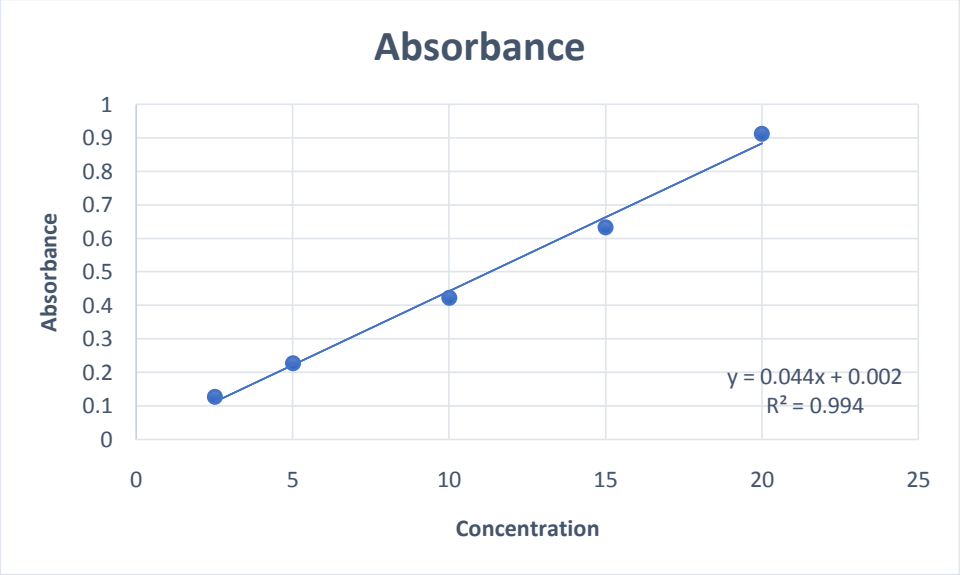

Fig 2 Calibration cure of candesartan in methanol

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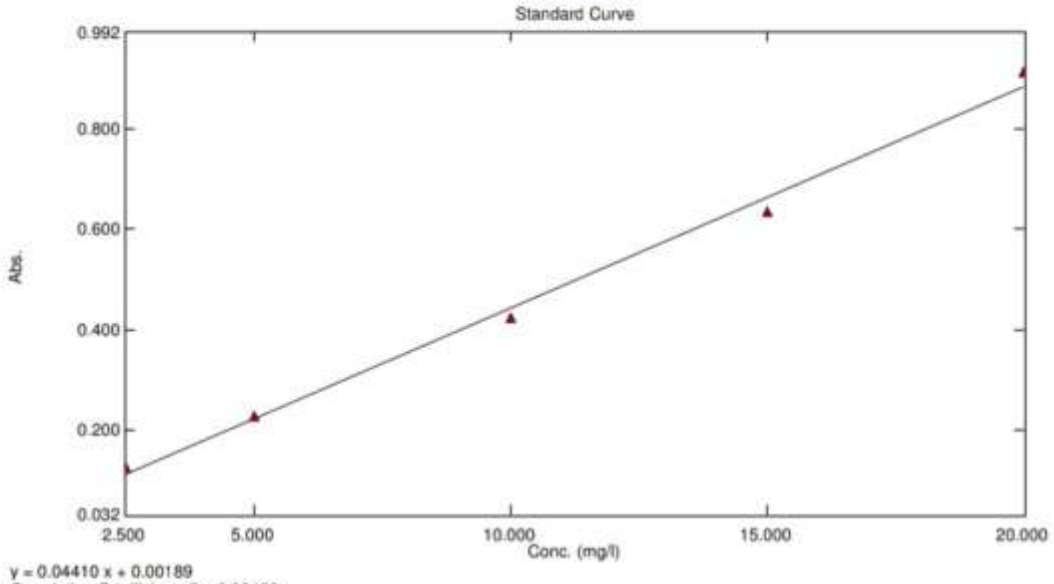

y = 0.04410 x + 0.00189
Correlation Coefficient r2 = 0.99420

Standard Table

	Sample ID	Type	Ex	Conc	WL253.0	Wgt.Factor	Comments
1	2.5ppm	Standard		2.500	0.127	1.000	
2	5ppm	Standard		5.000	0.228	1.000	
3	10ppm	Standard		10.000	0.423	1.000	
4	15ppm	Standard		15.000	0.634	1.000	
5	20 ppm	Standard		20.000	0.912	1.000	

Fig 3 Candesartan calibration cuurve

Drug excipient compatibility study:
Fourier transform infrared spectroscopy

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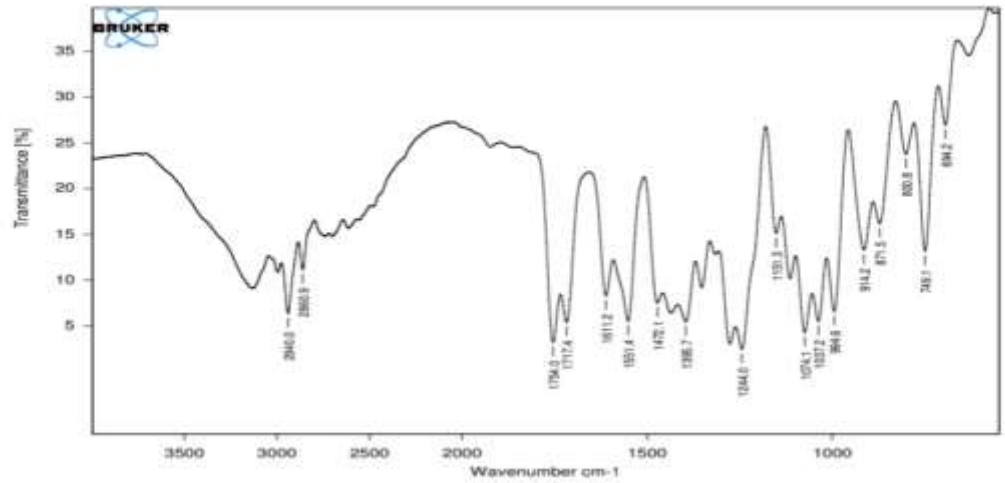

Fig 4 FTIR Spectrum of candesartan

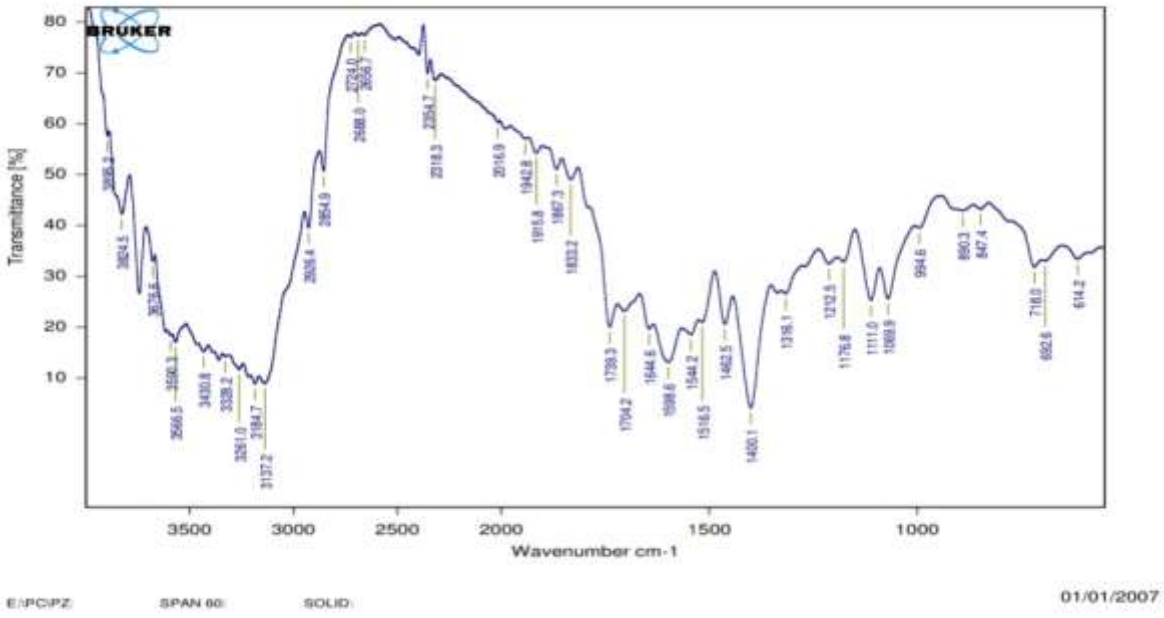

Fig 5 FTIR Spectrum of Span-60

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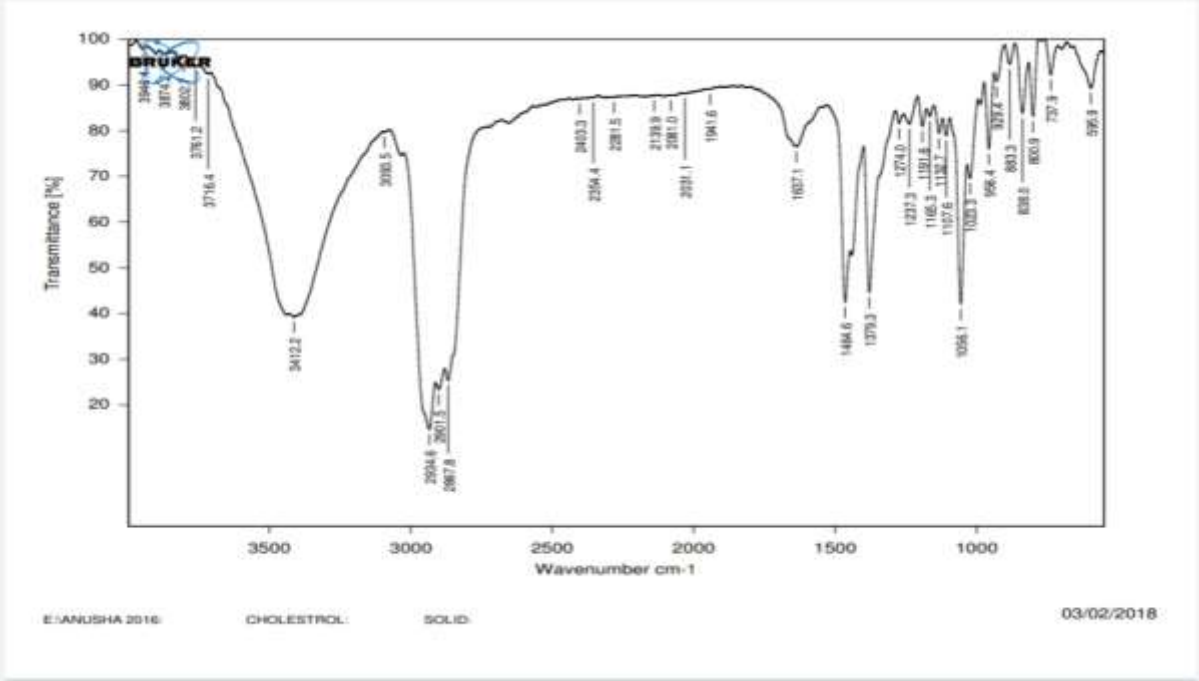

Fig 6 FTIR Spectrum of Cholesterol

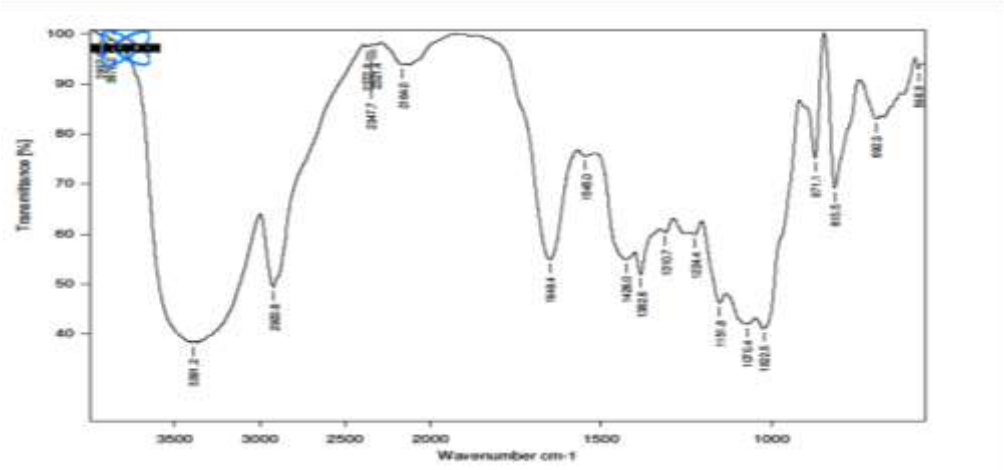

Fig 7 FTIR Spectrum of Guar gum

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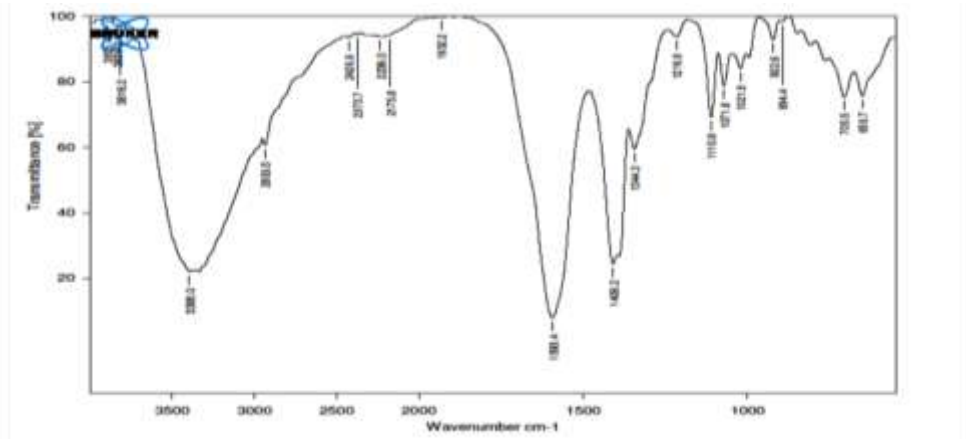

Fig 8 FTIR Spectrum of Sodium alginate

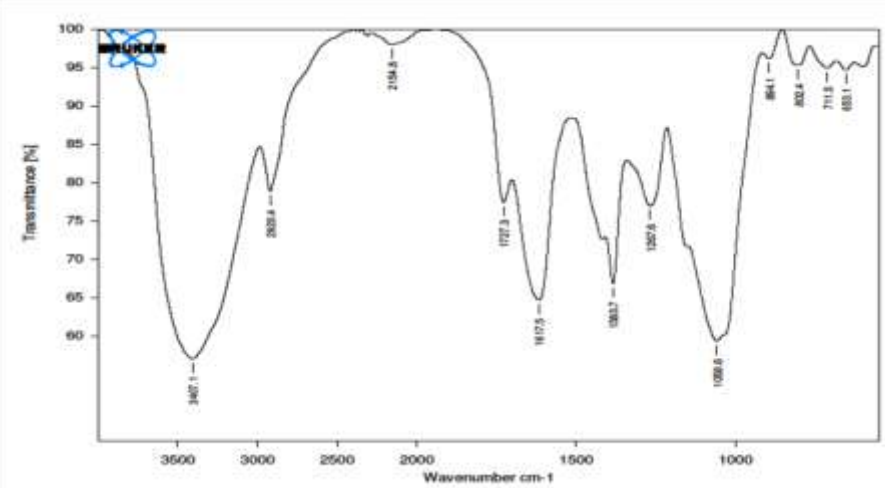

Fig 9 FTIR Spectrum of Xanthan gum

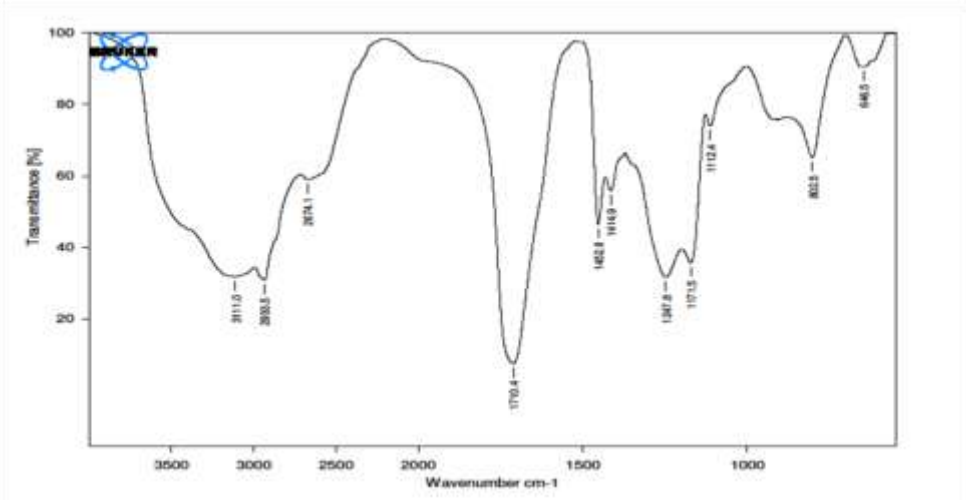

Fig 10 FTIR Spectrum of Carbopol

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Entrapment efficiency:

Table 7 % Drug entrapped

Formulation code	% Entrapment efficiency
Candi F1	71
Candi F2	73
Candi F3	76
Candi F4	80
Candi F5	84
Candi F6	87
Candi F7	93
Candi F8	83
Candi F9	85
Candi F10	89

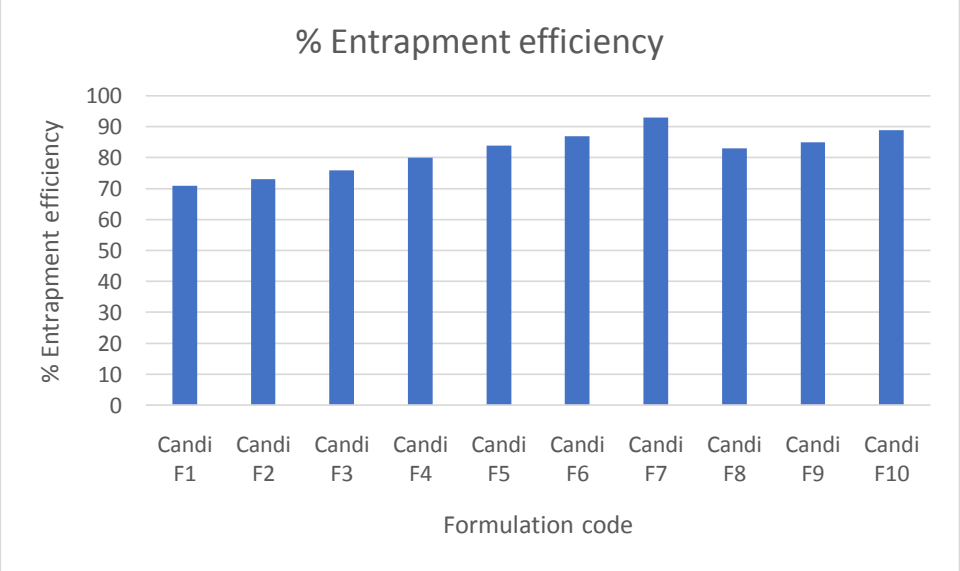

Fig 11 % Entrapment efficiency

Clarity Test:

Niosomal floating gel formulation was found to be viscous white gel, All the formulations were free from particles.

Table 8 Clarity of niosomal formulation

Formulation code	Clarity
CANDI F1	++
CANDI F2	++
CANDI F3	+++
CANDI F4	+++
CANDI F5	+++
CANDI F6	+++
CANDI F7	+++
CANDI F8	++

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CANDI F9	+++
CANDI F10	+++

pH Value:
The pH values of all the formulations were measure using digital pH meter at room temperature. The pH of all topical niosomal gels were found to be:

Table 9 pH of niosomal floating gel formulation

Formulation codes	pH
CANDIFSG1	6.5
CANDIFSG2	6.6
CANDIFSX1	6.5
CANDIFSX2	6.42
CANDIFSC1	6.5
CANDIFSC2	6.21
CANDIFGX1	6.74
CANDIFGX2	6.5
CANDIFGC1	6.72
CANDIFGC2	6.76
CANDIFXC1	6.3
CANDIFXC2	6.4
CANDIFSGX	6.5
CANDIFSGXC	6.8

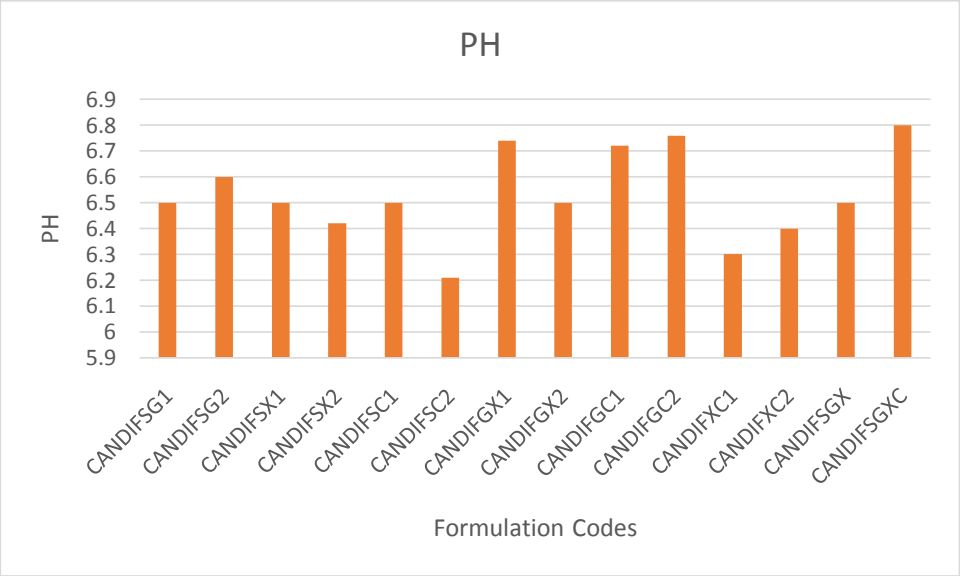

Fig 12 pH

Homogeneity:
All the formulations were prepared showed good homogeneity clear and without lumps.

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Table 10 Homogeneity of niosomal formulation

Formulation code	homogeneity
Candi F1	Good
Candi F2	Good
Candi F3	Good
Candi F4	Good
Candi F5	Good
Candi F6	Good
Candi F7	Good
Candi F8	Good
Candi F9	Good
Candi F10	Good

Fluorescence microscopy: The following image shows the niosomal formulation under fluorescence microscope.

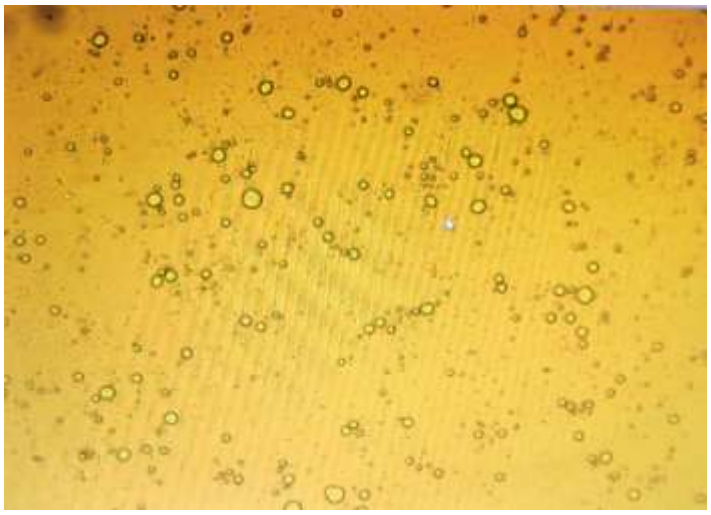

Fig 13 Candesartan niosomal formulation (CANDIF7) without drug

The following image shows candesartan niosomal formulation under fluorescence microscope.

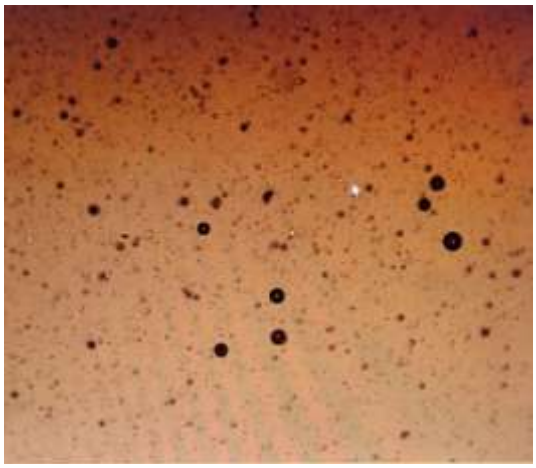

Fig 14 Candesartan niosomal formulation (CANDIF7) with drug

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In vitro drug diffusion studies:

In vitro drug release studies were carried out in franz diffusion cell.

Table 11 % Cumulative drug release of niosomal gel formulation ±standard deviation (n=3)

Time in Hrs	CANDIF1	CANDIF2	CANDIF3	CANDIF4	CANDIF5	CANDIF6	CANDIF7	CANDIF8	CANDIF9	CANDIF10
0	0	0	0	0	0	0	0	0	0	0
1	3±0.20	2.5±0.92	2.7±0.50	3.4±0.81	3.8±0.97	4.1±0.88	6.4±0.21	5.2±0.54	4.8±0.22	5.4±0.16
2	6.4±0.64	4.1±0.87	8.7±0.59	9.8±0.76	10.7±0.22	9.8±0.67	16.3±0.90	10.4±0.80	10.4±0.71	7.2±0.23
3	8.1±0.72	9.6±0.78	16.7±0.21	14.6±0.56	14.8±0.45	12.8±0.76	24.9±0.99	16.8±0.65	12.3±0.53	9.7±0.92
4	12.3±0.57	15±0.67	20.4±0.40	21.2±0.98	24.7±0.44	18.3±0.57	32.8±0.70	21.4±0.34	18.6±0.42	12.2±0.88
5	18.3±0.90	29.4±0.69	28.4±0.81	29.7±0.55	32.1±0.76	28.1±0.29	41.2±0.57	32.6±0.21	26.4±0.27	24.6±0.57
6	28.1±0.54	45.2±0.23	34.8±0.91	32.6±0.38	40.1±0.57	37.6±0.75	52.7±0.77	48.2±0.71	34.9±0.96	30.3±0.77
7	35.5±0.32	50.1±0.53	46.7±0.62	38.4±0.79	48.7±0.77	48.4±0.89	66.8±0.98	60.4±0.27	46.3±0.69	42.3±0.34
8	40.9±0.33	55.1±0.45	52.2±0.52	48.2±0.81	56.4±0.43	66.5±0.49	79.4±0.55	77.4±0.98	57.4±0.59	54.8±0.66
12	44.3±0.26	57.1±0.29	55.1±0.39	52.3±0.18	68.9±0.67	70.1±0.39	87.6±0.65	81.2±0.26	77.1±0.88	68.2±0.89
24	52.3±0.4	60.1±0.33	60.5±0.98	68.5±0.21	72.5±0.52	74.5±0.76	94.8±0.32	85.4±0.33	82.7±0.71	78.5±095

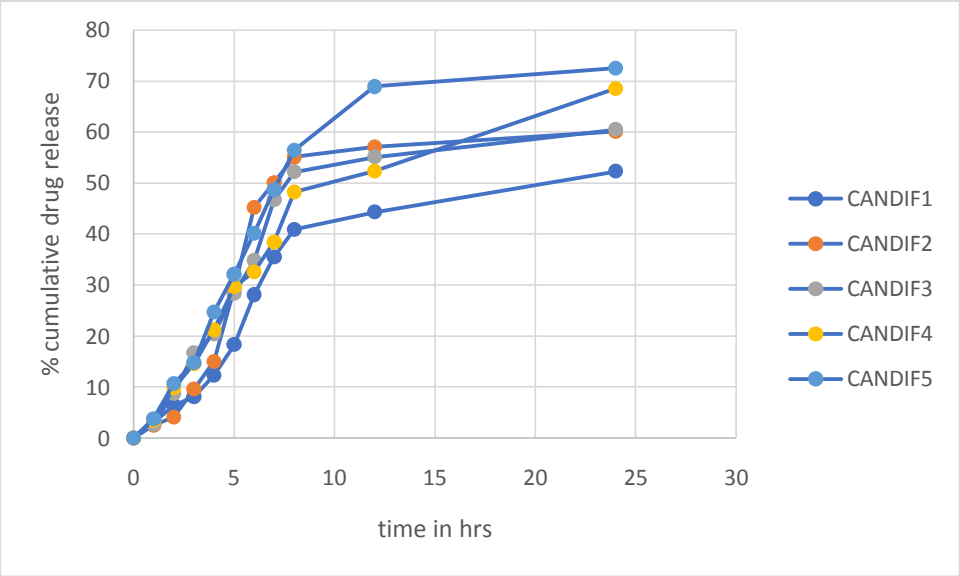

Fig 15 % Cumulative drug release of candesartan niosomal formulation F1 to F5

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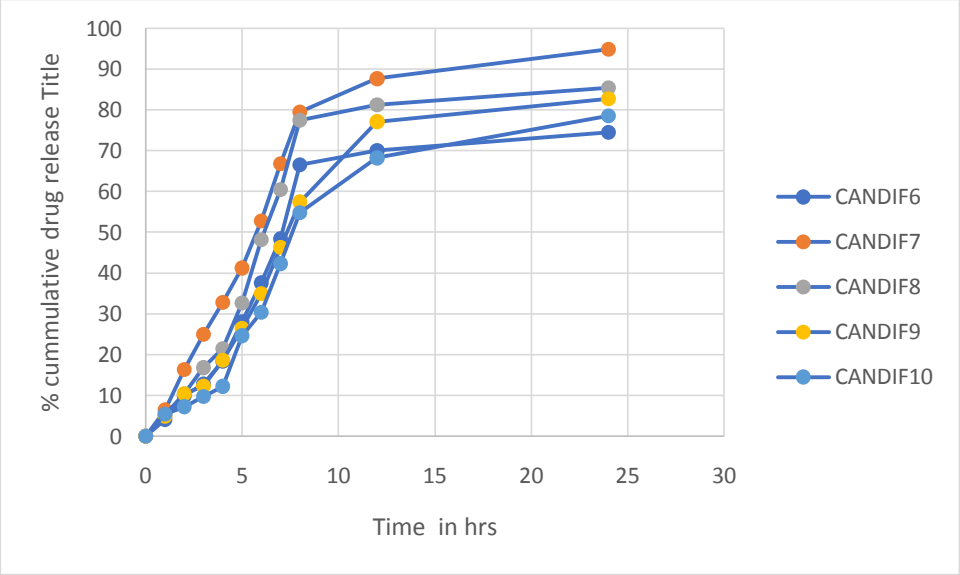

Fig 16 % Cumulative drug release of candesartan niosomal formulation F6 to F10

Zeta sizer: The average particle size of the formulation CANDIF7 was found to be 66.16 and the PDI was 0.467.

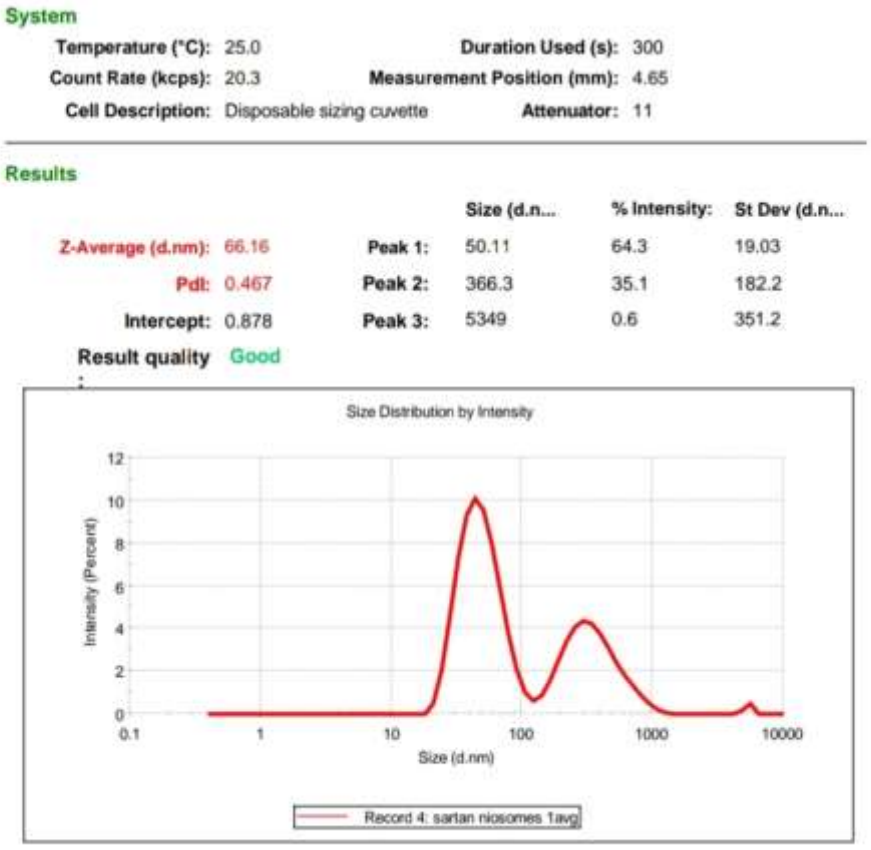

Fig 17 Particle size determination of CANDIF7 formulation

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In vitro drug diffusion studies: The samples are withdrawn from the receptor compartment at specified time intervals and are analysed in using and cumulative % drug release was calculated against time.

Table 12 Invitro drug release of candesartan niosomal floating gel formulation ± standard deviation (n=3)

Time (in hrs)	CANDIFSG1	CANDIFSG2	CANDIFSX1	CANDIFSX2	CANDIFSC1	CANDIFSC2	CANDIFGX1	CANDIFGX2	CANDIFGC1	CANDIFGC2	CANDIFXC1	CANDIFXC2	CANDIFSGX	CANDIFSGXC
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	12.18±0.88	18.45±0.76	16.55±0.37	13.14±0.67	8.11±0.49	15.21±0.75	17.31±0.76	14.72±0.40	6.16±0.66	8.66±0.70	7.6±0.17	9.06±0.15	25.77±0.79	30.01±0.43
2	14.89±0.21	23.76±0.89	22.20±0.58	17.05±0.79	14.70±0.72	21.77±0.39	25.05±0.23	17.90±0.29	10.77±0.43	14.09±0.29	15.40±0.55	17.44±0.85	33.06±0.67	39.57±0.33
3	19.08±0.78	26.58±0.77	27.08±0.99	26.50±0.86	23.65±0.28	27.14±0.77	33.54±0.98	26.43±0.87	13.61±0.55	17.50±0.77	23.43±0.19	29.09±0.57	39.76±0.34	47.33±0.17
4	21.54±0.36	30.06±0,54	31.90±0.49	32.67±0.48	27.34±0.22	31.54±0.89	47.40±0.54	32.55±0.28	23.88±0.99	22.40±0.63	37.08±0.26	39.45±0.66	44.07±0.21	53.07±0.87
5	23.07±0.22	35.21±0.27	37.51±0.28	40.43±0.75	31.08±0.14	35.34±0.99	53.06±0.65	37.20±98	29.09±0.54	27.07±0.44	40.04±0.76	43.55±0.61	49.09±0.44	56.57±0.54
6	26.71±0.76	43.06±0.32	45.12±0.88	43.07±0.95	35.54±0.92	41.67±0.58	61.50±0.43	43.31±0.56	35.60±0.34	32.66±0.91	43.33±0.98	49.29±0.76	56.88±o.32	64.43±0.87
7	30.11±0.98	47.03±0.66	54.58±0.79	47.04±0.55	37.90±0.81	47.89±0.44	65.32±0.33	46.12±0.34	38.55±0.69	35.04±0.98	47.60±0.89	52.09±0,99	67.64±0.93	71.39±0.57
8	33.90±0.17	50.08±0.92	68.12±0.63	60.67±0.37	45.33±0.29	53.44±0.96	67.80±0.32	53.88±0.54	44.11±0.92	39.33±0.42	57.67±0.66	59.55±0.43	73.34±0.21	83.07±0.74
12	38.05±0.55	57.97±0.47	70.66±0.78	65.58±0.44	53.60±0.36	57.44±0.54	70.01±0.19	63.32±0.67	47.50±0.51	44.30±0.11	59.58±0.45	67.43±0.32	79.02±0.73	87.07±0.25
24	42.99±0.66	65.57±0.76	74.48±0.33	68.64±0.78	58.01±0.59	62.43±0.19	78.66±0.22	69.29±0.55	56.43±0.32	48.07±0.49	63.04±0.54	68.66±0.71	86.71±0.65	93.90±0.43

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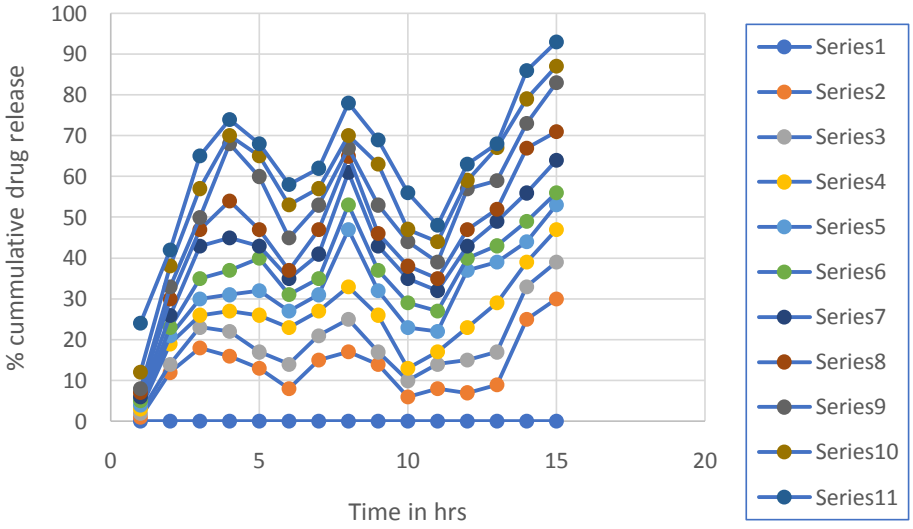

Fig 18 % Drug release of candesartan niosomal floating gel formulation

Kinetic drug release:

Table 13 Drug release kinetics of optimized niosomal floating gel formulation (CANDIFSGXC)

Time in Hrs	% Cummulative Drug Release	% Drug remaining	Square root of time	Log time	Log % CDR	Log % drug remaining	cube root of % drug remaining(wt)	W0-Wt
0	0	100	0	0	0	2	4.641588834	0
1	30	70	1	0	1.477121	1.84509804	4.1212853	0.52
2	39	61	1.414213562	0.30103	1.591065	1.785329835	3.936497183	0.71
3	47	53	1.732050808	0.477121	1.672098	1.72427587	3.756285754	0.89
4	53	47	2	0.60206	1.724276	1.672097858	3.60882608	1.04
5	56	44	2.236067977	0.69897	1.748188	1.643452676	3.530348335	1.11
6	64	36	2.449489743	0.778151	1.80618	1.556302501	3.301927249	1.34
7	71	29	2.645751311	0.845098	1.851258	1.462397998	3.072316826	1.57
8	83	17	2.828427125	0.90309	1.919078	1.230448921	2.571281591	2.07
12	87	13	3.464101615	1.079181	1.939519	1.113943352	2.351334688	2.29
24	93	7	4.898979486	1.380211	1.968483	0.84509804	1.912931183	2.73

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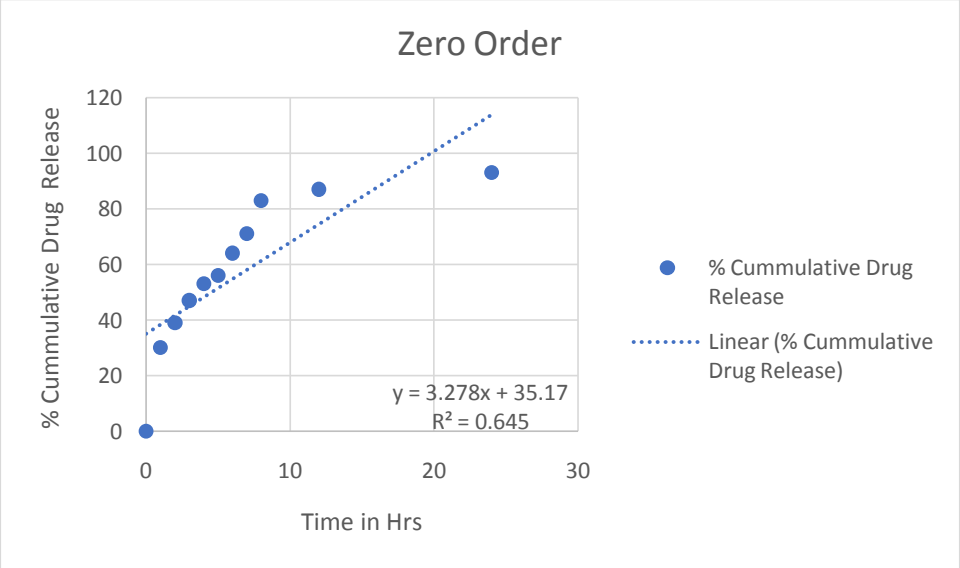

Fig 19 Zero order kinetics

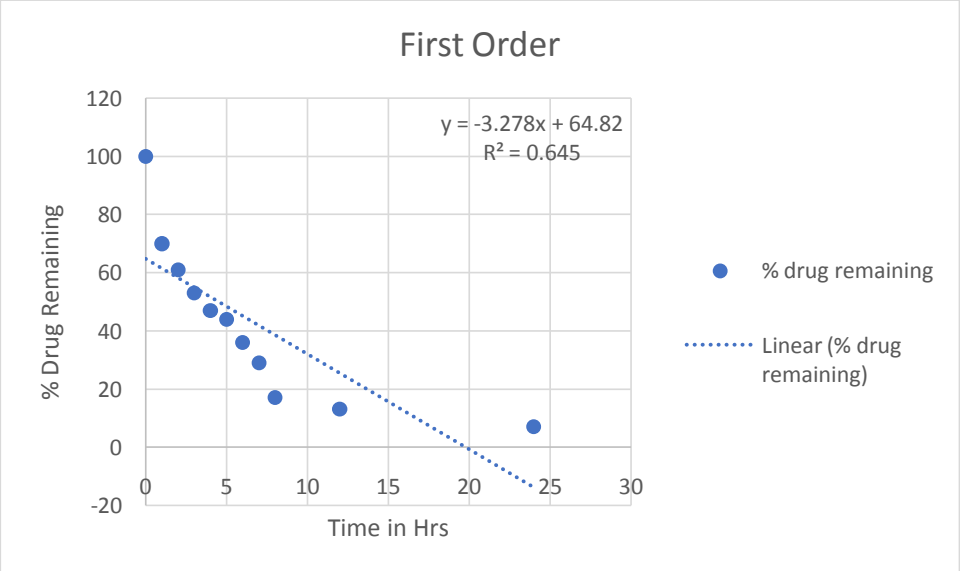

Fig 20 First order Kinetics

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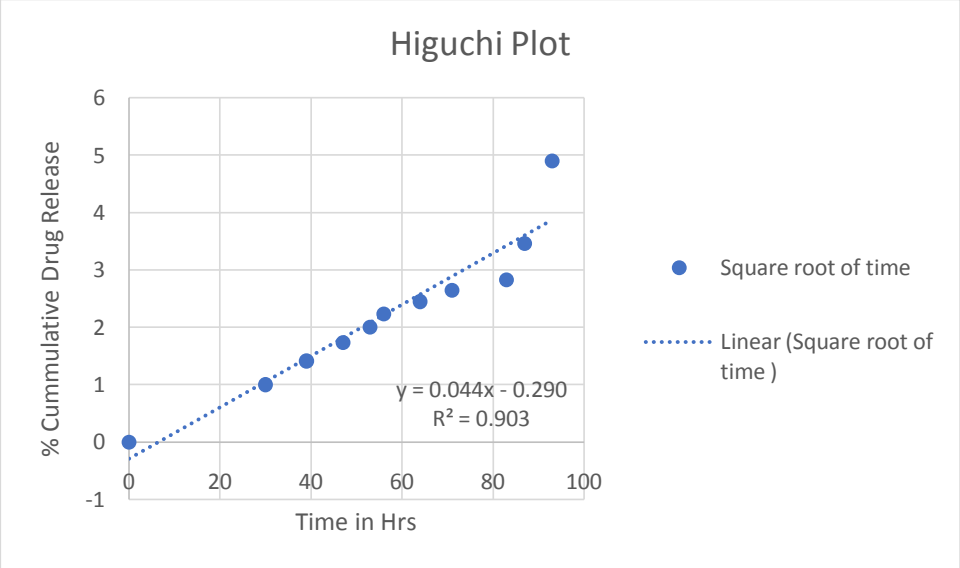

Fig 21 Higuchi plot

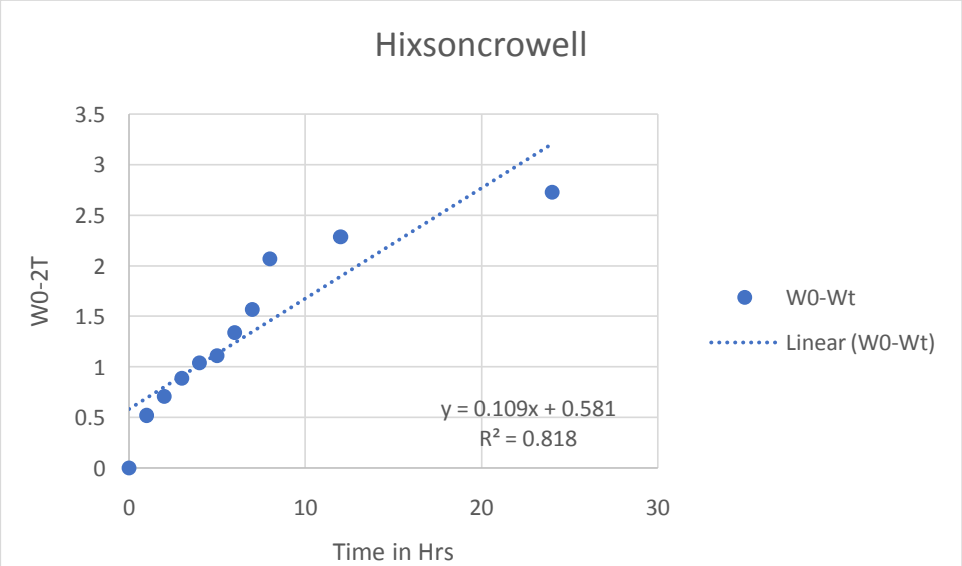

Fig 22Hixsoncrowell plot

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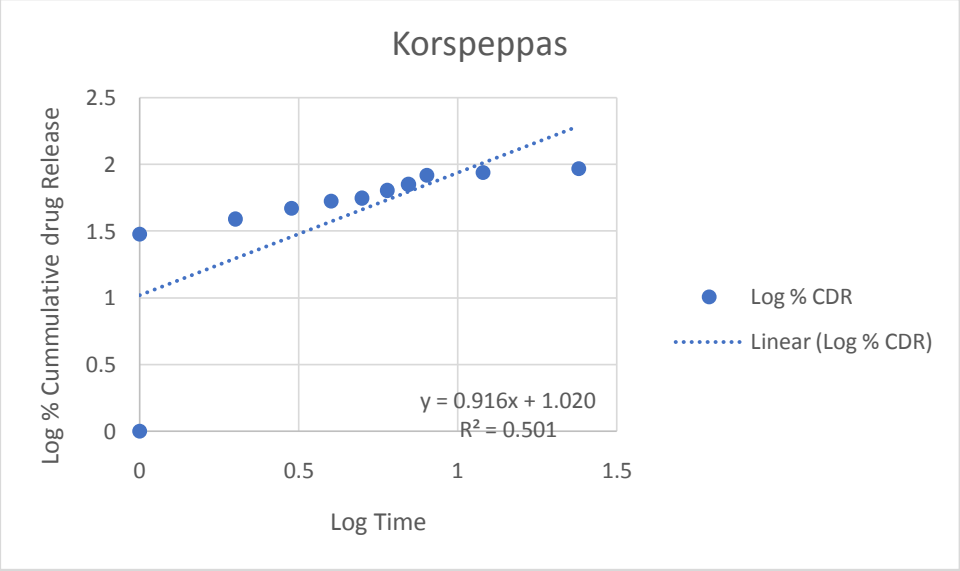

Fig 23Korspeppas model

Table 14 Drug release kinetics of optimized floating gel formulation (CANDIFSGXC)

Kinetics Model	**r^2 Value**
Zero order	0.6458
First order	0.6458
Higuchi	0.9037
Korsmayer- Peppas kinetics	0.5018
Hixson crowell kinetics	0.8189

Stability studies
pH:

Table 15 pH of optimized formulation CANDIFSGXC

Time (days)	pH of CANDIFSGXC
0	6.8±0.3
30	6.7±0.2
60	6.5±0.2
90	6.45±0.3
120	6.3±0.3

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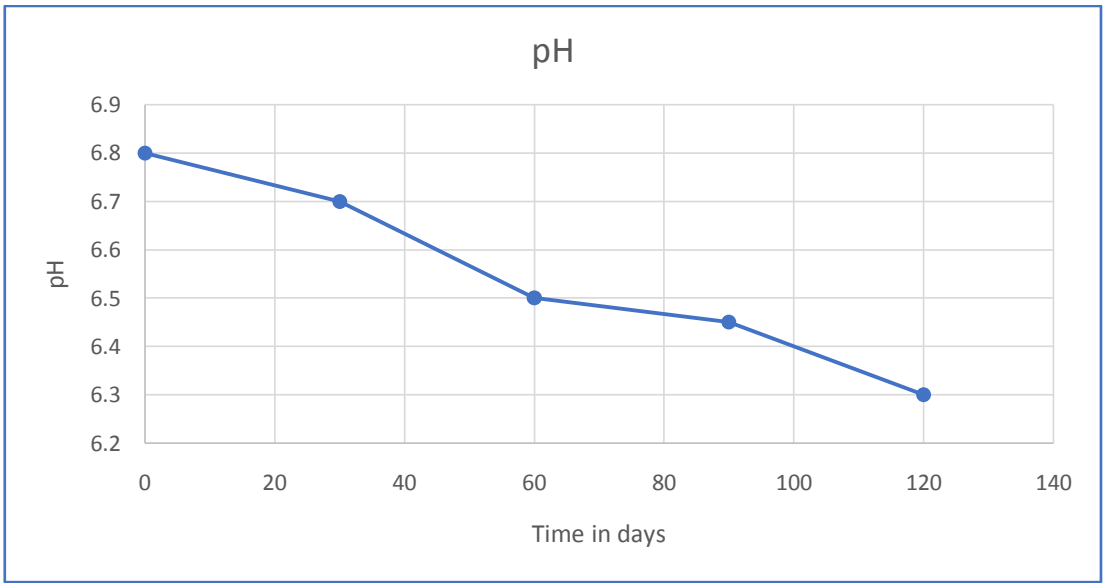

Fig 24 pH of optimized formulation (CANDIFSGXC)

Table 16 Stability studies of formulation CANDIFSGXC value in mean of cumulative % drug release ± standard deviation (n=3)

%Drug release	Time in days				
	1	30	60	90	120
CANDIFSGXC	92.68±0.25	92.26±0.24	90.93±0.04	89.88±0.57	87.25±0.54

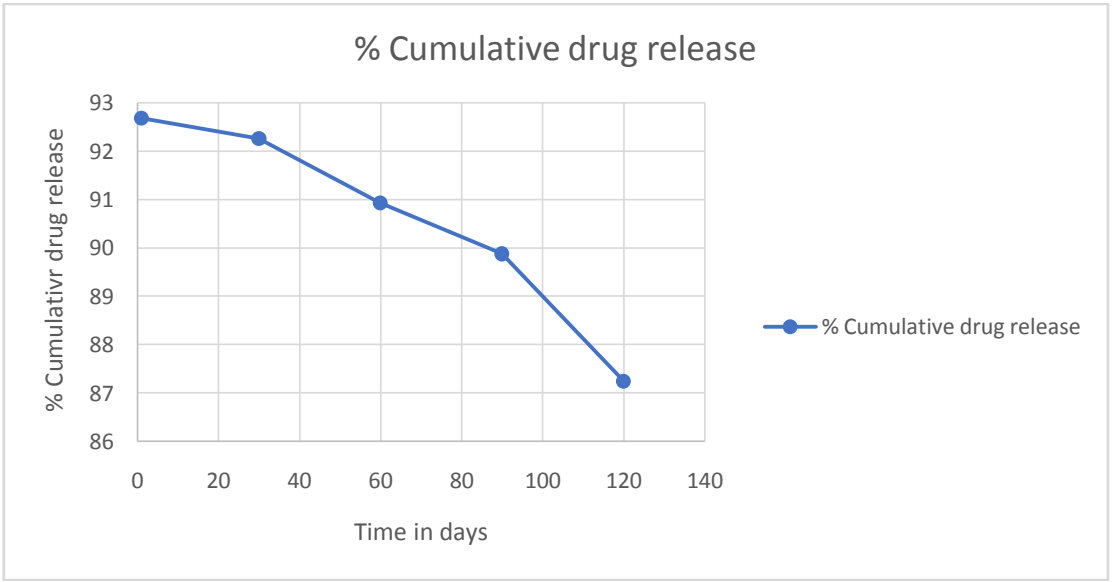

Fig 25 Stability studies of formulation CANDIFSGXC

Values in mean of cumulative drug release ± standard deviation (n=3).

Minor changes in parameters are observed conforming the stability of selected optimized formulation.

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III. SUMMARY AND CONCLUSION

Niosomes drug delivery method is a novel method and effective method used for drug delivery. Niosomes are prepared by non-ionic surfactants and cholesterol. Niosomes was prepared using hand shaking method. The niosomes characteristics are influenced by different factors like method of preparation, drug, structure, cholesterol and as well as type of surfactant used. Nioasomes and liposomes are osmotically active and chemically stable and improve the stability of the drug. The drug is encapsulated and delivered. They do not require special conditions for manufacture like handling, protection or storage as well as industrial manufacturing. They provide various benefits over other drug delivery systems. There are many advantages like being cheap and chemically stable. But are associated with notable problems with respect to physical stability like fusion, aggregation, sedimentation as well as leakage and storage. Hence the formulations are entrapped in gels to increase the stability. The formulation having drug, cholesterol and surfactant ratio of 1:1:7 providing higher drug release. The CANDIF7 formulation was found to be the optimum formulation and showed good results. Further the selected formulation was combined with gelling agents and prepared the floating gel formulation (CANDIFSGXC). The formulation is further evaluated and concluded that the candesartan niosomal floating gel formulation was found to be optimum and showed prolonged drug release.

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