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FORMULATION DEVELOPMENT AND INVITRO EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF NATEGLINIDE BY USING NATURAL POLYMERS

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Abstract:

For treating diabetes, it has been considered important that both a post prandial blood glucose level and a fasting blood glucose level are decreased to make them to normal levels. Nateglinide [N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine] is a novel mealtime glucose regulator approved for the treatment of type II diabetes mellitus. Once a day sustained release matrix tablets of nateglinide was prepared by using natural polymers k-carrageenan,lambda carrageenan and locust bean gum. Natural polymers were selected due to their easy availability and cheaper in coast and we can get standard uniformity and combinations of two different gums carrageenan and locust been gum were formulated in different ratios to exploit the rheological synergism between two gums in order to achive once a day matrix tablets of nateglinide further formulations were prepared from the formulations exhibited maximum retardation the controlled or sustained release formulations of nateglinide would be more useful than the nateglinide immediate release tablets from the new point of side effects improvement of compliance to patients and to enable to control of both post prandial blood glucose level and fasting blood glucose level for moderate and sever diabates patients. Hence an attempt was made to develop a sustained release oral dosage form of nateglinide instead of immediate release tablet.

Keywords: *Nateglinide, Matrix Tablets, Sustained Release, Natural Polymers.*

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INTRODUCTION:

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes[1]. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose'[2]. The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. The desire to maintain a near constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use[3]. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained or controlled release drug delivery systems [4]. Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers [5]. The goal of an extended release dosage form is to maintain therapeutic drug level in plasma for extended period of time. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form.[7-11] Because of increased complication complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems.[12]Matrix systems are widely used for the purpose of sustained release.

The oral sustained release drug delivery system of nateglinide can be formulated using various synthetic as well as natural hydrophilic polymers. The biodegradable nature and easy availability of the natural polymers makes them suitable for using as a sustained release polymer. The natural polymers also exhibit a rheological synergism between them when two polymers are mixed together. By using this property of the natural polymers can be used to reduce the total polymer concentration from the sustained release matrix tablet and once a day formulation of the nateglinide can be formulated containing least amount of polymer.

Nateglinide [N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine] is a novel mealtime glucose regulator approved for the treatment of type II diabetes mellitus. Nateglinide has a rapid onset and short duration of insulinotropic action that results in reduction of mealtime glucose rise and lowers the postabsorptive potential for hypoglycemia in humans and experimental animals. The main objectives are to prepare and evaluate once a day sustained release matrix tablet of Nateglinide, to reduce the total polymer concentration using rheological synergism between two natural gums, to study the *invitro* performance of matrix tablet.

MATERIALS AND METHODS:

Chemicals and reagents are taken from different suppliers such as Nateglinide from Glenmark pharmaceuticals ltd, K- Carrageenan from Otto kemi Pvt. Ltd, λ- Carrageenan from Lucid Colloids ltd, Locust bean gum from Research lab – fine chem ltd, Colloidal silicon dioxide from Dekkan Pharmaceuticals ltd, Magnesium stearate from Loba chemie pvt. Ltd, Lactose monohydrate from Loba chemie pvt. Ltd, Polyvinyl pyrrolidone K – 30 from Loba chemie pvt. ltd.

Preformulating [13-17]:

Organoleptic properties

Color and nature

Transferred small quantity of the sample on a white piece of paper spreaded the powder and examined visually.

Physical characteristics:

Flow properties

$$\tan^{(H/r)}$$

Where,
h = Angle of the reposeh = Height of the heap r = Radius of the heap

Hausner ratio:
Hausner ratio is related to interparticle friction and, as such used to predict powder flow properties.

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

Melting point:
It is one of the parameters to judge the purity of crude drug. In case of purechemicals, melting points are very sharp and constant**.**

Solution properties:
pH of the solution:
Weighed and transferred accurately about 1.0 g of sample in a 200ml clean and dried beaker, dissolved in carbondioxide free water and made up the volume to 100mlwith same solvent, mixed. Read the pH of freshly prepared solution by using precalibrated pH meter. The results are shown in results and discussion.

Identification of drug and compatability study:
Drug –excipient compatibility studies
In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect stability of the drug. Knowledge of drug-excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information is already be in existence for known drugs. For new drugs or new excipients, the pre formulations scientist must generate the needed information.

By physical observation:
It was determined as per procedure given in method section the following table illustrated the result.

Table.No. 1: Physical compatibility studies

Test	Observation	Inference
Physical compatibility	No change of color	These materials are compatible for formulation

Procedure by FT-IR Studies:
The IR spectrums of nateglinide with excipients were taken by preparing dispersion indry potassium bromide under dry condition. Superimposed these spectra. The transmission minima (absorption maxima) in the spectra obtained with the sample in corresponded in position and relative size to those in the spectrum obtained with the standards.

UV Spectroscopic Method For Analysis Of Nateglinide:
A. UV spectroscopy: (Determination of λ max):
Nateglinide was accurately weighed and dissolved in the solvent (Phosphate buffer 6.8) to obtain solution of 100µg/ml. UV spectrum was run from 200-400nm and λ_{max} was recorded using UV spectrophotometer.

Preparation of calibration curve of nateglinide:
Nateglinide solution of 100µg/ml was prepared in phosphate buffer pH 6.8 and UV spectrum was recorded in the wavelength range from 200-400 nm.

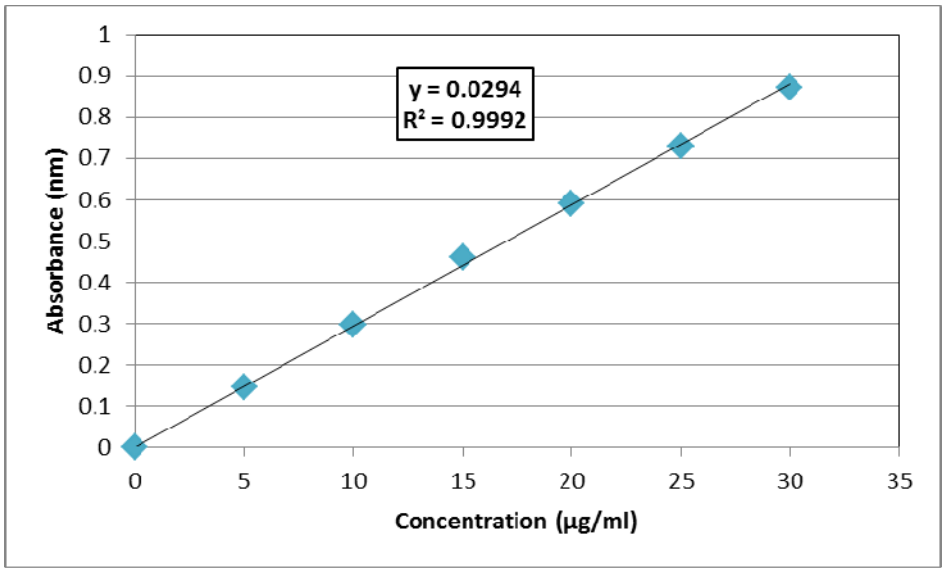
Standard stock solution: 100 mg of nateglinide was accurately weighed and transferred to 100ml volumetric flask and dissolved in phosphate buffer pH 6.8 to get solution of concentration 1000 µg/ml and this solution was further diluted suitably to get solution of concentration 50 µg/ml.

Working stock solution: A series of nateglinide solutions ranging from 5 to 30 µg/ml was prepared from standard stock solution in phosphate buffer pH 6.8. The absorbance of all solutions was measured against phosphate buffer pH 6.8 as blank at 210 nm using UV spectrophotometer. Beer's law was obeyed in the concentration range of 5-30 µg/ml. The high values of regression coefficient (0.9992) estimated the linearity of relationship between concentration and absorbance.

Table.No. 2: Calibration curve for nateglinide

S.No.	Concentration(□g/ml)	Absorbance (nm)
1	0	0
2	5	0.145
3	10	0.297
4	15	0.459
5	20	0.591
6	25	0.729
7	30	0.873
Slope	0.0294	
R^2	0.9992	

Fig.No.1: Calibration curve of nateglinide in phosphate buffer pH 6.8



1. K – carrageenan

Table No.3: Composition of k - carrageenan basedmatrix tablets of nateglinide

Ingredients	F_1	F_2	F_3
Nateglinide	120	120	120
K - carrageenan	90	105	120
Colloidal silicon dioxide	3	3	3
Magnesium stearate	3	3	3
Lactose monohydrate	78	63	48
PVP K – 30	6	6	6

*****All the quantities are in mg

λ- carrageenan

Table No.4: Composition of λ- carrageenan basedmatrix tablets of nateglinide

Ingredients	F_4	F_5	F_6
Nateglinide	120	120	120
λ- carrageenan	90	105	120
Colloidal silicon dioxide	3	3	3
Magnesium stearate	3	3	3
Lactose monohydrate	78	63	48
PVP K – 30	6	6	6

*All the quantities are in mg

Locust bean gum

Table No.5: Composition of locust bean gum basedmatrix tablets of nateglinide

Ingredients	F_7	F_8	F_9
Nateglinide	120	120	120
Locust bean gum	90	105	120
Colloidal silicon dioxide	3	3	3
Magnesium stearate	3	3	3
Lactose monohydrate	78	63	48
PVP K – 30	6	6	6

*All the quantities are in mg

K – carrageenan + Locust bean gum
K – carrageenan + Locust bean gum combinations

Table No.6: Composition of k - carrageenan + locust bean gum combinations based matrix tablet of nateglinide

Ingredients	F_{10} (20:80)	F_{11} (40:60)	F_{12} (50:50)	F_{13} (60:40)	F_{14} (80:20)
Nateglinide	120	120	120	120	120
K – carrageenan	24	48	60	72	96
Locust bean gum	96	72	60	48	24
Colloidal silicon dioxide	3	3	3	3	3
Magnesium stearate	3	3	3	3	3
Lactose monohydrate	48	48	48	48	48
PVP K - 30	6	6	6	6	6

*All the quantities are in mg

A. K - carrageenan + Locust bean gum 40:60 combinations

Table No.7: Composition of k – carrageenan + locust bean gum 40:60 combinations-based matrix tablets of nateglinide

Ingredients	F_{15}	F_{16}	F_{17}	F_{18}	F_{19}
Nateglinide	120	120	120	120	120
K - carrageenan	21.6	19.2	16.8	14.4	12
Locust bean gum	86.4	76.8	67.2	57.6	48
Colloidal silicon dioxide	3	3	3	3	3
Magnesium stearate	3	3	3	3	3
Lactose monohydrate	60	72	84	96	108
PVP K - 30	6	6	6	6	6

*****All the quantities are in mg

λ – carrageenan + Locust bean gum

A. λ – carrageenan + Locust bean gum combinations

Table No.8: Composition of λ - carrageenan + locust bean gum combinations-based matrix tablets of nateglinide

Ingredients	F_{20} (20:80)	F_{21} (40:60)	F_{22} (50:50)	F_{23} (60:40)	F_{24} (80:20)
Nateglinide	120	120	120	120	120
λ – carrageenan	24	48	60	72	96
Locust bean gum	96	72	60	48	24
Colloidal silicon dioxide	3	3	3	3	3
Magnesium stearate	3	3	3	3	3
Lactose monohydrate	48	48	48	48	48
PVP K – 30	6	6	6	6	6

*****All the quantities are in mg

B. λ - carrageenan + Locust bean gum 20:80 combinations

Table No.9: Composition of λ – carrageenan + locust bean gum 20:80 combinations-based matrix tablets of nateglinide

Ingredients	F_{25}	F_{26}	F_{27}
Nateglinide	120	120	120
λ – carrageenan	21.6	19.2	16.8
Locust bean gum	86.4	76.8	67.2
Colloidal silicon dioxide	3	3	3
Magnesium stearate	3	3	3
Lactose monohydrate	60	72	84
PVP K – 30	6	6	6

*****All the quantities are in mg

Determination of drug release kinetics:
Korsemeyer-peppas model -log cumulative % drug released vs. log time
Zero order- kinetic model
Zero order release would be predicted by the following equation.

$$A_t = A_o - K_o t$$

Where,
A_t -Drug release at time't'
- - Initial drug concentration
A_{o_o} -Zero order rate constant (hr^{-1})

When the data plotted as cumulative % drug release Vstime and the plot is linear,then the data obeys Zero-order equal to K_o.
First order kinetics
First order release would be predicted by the following equation

$$LogC = logC_o - K_t/2.303$$

Where,
Log C - Amount of drug remained at time 't' $logC_o$ - initial drug concentration
K - first order rate constant (hr^{-1})

Korsemeyer-peppas model.

$$Mt/M\alpha = Kt^n$$

Where,
Mt/M□ - The fraction of drug released at 't'
K - Constant incorporating structural and geometrical characteristics ofthe drug / polymer system
n - Diffusion exponent related to mechanism the drug release

RESULTS AND DISCUSSION:

Pre-formulation studies:

Organoleptic properties: The resultsare illustrated in following table.

Table 10. Organoleptic properties

Test	Specifications/limits	Observations
Color	White, Crystalline powder	White, Crystalline powder
Odour	Odorless, Bitter taste	Odorless, Bitter taste

The results comply as per specifications

Angle of repose: The results are illustrated in following table**.**

Table 11. Flow properties

Material	Angle of repose
Nateglinide	27□.14"

The result shows that drug having poor flow

Bulk density and tapped density: The results are illustrated in table**.**

Table 12. Density

Materials	Bulk Density(gm/ml)	Tapped density(gm/ml)
Nateglinide	0.19	0.26

Powder compressibility: The results are illustrated in table**.**

Table 13. Powder compressibility

Material	Compressibility index	Hausner ratio
Nateglinide	31.42%	1.18

The results shows that drug having poor flow property

Melting point: The results are illustrated in following table**.**

Table 14. Melting point

Material	Material point range	result
Nateglinide	137 □C	Complies

The result complies as per specification.

Solution properties:

pH of the solution: The results are illustrated in following table**.**

Table 15. pH

Material	Test	Specification	Observation
Nateglinide	pH	6.5	6.5

The result complies as per specification

Solubility: The results are illustrated in following table.

Table 16. Solubility

Test	Specification	Result
solubility	soluble in methanol, ethanol, chloroform, dissolved in acetone,ethyl ether, almost insoluble in water.	Complies

The result complies as per specification.

DRUG-EXCIPIENT COMPATABILITY STUDIES

Table 17. Drug – Excipients Compatibility Study Results

Drug + Excipients	Initial	After 1 month at		Compatible
		40^0C/75%RH	60^0C	
Drug	White powder	No change	No change	Yes
Drug + K- Carrageenan	White powder	No change	No change	Yes
Drug + λ- Carrageenan	White powder	No change	No change	Yes
Drug + Locust bean gum	White powder	No change	No change	Yes
Drug + Excipients	White powder	No change	No change	Yes

IR GRAPHS

Fig. 2 FT-IR of Nateglinide

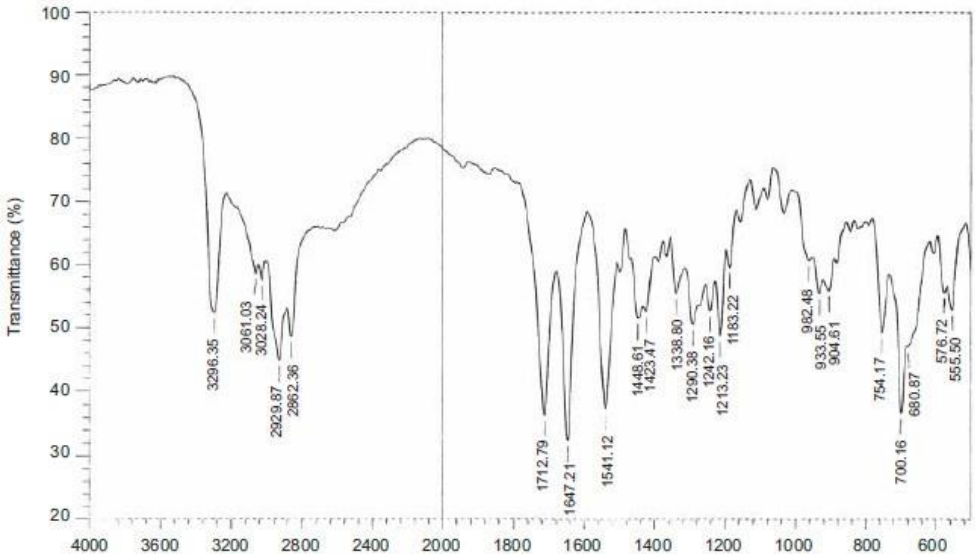


Fig. 3 FT-IR Graph of Formulation

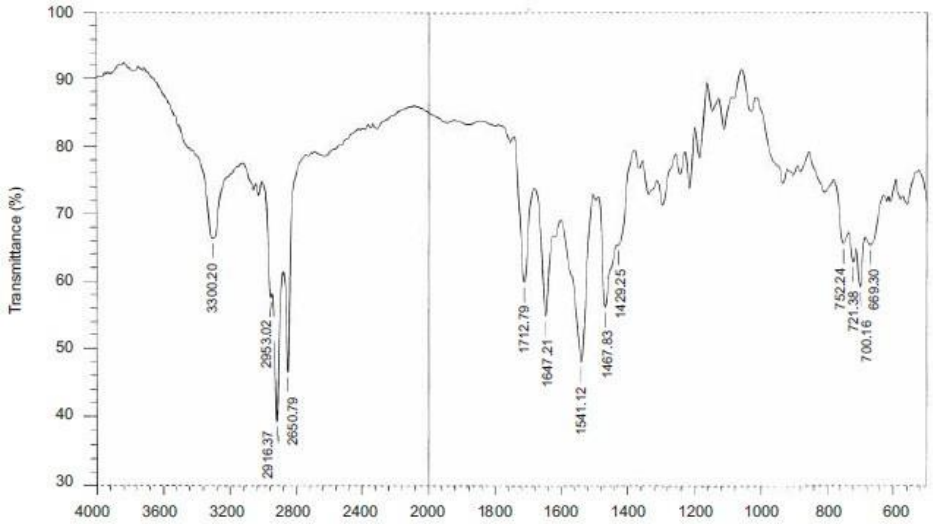


Table.No.18: Band Assignments for the Infrared Absorption Spectrumof Nateglinide

Band Energy (cm-1)	Assignment
1280 - 1431	carboxyl, carboxylate
1651	carbonyl
2866 - 3047	C-H stretching
1714	C=O
3298	N-H stretching
1296	C-O stretching
1446	C-O-H stretching

PRECOMPRESSION STUDIES:
EVALUATION OF TABLETS:

Table No 19: EVALUATION OF GRANULES:

Batch NO.	Angle of Repose(□)	Bulk Density (g/ml)	Tapped Density(g/ml)	Carr's Index (□)	Huasner Ratio
F1	21□32□	0.2574	0.3201	10.17	1.09
F2	22□54□	0.2641	0.3279	10.31	1.07
F3	21□52□	0.2678	0.3245	9.96	1.08
F4	28□37□	0.2745	0.3360	10.12	1.07
F5	27□31□	0.2792	0.3374	14.78	1.12
F6	26□87□	0.2748	0.3350	13.89	1.16
F7	24□63□	0.2749	0.3369	13.97	1.14
F8	24□67□	0.2801	0.3374	13.45	1.13
F9	23□14□	0.2841	0.3403	13.78	1.11
F10	25□47□	0.2814	0.3407	14.07	1.09
F11	26□92□	0.2874	0.3464	14.74	1.09
F12	24□85□	0.2799	0.3542	14.07	1.16
F13	25□03□	0.2745	0.3571	14.95	1.11
F14	24□31□	0.2868	0.3498	14.64	1.12

Table No 20: EVALUATION OF GRANULES:

Batch NO.	Angle of Repose(□)	Bulk Density (g/ml)	Tapped Density(g/ml)	Carr's Index (□)	Huasner Ratio
F15	26□03□	0.2823	0.3123	09.32	1.12
F16	26□47□	0.2831	0.3214	10.95	1.13
F17	27□09□	0.2932	0.3675	10.47	1.14
F18	26□91□	0.2945	0.3374	11.31	1.12
F19	27□33□	0.2846	0.3235	12.29	1.09
F20	27□93□	0.2753	0.3492	12.45	1.17
F21	28□17□	0.2785	0.3345	12.78	1.16
F22	28□54□	0.2714	0.3975	12.64	1.18
F23	29□08□	0.2681	0.3374	13.74	1.11
F24	28□02□	0.2574	0.3312	13.17	1.13
F25	26□51□	0.2968	0.3607	14.71	1.12
F26	26□75□	0.2734	0.3471	14.46	1.16

EVALUATION OF NATEGLINIDE TABLETS:

Table. No: 21. WEIGHT VARIATION AND FRIABILITY:

Batch. No	Weight Variation (%)	Friability (%)	Thickness (mm)	Hardness (Kg/cm^2)
F1	301±1.52	0.21	4.12±0.2	8.07
F2	304±2.37	0.23	4.03±0.2	7.92
F3	298±1.44	0.33	4.22±0.1	8.14
F4	320±1.86	0.42	4.31±0.1	7.54
F5	312±2.56	0.41	4.07±0.1	7.92
F6	303±2.13	0.23	4.12±0.1	7.61
F7	304±1.52	0.24	4.06±0.2	7.47
F8	318±1.49	0.20	4.19±0.3	7.42
F9	290±2.37	0.18	4.38±0.2	8.10
F10	312±1.91	0.25	4.12±0.1	8.32
F11	309±1.34	0.24	4.16±0.2	8.23
F12	317±2.03	0.35	4.14±0.2	8.14
F13	309±1.92	0.27	4.23±0.2	7.76
F14	303±1.66	0.52	4.08±0.1	7.91

Table. No: 22. WEIGHT VARIATION, FRIABILITY THICKNESS & HARDNESS

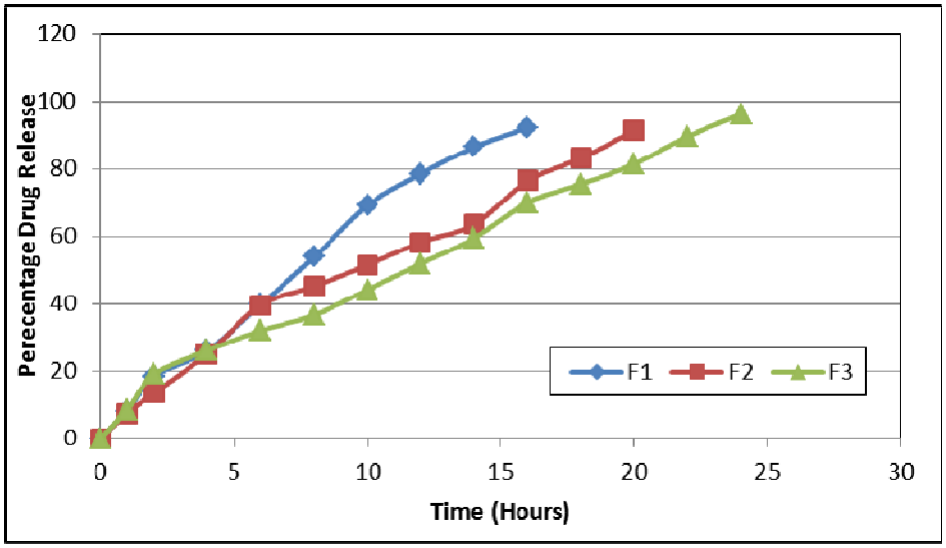
Batch. No	Weight Variation (%)	Friability (%)	Thickness (mm)	Hardness (Kg/cm^2)
F15	320±2.12	0.16	4.01±0.1	8.09
F16	309±1.03	0.34	4.03±0.1	8.32
F17	314±1.47	0.31	4.12±0.2	8.14
F18	306±1.42	0.24	4.62±0.3	8.45
F19	313±2.03	0.23	4.03±0.1	8.15
F20	312±1.74	0.29	4.08±0.2	7.92
F21	303±1.92	0.41	4.31±0.2	7.65
F22	291±2.04	0.36	4.26±0.1	8.19
F23	289±1.92	0.24	4.12±0.3	8.74
F24	301±1.25	0.31	4.14±0.2	8.31
F25	316±1.36	0.17	4.19±0.2	8.47
F26	303±1.23	0.24	4.27±0.1	8.23

K – Carrageenan

Table.No. 23. In vitro drug release profile of F_1 – F_3

Time (hours)	BATCH NO.		
	F1	**F2**	**F3**
1	8.20	7.48	8.53
2	18.39	13.52	19.03
4	26.08	25.11	26.15
6	39.72	39.58	31.96
8	53.79	45.09	36.61
10	69.13	51.44	44.13
12	78.51	58.19	51.83
14	86.40	63.52	59.44
16	92.16	76.43	69.97
18		83.10	75.44
20		91.30	81.39
22			89.55
24			96.21

Fig 4. In vitro drug release profile of F_1 – F_3

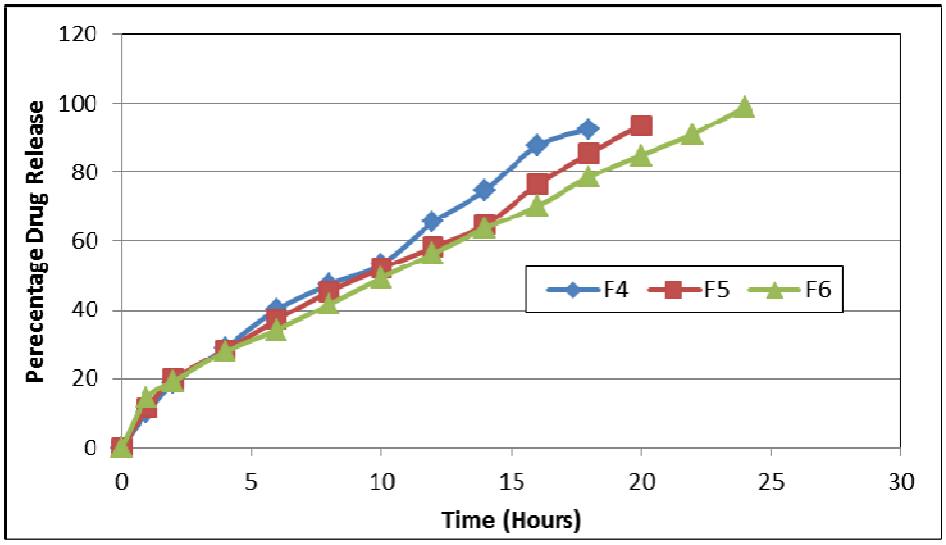


λ – Carrageenan

Table.No. 24. In vitro drug release profile of F_4 – F_6

Time (hours)	BATCH NO.		
	F4	F5	F6
1	10.32	11.59	14.53
2	18.69	19.77	19.22
4	29.03	28.13	27.90
6	40.12	37.12	34.22
8	47.39	45.33	41.56
10	53.12	51.97	49.29
12	65.44	58.20	56.33
14	74.70	64.66	63.70
16	87.53	76.23	70.08
18	92.39	85.40	78.54
20		93.56	84.89
22			91.05
24			98.89

Fig 5. In vitro drug release profile of F4-F6

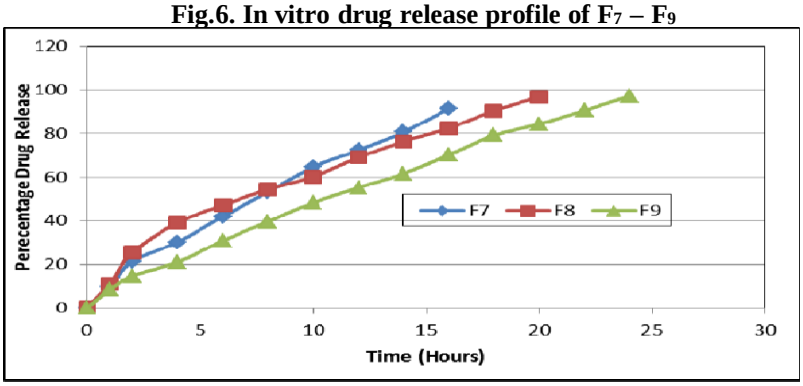


Locust bean gum [LBG]

Table.No. 25. In vitro drug release profile of F_7 – F_9

Time (hours)	BATCH NO.		
	F7	F8	F9
1	09.68	11.27	08.32
2	21.33	25.41	14.71
4	30.21	39.17	21.07
6	41.96	47.14	30.82
8	53.22	54.41	39.71
10	64.56	60.19	48.27
12	72.39	69.02	55.14
14	80.66	76.41	61.63
16	91.53	82.50	70.24
18		90.47	79.14
20		96.74	84.33
22			90.56
24			97.19

Fig.6. In vitro drug release profile of F_7 – F_9

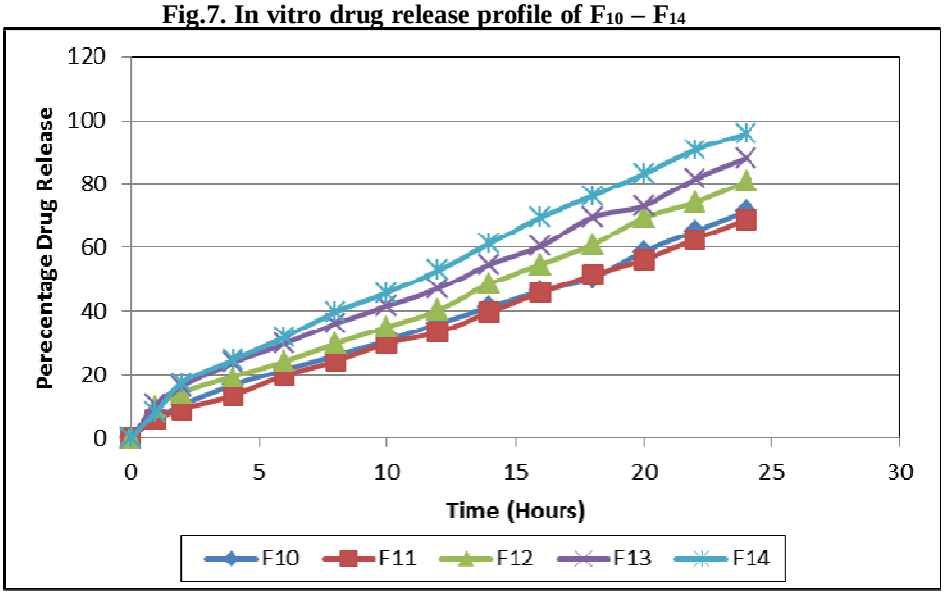


K – carrageenan + Locust bean gum
K – carrageenan + Locust bean gum combinations

Table.No. 26. In vitro drug release profile of F_{10} – F_{14}

Time (hours)	BATCH NO.				
	F10	F11	F12	F13	F14
1	6.24	05.93	09.62	10.47	8.21
2	10.41	09.14	14.27	16.21	17.43
4	16.70	13.42	19.43	23.83	24.71
6	21.51	19.74	24.17	29.72	31.84
8	26.07	24.34	29.82	36.14	39.81
10	30.74	29.91	35.07	41.57	45.77
12	36.14	33.40	40.33	47.13	52.86
14	41.29	39.72	48.64	54.71	61.28
16	46.30	45.81	54.73	60.43	69.56
18	50.47	51.34	60.81	69.57	76.25
20	58.67	56.17	69.40	73.14	83.17
22	65.12	62.55	74.21	81.57	90.74
24	71.45	68.88	80.75	88.15	95.87

Fig.7. In vitro drug release profile of F_{10} – F_{14}

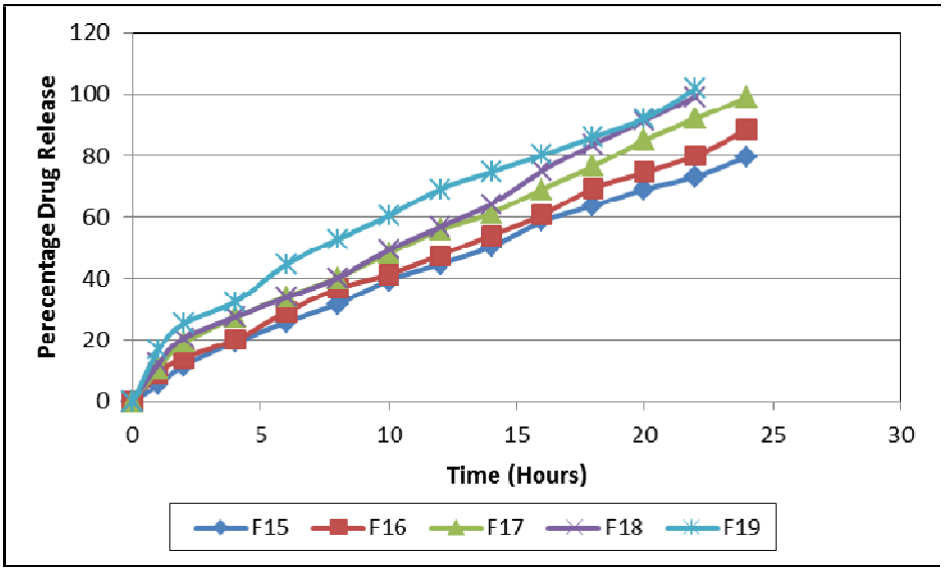


A. K - carrageenan + Locust bean gum 40:60 combinations

Table.No. 27. In vitro drug release profile of F_{15} – F_{19}

Time (hours)	BATCH NO.				
	F15	F16	F17	F18	F19
1	05.31	09.17	10.71	12.42	16.88
2	11.78	14.24	19.22	20.71	25.40
4	19.26	20.14	27.34	27.48	32.46
6	25.87	29.14	34.19	33.85	44.58
8	31.74	36.72	40.28	40.24	52.86
10	39.45	41.34	48.17	49.33	60.44
12	44.67	47.60	55.83	56.81	69.14
14	50.41	54.12	61.24	64.27	74.65
16	58.62	60.71	69.17	75.08	80.19
18	63.77	69.48	76.57	83.72	86.17
20	69.12	74.52	85.14	91.47	92.12
22	73.20	80.12	92.12	99.21	101.83

Fig.8. In vitro drug release profile of F_{15} – F_{19}

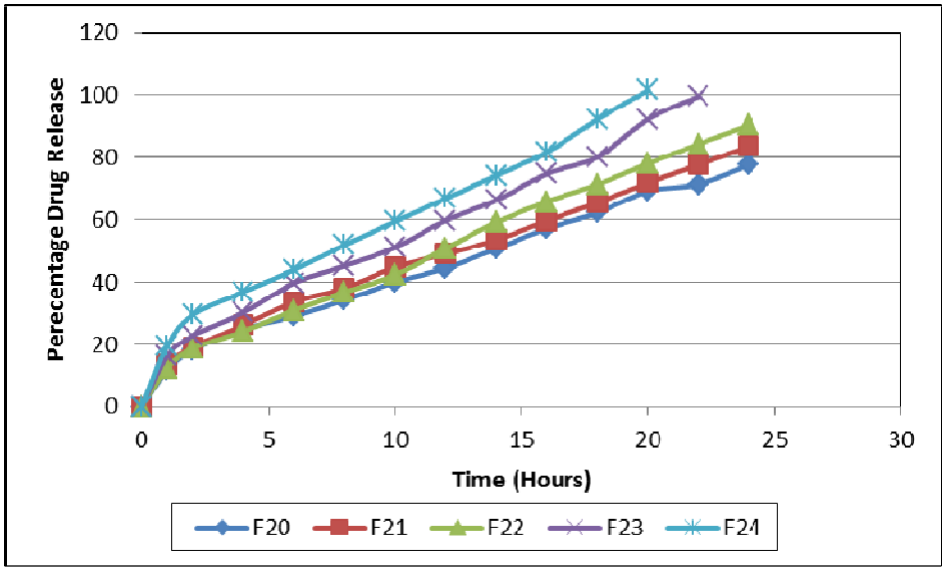


λ – carrageenan + Locust bean gum
λ – carrageenan + Locust bean gum combinations

Table.No. 28. In vitro drug release profile of F_{20} – F_{24}

Time (hours)	BATCH NO.				
	F20	F21	F22	F23	F24
1	11.78	13.37	12.44	16.41	19.74
2	18.35	19.12	18.75	22.77	29.45
4	24.89	26.22	24.22	30.22	36.88
6	29.08	33.64	30.95	39.72	43.95
8	34.24	38.09	36.74	45.21	51.93
10	39.96	44.78	42.33	51.17	59.48
12	44.47	49.08	50.87	59.84	66.85
14	50.78	53.57	59.24	66.30	74.24
16	57.20	59.74	65.85	74.81	81.75
18	62.28	65.51	71.39	80.17	92.24
20	69.14	71.92	78.09	92.28	101.63
22	71.45	77.69	84.33	99.61	

FIg.9. In vitro drug release profile of F_{20} – F_{24}

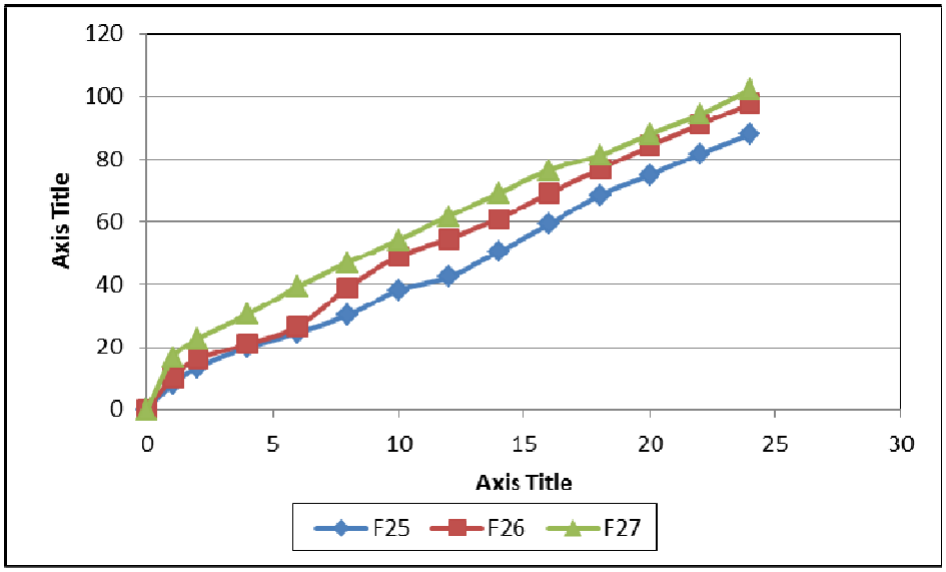


A. λ - carrageenan + Locust bean gum 20:80 combinations

Table.No. 29. In vitro drug release profile of F_{25} – F_{27}

Time (hours)	BATCH NO.		
	F25	F26	F27
1	08.31	10.47	16.48
2	13.45	16.17	22.64
4	19.97	21.08	30.47
6	24.63	26.65	39.38
8	30.24	39.14	47.08
10	38.22	48.92	54.22
12	42.38	54.67	61.84
14	50.52	61.07	69.22
16	59.22	69.24	76.54
18	68.54	76.72	81.26
20	74.91	84.24	87.92
22	81.65	91.02	94.24
24	88.05	97.75	102.35

Fig.10. In vitro drug release profile of F_{25} – F_{27}



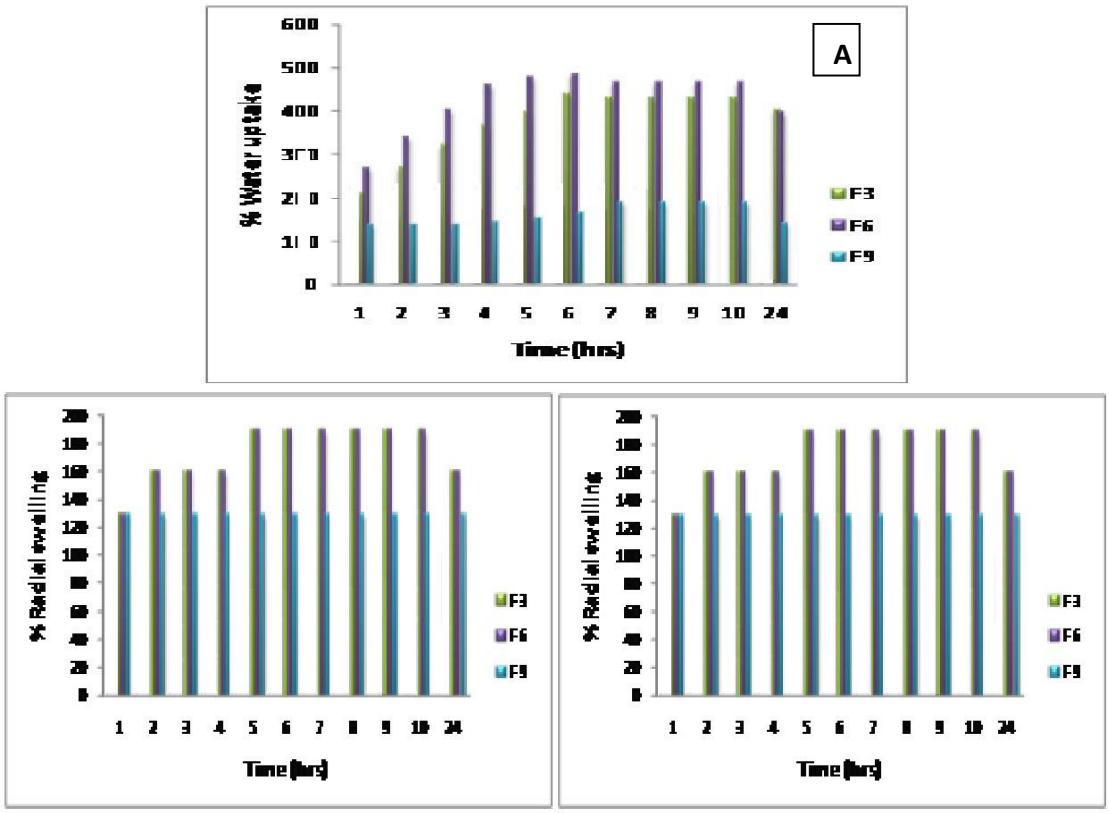
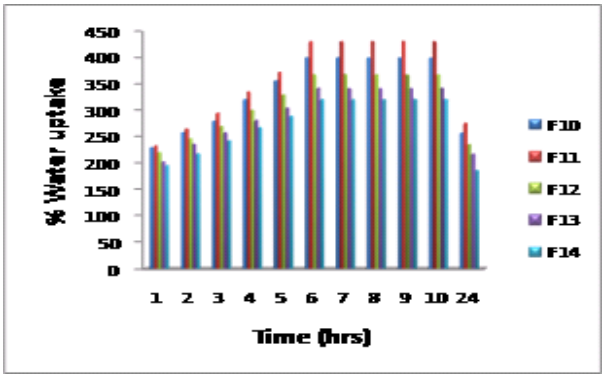
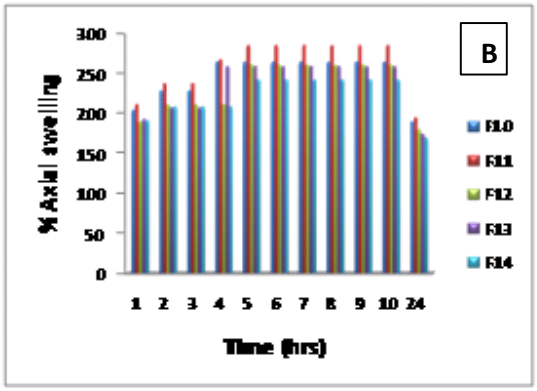
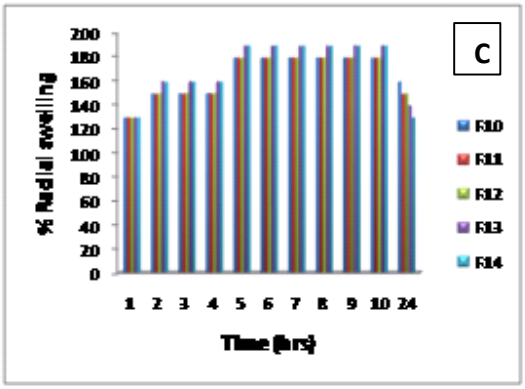


Fig.11. A. Water uptake study of formulations, F_3, F_6 and F_9
B. Axial swelling study of formulations, F_3, F_6 and F_9
C. Radial swelling study of formulations, F_3, F_6 and F_9
K – carrageenan + Locust bean gum

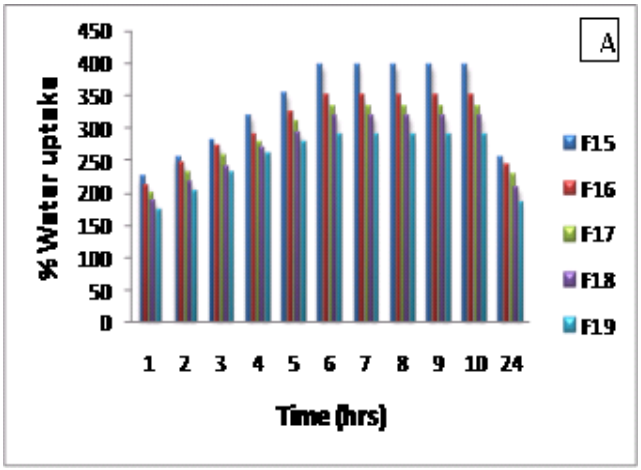
A.K – Carrageena
Fig.20. A. Water uptake study of formulations F_{10}, F_{11}, F_{12}, F_{13} and F_{14}
B.Axial swelling study of formulations F_{10}, F_{11}, F_{12}, F_{13} and F_{14}
C.Radial swelling study of formulations F_{10}, F_{11}, F_{12}, F_{13} and F_{14}

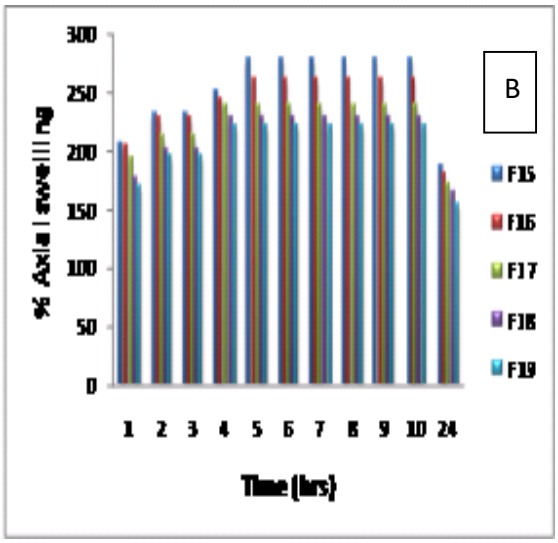






B. K – Carrageenan and locust bean gum 40:60 combinations





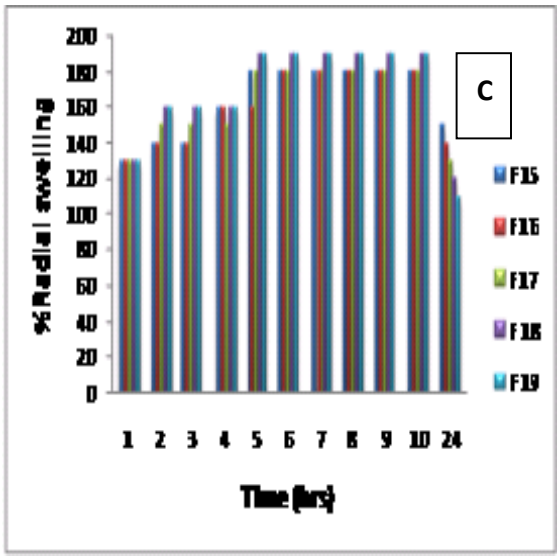
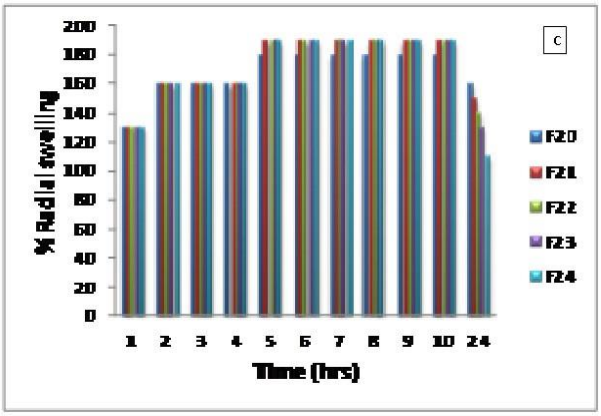
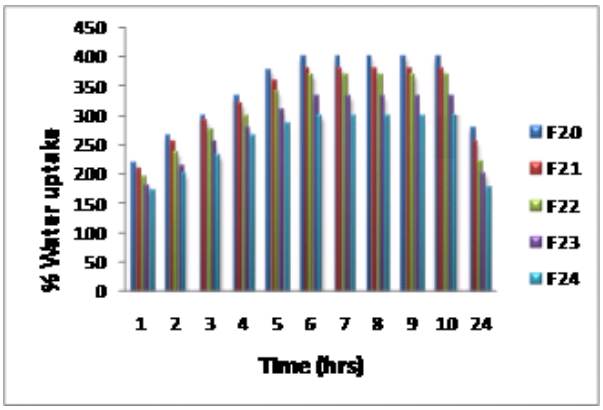


Fig.12. A. Water uptake study of formulations F_{15}, F_{16}, F_{17}, F_{18} and F_{19}
B. Axial swelling study of formulations F_{15},F_{16}, F_{17}, F_{18} and F_{19}
C. Radial swelling study of formulations F_{15}, F_{16}, F_{17}, F_{18} and F_{19}

λ – carrageenan + Locust bean gum
A.λ - carrageenan and locust bean gum combinations





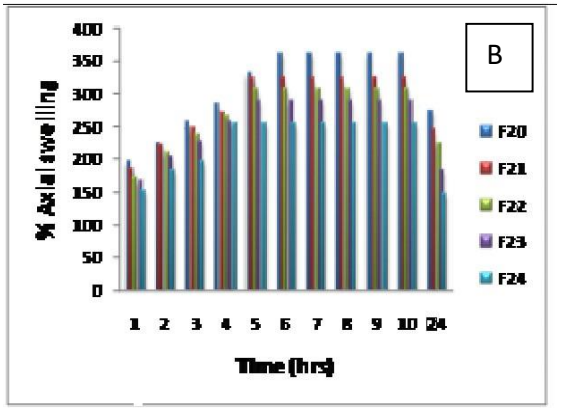


Fig.22.A. Water uptake study of formulations F_{20}, F_{21}, F_{22}, F_{23} and F_{24}

A. Axial swelling study of formulations F_{20}, F_{21}, F_{22}, F_{23} and F_{24}

B. Radial swelling study of formulations F_{20}, F_{21}, F_{22}, F_{23} and F_{24}

B. λ - carrageenan and locust bean gum 20:80 combinations

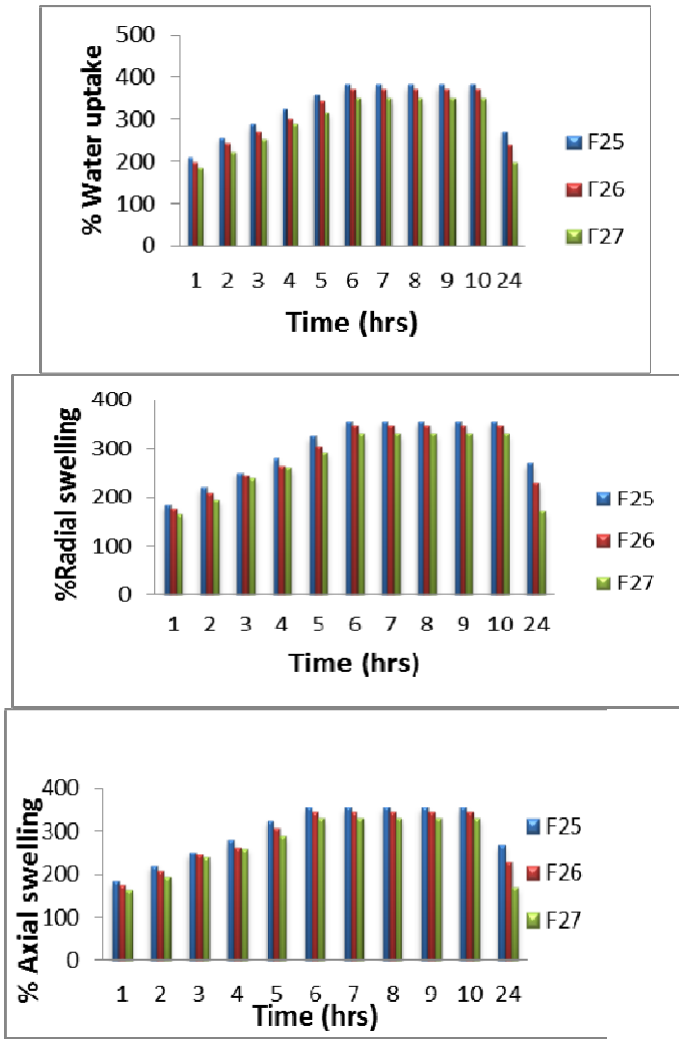


Fig.13. A. Water uptake study of formulations F_{25}, F_{26} and F_{27}
B. Axial swelling study of formulations F_{25}, F_{26} and F_{27}
C. Radial swelling study of formulations F_{25}, F_{26} and F_{27}

Drug Release Kinetics

Table.30. Drug release parameters for selected formulations

Formulation	n values	R^2	k values	Best fit model
F_{13}	0.9748	0.9897	4.2354	Peppas
F_{16}	0.9448	0.9897	4.2416	Peppas
F_{19}	0.7997	0.9935	4.1579	Peppas
F_{17}	0.8026	0.9968	4.1625	Peppas
F_{26}	0.7458	0.9914	4.1145	Peppas

SUMMARY:

Nateglinide [N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine] is a novel, highly physiologic, mealtime glucose regulator approved for the treatment of type II diabetes mellitus. Nateglinide is a BCS class II (Insoluble, highly permeable) drug. The plasma half life of nateglinide is 1.5h and bioavailability of 73%. The usual oral dosage regimen is 60— 180mg taken 3 times a day for nateglinide immediate release tablets. The controlled or sustained release formulation of nateglinide would be more useful than the nateglinide immediate release tablets from the view point of avoidance of side effect, improvement of compliance to patients and to enable control of both post prandial blood glucose level and fasting blood glucose level for moderate and severe diabetes patients. Hence, an attempt was made to develop a sustained-release (SR) oral dosage form of nateglinide instead of IR tablet.

The present work studied the natural polymer based once a day matrix tablet of nateglinide. From the wide range of hydrophilic polymers, k – carrageenan, λ – carrageenan and locust bean gum. Combinations of the two different gums k- carrageenan and locust bean gum and λ-carrageenan and locust bean gum were formulated in different ratios 20:80, 40:60, 50:50, 60:40 and 80:20 to exploit rheological synergism between two gums. Further the formulations were prepared dorm the formulation which exhibited maximum retardation such that each contains 10% less polymer concentration than the previous formulation in order to achieve the once a day matrix tablet of nateglinide containing least amount of polymer. The blends were prepared by non-aqueous wet granulation techniques with lactose as a diluent in formulations. The dried blends were compressed with other necessary excipients. The tablets were evaluated for hardness, thickness, drug content uniformity, in-vitro drug release studies for 24 hours (USP dissolution apparatus II, phosphate buffer-pH 6.8, 50 rpm, 37±0.5ºC), water uptake studies, swelling studies and in of the matrix tablet. The amount of Nateglinide released from the tablet formulations was estimated at 210nm using a UV spectrophotometer. The kinetic analysis of selected formulations were performed and found to follow Korsmeyer-Peppas model through non-fickian transport mechanism.The following conclusions can be drawn from the above study.

From the results obtained we can conclude that the polymers selected for the study, can be used individually for the sustained drug delivery of nateglinide locust bean gum was used in combination with k-carrageenan and λ-carrageenan in 60:40 and 20:80 ratios respectively with least in vitro drug release and can be used to reduce the concentration of polymer from the tablet.30% polymer reduction in case of k-carrageenan and locust bean gum and 20% with λ-carrageenan and locust bean gum combination was achieved.

CONCLUSION:

Once a day sustained release matrix tablets of nateglinide was prepared by using natural polymers k-carrageenan,lambda carrageenan and locust bean gum. Natural polymers were selected due to their easy availability and cheaper in coast and we can get standard uniformity and combinations of two different gums carrageenan and locust been gum were formulated in different ratios to exploit the rheological synergism between two gums in order to achive once a day matrix tablets of nateglinide further formulations were prepared from the formulations exhibited maximum retardation the controlled or sustained release formulations of nateglinide would be more useful than the nateglinide

immediate release tablets from the new point of side effects improvement of compliance to patients and to enable to control of both post prandial blood glucose level and fasting blood glucose level for moderate and sever diabates patients.

Hence an attempt was made to develop a sustained release oral dosage form of nateglinide instead of immediate release tablet.

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