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Formulation, Characterization and Evaluation of the Nateglinide floating Drug delivery system.

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Abstract

Oral controlled-release drug delivery systems are designed to deliver drugs at a predictable time, thereby increasing efficacy, reducing side effects, and helping to increase drug bioavailability. In addition to various application methods, the safest, easiest and most convenient method is the oral method, as it has many advantages in terms of cost, ease of management and relations with the patient. The disadvantages of prescriptions can be overcome using technology that led to the development of CRDDS. This new technique could help transform pain management with many therapeutic benefits. Four types of EC, EC: HPMC 5, 100 and 4000 cps formulations were developed, optimized and evaluated, respectively.The formulations are available in the right size and have good in vitro compatibility. All formulations have high drug encapsulation efficiency and product yield. The drug-polymer ratio, rotational speed, and emulsifier concentration affect the shape, size, and other parameters during operation. The short half-life allows rapid elimination of NG, thereby facilitating delivery from the gastrointestinal tract.

Key Words: Floating drug delivery, sustained release, microspheres.

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Introduction

Obviously, the effect of the drug depends not only on its pharmacological action, but also on the effectiveness of administration at the site of action. Therefore, interest in the latter contributes to the development of many new drug delivery systems to improve drug performance for maximum activity is a controlled current release to control drug levels in therapy. However, there is a large variation in drug concentration in plasma. Many attempts have been made to improve existing treatments. New drug delivery systems can increase the bioavailability of drugs. Buoyancy operation, or power consumption, is lower than when buoyancy is not sufficient to float and stay afloat in stomach contents, regardless of dwell time. Most drugs float better in the large intestine. The advantage of the drug delivery system is that after oral administration; the release form will remain in the stomach and release the drug in a controlled and prolonged manner, allowing the product to continue to the upper GI area of absorption. As a support release, the floating form

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has many advantages and this has been demonstrated in several recent releases. Because absorption is limited to the upper GI tract, drugs with poor bioavailability can be delivered effectively by increasing their absorption and increasing their bioavailability. The oral Controlled Release System is designed to deliver the drug at a predictable time, thereby increasing efficacy, reducing side effects, and helping to increase the bioavailability of the drug. In addition to various application methods, the safest, easiest and most convenient method is the oral method, as it has many advantages in terms of cost, ease of management and relations with the patient. The disadvantages of prescriptions can be overcome using technology that led to the development of CRDDS. This new technique could help transform pain management with many therapeutic benefits...

Materials and methods

Nateglinide, an oral nateglinide used for insulin release, was selected for this study. Nateglinide is indicated only in type 2 diabetes as an alternative to sulfonylureas or in addition to metformin/long-acting insulin. People with liver disease should not use it. Nateglinide is the first nateglinide derivative designed to normalize blood glucose levels after meals. It represents a rapid, short-term insulin release.Ethylcellulose (or ethylcellulose) is a derivative of cellulose in which some of the hydroxyl groups in the back sugar units have been changed to ether groups. The amount of ethyl may vary depending on the manufactureris mainly used as a film material for coating, vitamins and medicines, and as a thickener in cosmetics and industrial processes.Hypromellose (INN), short for hydroxypropyl methylcellulose (HPMC), is a semi-synthetic, inert, viscoelastic polymer used in eye drops and as an excipient and in controlled release into a variety of products in oral pharmaceuticals.Hypromellose as a food additive is an emulsifier, thickener and suspending agent and replaces animal gelatin.

Experimental:

The ascending microspheres were prepared with a slight modification of the solvent diffusion evaporation method (Kawashima et al., 1992). Both EC and 0.1% PEG (as surfactant) were dissolved in a 1:1 mixture of ethanol and dichloromethane at room temperature. The drug is dispersed in the polymer solution.The slurry was added slowly into 80 ml of water containing polyvinyl alcohol emulsifier (0.46% w/v). The system was stirred for 1 hour using a fan stirrer to evaporate the organic solvent. The prepared microspheres were thoroughly washed 3-4 times with distilled water, dried at room temperature for 1 hour and finally stored in a desiccator equipped with molten calcium chloride. Combinations of different methods are suggested in

Effect of Process Variables on Microspheres

For optimization of drug loaded floating microspheres of EC following process variables were studied:

- Effect of varying polymer ratio
- Effect of varying drug concentration
- Effect of varying emulsifier concentration

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- Effect of varying stirring rate

Table 1 Formulation code and composition of EC microspheres

Batch Code	Amount of EC (mg)	Concentration of emulsifying agent (%)	Stirring Rate (rpm)	Amount of drug (mg)
E1	10	0.48	900	10
E2	20	0.48	900	10
E3	30	0.48	900	10
E4	20	0.48	600	10
E5	20	0.48	1200	10
E6	20	0.68	900	10
E7	20	0.88	900	10
E8	20	0.48	900	20
E9	20	0.48	900	30

Morphological study using SEM

The morphology of the prepared microspheres was studied using scanning electron microscopy, which helped to establish the relationship between the surface patterns. SEM is superior to light microscopy because higher resolutions up to 10-20 nm can be achieved compared to 200-300 nm light microscopy. SEM studies were performed using a Jeol JSM-1600 in Tokyo, Japan. Prepared microspheres are lightly sprinkled on the double-sided adhesive tape fixed on the aluminum rod. A layer at a temperature of approximately 300°A is vacuum coated using a vacuum cleaner and the pattern is randomly scanned and photographed.

The SEM image is shown in Figure 1.FTIR spectral analysis

Inspection of a sample by FTIR verifies the chemical integrity of the drug and the polymer used in the design. Spectra were obtained from Bruker (Laboratory India) FTIR spectrometer, Germany. Choose a scanning range of 400 to 4000 cm-1 with a resolution of 1 cm-1. The sample was prepared by mixing 1 mg of the formulation with 300 mg of potassium bromide dry powder (FTIR grade); this powder was spread evenly in the mold and compressed by vacuum at a pressure of 10 tons. Mount the prepared disk in the eye of the FTIR spectrophotometer and record the spectrum.The spectrum is shown in Figure 2. Between the spectral positions and relative absorption bands obtained for pure drug, placebo, and NG-loaded microspheres compared and shown in Table 3.

Drug entrapment efficiency

Each batch of floating microspheres containing 50 mg of drug was accurately measured and pulverized. The powdered microspheres were taken up in ethanol (10ml). After 12 hours, the

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solution was transferred to Whatmann filter paper No. filtered using 1. 1. 44. After proper dilution, record the absorbance of the sample at 247 nm using a UV spectrophotometer and estimate the retention using the formula below..

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content}} \times 100$$

In vitro buoyancy was determined by placing 50 mg of the formulation in 100 ml of SGF (pH 1.2) containing Tween 20 (0.02% w/v) and mixing at 100 rpm using a magnetic stirrer. The floating microsphere layer was separated from said microspheres by visualization after 12 hours. The two granules were dried and weighed separately.

Determine the buoyancy of the microsphere using the formula below.

$$\text{Buoyancy (\%)} = Wf / (Wf + WS) \times 100 \quad \ldots\ldots\ldots\ldots\ldots (10)$$

Where Wf and Ws are the respective weights of the floated and settled microparticles.

The results of percent yield, drug entrapment efficiency and percent buoyancy for all the batches were reported in Table 2

Table 2 Percent buoyancy, entrapment efficiency and yield of EC microspheres

Batch code	Buoyancy (%)	Drug Entrapment (%)	Yield (%)
E1	81.51 ± 1.1	63.38 ± 2.4	68.44 ± 4.6
E2	80.41 ± 2.4	68.33 ± 2.2	76.55 ± 2.5
E3	78.67 ± 2.2	72.22 ± 4.1	79.41 ± 3.6
E4	84.41 ± 3.2	65.37 ± 2.2	72.52 ± 2.3
E5	71.61 ± 2.4	60.31 ± 5.1	68.57 ± 5.4
E6	77.22 ± 3.3	62.35 ± 1.5	74.42 ± 2.3
E7	76.63 ± 1.1	58.23 ± 1.7	72.56 ± 1.2
E8	76.64 ± 3.2	71.37 ± 2.2	76.44 ± 3.2
E9	73.68 ± 4.0	73.26 ± 3.3	78.53 ± 2.5

All values are represented as mean ± SD (n=3).

A stationary paddle dissolution apparatus (Veego, VDA-6DR, USPStd) was used to measure drug release from formulations. Resuspend microspheres equivalent to 16 mg of solution in 0.1N HCl containing Tween 20 (0.02% w/v). The temperature was maintained at 37 ± 0.5°C, 100rpm. Tank conditions are maintained during the course. At 30 minute intervals, 1 ml of sample was removed, filtered through a 5 µm filter and analyzed spectrophotometrically at 247 nm. Calculation of the percentage of drug released using a standard calibration curve.

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Results and Discussion

SEM analysis

The SEM images shown below show that the prepared microparticles are irregular, perfect spheres with smooth edges and density. There are many pores and interparticle spaces on the surface of the microspheres. The ruptured surface indicates the hollow nature of the microspheres, which helps them maintain the buoyancy of the GI fluid (Figure 1B).

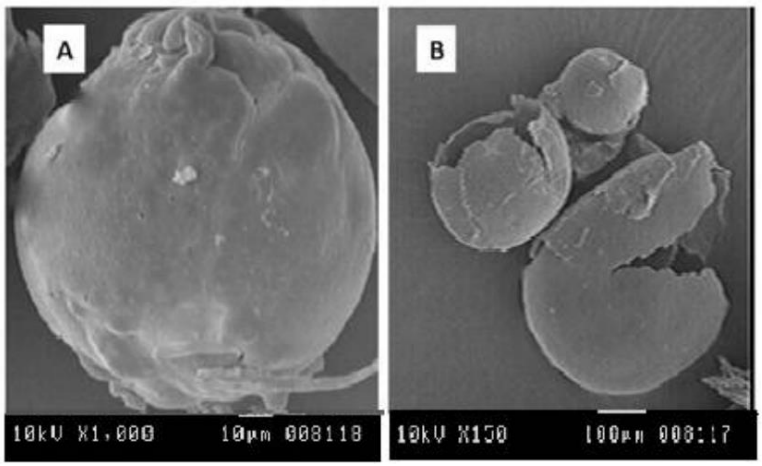

Fig. 1: SEM images: A) Spherical shaped EC microsphere and B) Ruptured surfaceshowing hollow nature of microspheres.

FTIR analysis

FTIR spectra of drug-loaded EC microspheres clearly show a characteristic peak not found in the spectra of placebo microspheres (without drug). The positions of the characteristic peaks found in the drug and nateglinide-loaded microspheres are summarized in Table 3. The results show that neither ethyl cellulose nor the formulation increases the stability of the drug (Figure 2).

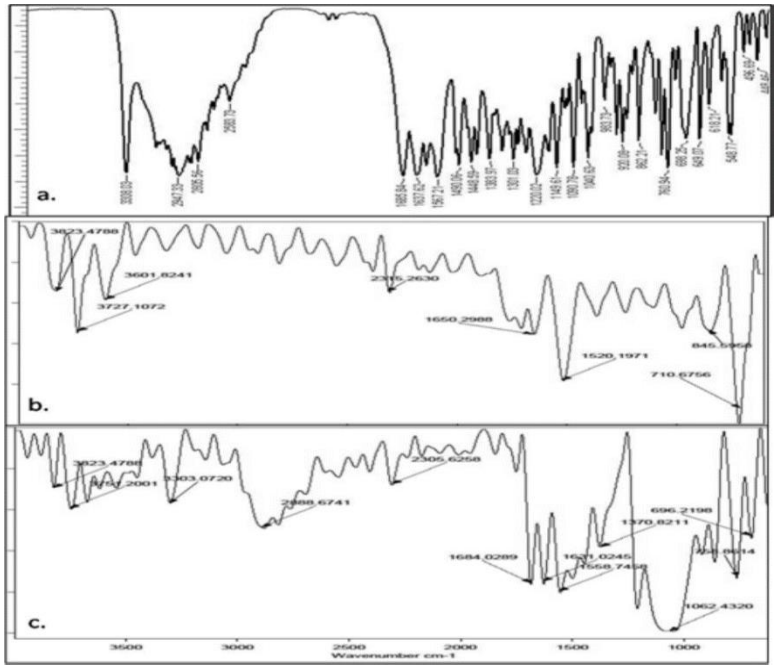

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Fig. 2: FTIR spectrum of (a) Nateglinide, (b) Placebo EC microspheres and (c)Drug loaded microspheres.

Table 3 Results of FTIR spectra of NG and NG loaded microspheres

In-vitro drug release study

An analysis of drug release studies reveals "no initial burst effect" in EC formulations; indicates homogenous distribution of drug (Table 4). The release rate of NG decreases from 68.2 – 60.2% as the EC concentration was increased in formulation E1 to E3. As the presence of drug closer to the surface for release is decreased owing to in polymer concentration. The release of drug is not very high, only 70.2 % NG was the maximum release, owing to hydrophobic characteristics of EC. Drug release is also less during initial hours of study as the solubility of EC in gastric fluid is poor. Fig. 3 shows the controlled release of drug from all the formulations.Slight increase in rate of release of NG was observed with increase in stirring speed from 600 to 1200 rpm. This may be due to reduced size of the particle with increasing stirring speed, thus exposing large surface area in the medium for drug release. A reduction in particle size is also observed with increasing concentration of emulsifier from 0.46-0.86 There by release of drug is increased from 65.1-69.6 %. Increase in drug concentration does not significantly influence the release of drug from the

S.No.	System	N-H (cm^{-1})	C-H (cm^{-1})	C=O (cm^{-1})	N-H bending
1.	Drug (NG)	3208.03	2957.33	1655.84	1677.62
2.	NG loaded microspheres	3203.07	2838.67	1664.02	1661.02

formulations.

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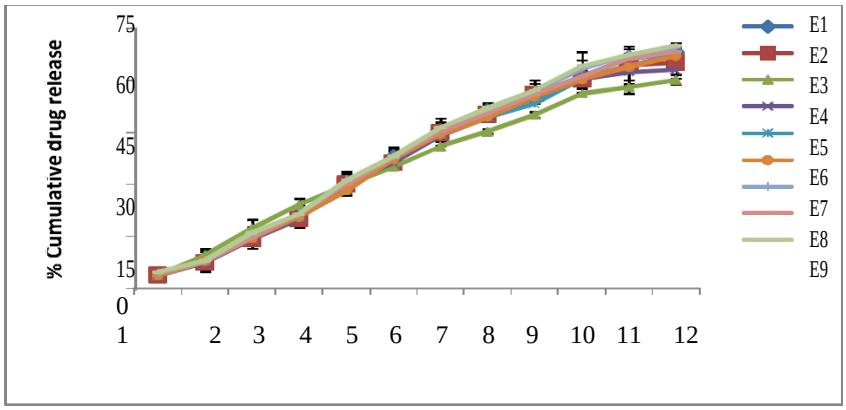
Table 4 Results of *in-vitro* drug release from EC microspheres

Time (h)	Mean % drug released								
	E1	**E3**	**E3**	**E5**	**E5**	**E8**	**E7**	**E8**	**E6**
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	5.1 ± 0.3	3.7 ± 0.3	3.7 ± 0.8	3.7 ± 0.5	3.6 ± 0.8	3.8 ± 0.6	5.5 ± 0.8	5.3 ± 0.8	5.8 ± 0.3
2	7.6 ± 0.6	7.5 ± 0.8	6.5 ± 1.6	7.5 ± 0.6	7.8 ± 3.6	7.8 ± 0.5	7.6 ± 0.3	7.8 ± 0.6	7.6 ± 0.5
3	15.8 ± 0.7	15.1 ± 1.3	17.1 ± 3.8	15.1 ± 1.8	15.5 ± 3.0	15.5 ± 0.3	15.8 ± 0.8	15.8 ± 3.1	15.6 ± 0.5
4	31.5 ± 1.5	30.3 ± 0.5	35.1 ± 1.8	30.1 ± 3.8	30.7 ± 3.5	30.7 ± 0.7	31.5 ± 1.3	31.5 ± 1.1	31.5 ± 3.8
5	30.3 ± 1.8	30.5 ± 0.5	36.8 ± 0.5	30 ± 0.7	38.5 ± 0.8	38.3 ± 1.3	31.3 ± 3.5	30.3 ± 1.8	31.3 ± 1.8
6	37.8 ± 3.1	38.3 ± 0.6	35.3 ± 0.7	38.3 ± 0.8	37.1 ± 0.5	37.3 ± 3.5	38.3 ± 1.8	37.8 ± 1.5	38.3 ± 3.5
7	55.5 ± 1.6	55.1 ± 1.3	51 ± 0.1	55.6 ± 0.3	55.5 ± 0.3	55.5 ± 3.3	55.6 ± 1.6	55.3 ± 0.7	58.5 ± 3.8
8	50.6 ± 0.3	50.3 ± 0.7	55.3 ± 0.8	56.3 ± 0.6	56.5 ± 0.8	56.5 ± 1.5	51.5 ± 1.5	50.5 ± 1.8	53 ± 1.5
9	58.1 ± 0.8	58.1 ± 0.8	50.1 ± 0.8	55.1 ± 1.8	53.5 ± 0.1	55.5 ± 0.3	57.1 ± 3.6	58.1 ± 1.8	57.1 ± 3.0
10	81.3 ± 0.7	80.3 ± 0.3	58.3 ± 0.3	80.3 ± 3.8	80.7 ± 0.8	80.3 ± 0.7	83.3 ± 3.8	81.3 ± 3.5	85.3 ± 5.0
11	88.5 ± 0.3	85.5 ± 1.1	58.1 ± 1.6	83.5 ± 3.5	85 ± 0.5	85 ± 0.8	87.5 ± 3.5	88.5 ± 3.8	87.5 ± 0.3
12	88.3 ± 0.8	85.1 ± 1.3	80.3 ± 1.5	83.1 ± 3.8	87.5 ± 0.6	87.1 ± 3.8	86.8 ± 0.5	88.3 ± 3.0	70.3 ± 0.8



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Time in hours

Fig. 3: Percent cumulative drug release of EC microspheres

Preparation of NG Loaded EC and HPMC Floating Microspheres

Floating microspheres were prepared by same procedure as discussed in section 6.2. Different viscosity grades of HPMC (5, 100 and 4000 cps) were used along with EC to prepare three different types of formulations. Summary of various formulations prepared were presented in Table 5, 6, 7.

Table 5 Formulation and optimization of EC: HPMC (5cps) microspheres

Batch code	Ratio of EC: HPMC	Concentration of emulsifying agent (%)	Stirring Rate (rpm)	Amount of drug (mg)
A1	1:1	0.48	1000	10
A2	1:2	0.48	1000	10
A3	1:3	0.48	1000	10
A4	1:2	0.48	1000	10
A5	1:2	0.48	1200	10
A6	1:2	0.68	1000	10
A7	1:2	0.88	1000	10
A8	1:2	0.48	1000	20
A9	1:2	0.48	1000	30

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Table 6 Formulation and optimization of EC: HPMC (100cps) microspheres

Batch code	Ratio of EC: HPMC	Concentration of emulsifying agent (%)	Stirring Rate (rpm)	Amount of drug (mg)
B1	1:1	0.48	1000	10
B2	1:2	0.48	1000	10
B3	1:3	0.48	1000	10
B4	1:2	0.48	1000	10
B5	1:2	0.48	1200	10
B6	1:2	0.68	1000	10
B7	1:2	0.88	1000	10
B8	1:2	0.48	1000	20
B9	1:2	0.48	1000	30

Table 7 Formulation and optimization of EC: HPMC (4000cps) microspheres

Batch code	Ratio of EC: HPMC	Concentration of emulsifying agent (%)	Stirring Rate (rpm)	Amount of drug (mg)
C1	1:1	0.48	1000	10
C2	1:2	0.48	1000	10
C3	1:3	0.48	1000	10
C4	1:2	0.48	1000	10
C5	1:2	0.48	1200	10
C6	1:2	0.68	1000	10
C7	1:2	0.88	1000	10
C8	1:2	0.48	1000	20
C9	1:2	0.48	1000	30

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Characterization of microspheres

Characterization and evaluation of microspheres were performed. Results of micromeritics properties of prepared microspheres with different viscosity grades of HPMC are shown individually in Table 8– 9.

Table 8 Results of micromeritics properties of EC: HPMC (5cps) microspheres

Batch Code	Mean particle size (µm)	Bulk density	Tapped density	Carr's Index (%)	Hausner ratio	Angle of repose
A1	193.12 ± 1.0	0.73 ± 0.07	0.85± 0.18	15.28	1.16	32.7 ± 3º
A2	205.27 ± 2.7	0.74 ± 0.06	0.85 ± 0.26	15.11	1.16	26.1 ± 4º
A3	226.74 ± 3.0	0.76 ± 0.27	0.89 ± 0.02	15.77	1.17	34.6 ± 7º
A4	212.34 ± 1.0	0.75 ± 0.47	0.87 ± 0.07	14.95	1.16	36.4 ± 2º
A5	182.54 ± 1.4	0.71 ± 0.02	0.83 ± 0.11	15.63	1.17	34.3 ± 4º
A6	196.94 ± 5.8	0.74 ± 0.18	0.85 ± 0.16	16.11	1.17	36.2 ± 6º
A7	184.37 ± 5.2	0.75 ± 0.10	0.85 ± 0.24	14.90	1.16	34.1 ± 8º
A8	233.18 ± 6.5	0.75 ± 0.01	0.86 ± 0.54	16.04	1.20	37.2 ± 9º
A9	245.61 ± 9.4	0.76 ± 0.12	0.87 ± 0.98	16.90	1.18	37.1 ± 6º

Batch Code	Mean particle size (µm)	Bulk density	Tapped density	Carr's index (%)	Hausner ratio	Angle of repose
B1	222.41 ± 3.2	0.74± 0.06	0.86 ± 0.23	12.79	1.16	32.6 ± 3º
B2	235.15 ± 5.9	0.74± 0.32	0.85 ± 0.48	15.04	1.20	35.7 ± 1º
B3	252.34 ± 8.6	0.72 ± 0.78	0.84 ± 0.39	16.60	1.22	36.3 ± 4 º
B4	255.52 ± 6.3	0.71 ± 0.35	0.86 ± 0.10	18.64	1.21	38.7 ± 1º
B5	226.30 ± 4.2	0.75 ± 0.70	0.87 ± 0.80	16.90	1.18	28.4 ± 2º
B6	244.12 ± 3.5	0.66 ± 0.54	0.91 ± 0.64	24.33	1.30	35.8 ± 2º
B7	226.84 ± 1.5	0.73 ± 0.62	0.87 ± 0.81	16.18	1.22	28.9 ± 9º
B8	245.48 ± 8.3	0.72 ± 0.84	0.86 ± 0.41	15.47	1.19	35.1 ± 5º
B9	253.91 ± 2.8	0.68 ± 0.12	0.85 ± 0.98	18.76	1.24	37.8 ± 3º

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Table 10 Results of micromeritics properties of EC: HPMC (4000cps) microspheres

Batch code	Mean particle size (µm)	Bulk density	Tapped density	Carr's index (%)	Hausner ratio	Angle of repose
C1	334.34 ± 1.2	0.67 ± 0.24	0.85 ± 0.12	18.04	1.22	32.8 ± 3º
C2	320.32 ± 2.0	0.65 ± 0.48	0.83 ± 0.47	22.17	1.25	36.5 ± 2º
C3	359.07 ± 2.2	0.62 ± 0.54	0.82 ± 0.34	22.42	1.26	36.3 ± 7 º
C4	355.48 ± 7.2	0.66 ± 0.31	0.82 ± 0.25	18.27	1.24	36.8 ± 4º
C5	322.82 ± 2.1	0.71 ± 0.36	0.82 ± 0.21	18.54	1.23	37.2 ± 4º
C6	331.37 ± 1.5	0.65 ± 0.41	0.85 ± 0.38	21.93	1.25	38.9 ± 7º
C7	324.74 ± 2.3	0.65 ± 0.48	0.85 ± 0.35	21.68	1.27	36.7 ± 3º
C8	358.37 ± 3.5	0.64 ± 0.21	0.86 ± 0.65	22.61	1.28	39.1 ± 5º
C9	369.64 ± 2.7	0.63 ± 0.45	0.88 ± 0.31	24.58	1.33	38.6 ± 5º

The microspheres were characterized for percent buoyancy. The results of all the above parameters are summarized in Table 6.14 - 6.16 for three different formulations containing HPMC of different viscosity grades 5, 100 and 4000 cps respectively.Drug release (in-vitro) of all the formulations was studied. The drug release is reported in Table 11 to 13.

Analysis of drug release

Drug release from the microspheres was estimated to be 12 hours in simulated gastric juice. None of the samples showed a burst effect during release, indicating uniform drug distribution, which can also be attributed to low drug solubility in the environment. As the polymer increases from 1% to 3%, drug release decreases, resulting in 84.8% - 78.4%, 75.HPMC's levels of 5, 100, and 4000 cps were reduced by 2-70.2% and 71.2-64.4%, respectively. Since the drug release rate depends on the presence of the drug near the surface, as the polymer concentration increases, the amount of uncoated drug decreases and the release rate decreases (Behera et al., 2015)., 2008). In addition, small hollow spheres were prepared at low polymer concentrations, providing a large surface area for the dissolution medium, resulting in faster drug release. It was observed

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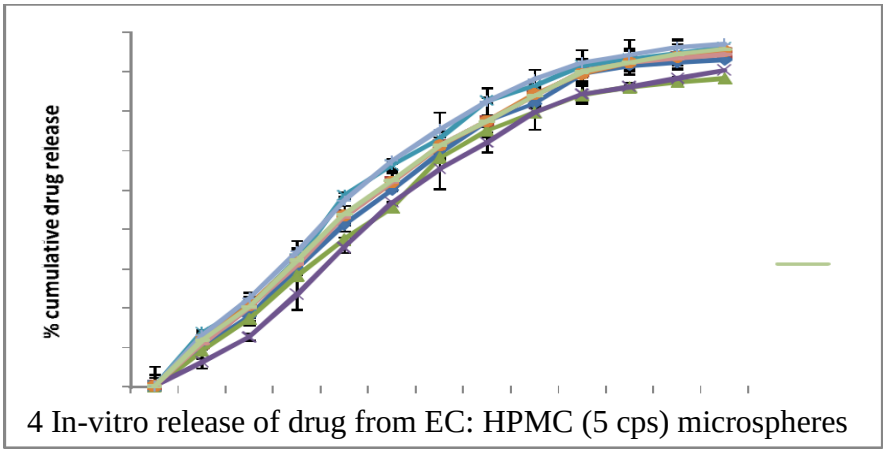
thatMicrospheres prepared by cutting higher values released the drug faster. Output increased from 80.5 to 86 as the rotation speed increased from 600 rpm to 1200 rpm.Samples prepared using 5, 100, and 4000 cps levels of HPMC were 4%, 70.8% to 77.4%, and 64.3% to 72.4%, respectively.As the agitation speed increases, the particle size becomes smaller, thus exposing more surface area to the dissolution medium for drug release. An increase in theemulsifier concentration did not affect drug release. A slight increase in drug release was observed when the emulsifier concentration was increased from 0.46% to 0.86%, possibly due to the formation of small microspheres.An increase in drug concentration had no significant effect on the drug release profile.

Table 11 Results of i*n-vitro* release from EC: HPMC (5 cps) microspheres

Time	Mean % drug released								
(h)	A2	A2	A4	A4	A1	A6	A7	A8	A9
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	22.2 ± 0.2	20.2 ± 0.4	9.2 ± 0.4	6.2 ± 0.8	24.8 ± 2.2	22.2 ± 1.0	24.2 ± 4.0	22 ± 2.4	22 ± 0.4
2	20.2 ± 0.8	28.2 ± 0.8	27.4 ± 2.2	22.8 ± 2.6	20.6 ± 2.0	20.7 ± 2.4	22.1 ± 2.2	20 ± 0.4	20.1 ± 2.4
3	42.2 ± 2.2	40.2 ± 2.4	28.4 ± 2.6	24.6 ± 0.9	42.1 ± 2.4	42.8 ± 4.2	44.1 ± 0.2	42.2 ± 2.4	42.2 ± 2.1
4	44.4 ± 0.1	42.4 ± 2.4	47.4 ± 2.2	41.4 ± 4.0	48.6 ± 0.6	44.1 ± 4.4	47.4 ± 0.9	44.4 ± 0.2	44.8 ± 1.0
5	12.2 ± 2.6	10.2 ± 0.2	41.1 ± 0.6	46.8 ± 2.2	16.4 ± 0.8	12 ± 2.4	17.4 ± 2.2	12.2 ± 2.6	12.1 ± 4.2
6	62.4 ± 0.4	19.4 ± 0.2	18.2 ± 0.8	11.4 ± 0.4	64.2 ± 2.2	62.2 ± 0.4	61.4 ± 0.6	62.4 ± 2.4	62.4 ± 2.4
7	67.1 ± 0.4	67.1 ± 0.6	61.2 ± 0.4	62.2 ± 1.2	72.8 ± 0.4	67.1 ± 0.8	72.1 ± 4.4	67.1 ± 4.1	67.1 ± 2.2
8	74.2 ± 0.7	72.2 ± 0.9	69.7 ± 2.8	69.8 ± 2.6	76.1 ± 0.6	74.1 ± 0.6	78.4 ± 4.1	74.2 ± 2.2	74.2 ± 2.4
9	80.2 ± 0.6	79.1 ± 2.2	74.2 ± 4.4	74.1 ± 2.4	82.6 ± 0.1	79.6 ± 2.2	82.4 ± 2.4	80.2 ± 2.4	80.2 ± 0.2
20	82.7 ± 0.4	82.7 ± 0.7	76.2 ± 2.4	76.4 ± 2.2	84.4 ± 4.0	82.4 ± 2.2	84.4 ± 4.2	82.4 ± 4.2	82.4 ± 0.1
22	84.7 ± 2.4	82.6 ± 2.1	77.4 ± 2.2	78.4 ± 0.4	84.8 ± 2.6	84.8 ± 4.0	86.4 ± 4.8	84.1 ± 2.0	84.1 ± 0.9
22	84.8 ± 2.2	84.2 ± 2.6	78.4 ± 0.6	80.1 ± 0.4	86.4 ± 4.2	81.4 ± 4.4	87.2 ± 2.2	84.1 ± 0.2	81.8 ± 0.7



4 In-vitro release of drug from EC: HPMC (5 cps) microspheres

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Table 12 Result of i*n-vitro* release from EC: HPMC (100 cps) microspheres

Time (h)	Mean % drug released								
	B1	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	1.7 ± 1.3	1.1 ± 0.3	6.3 ± 0.1	6.6 ± 0.3	7.1 ± 3.1	1.3 ± 0.1	7.6 ± 0.9	1.6 ± 3.1	1.3 ± 0.3
2	10.8 ± 0.3	9.3 ± 0.9	6.8 ± 0.8	7.3 ± 0.9	13.8 ± 0.6	9.6 ± 0.7	13.9 ± 1.3	9.6 ± 6.3	9.6 ± 0.9
3	31.9 ± 3.1	17.6 ± 1.1	11.1 ± 3.6	11.1 ± 0.6	31.3 ± 0.8	17.3 ± 3.6	33.1 ± 0.6	16.8 ± 0.9	17.3 ± 3.1
4	39.3 ± 0.9	38.1 ± 6.3	18.6 ± 1.1	18.6 ± 3.1	36.6 ± 3.3	38.1 ± 1.3	39.1 ± 0.8	36.8 ± 1.1	38.1 ± 3.1
5	38.9 ± 0.1	39.6 ± 3.3	37.1 ± 0.6	37.1 ± 0.6	61.3 ± 0.9	38.8 ± 3.3	67.3 ± 0.7	38.3 ± 1.3	38.8 ± 0.6
6	68.8 ± 0.6	68.6 ± 0.6	38.3 ± 0.7	38.3 ± 3.1	10.3 ± 3.1	68.6 ± 0.1	16.3 ± 1.3	68.1 ± 0.1	68.6 ± 1.3
7	11.1 ± 1.3	11.9 ± 0.8	68.6 ± 3.3	68.6 ± 6.6	18.1 ± 6.3	16.6 ± 0.9	66.8 ± 3.6	16.6 ± 0.3	17.1 ± 1.8
8	63.3 ± 6.3	61.6 ± 3.3	11.3 ± 1.9	11.3 ± 3.3	61.1 ± 3.3	61.6 ± 3.1	68.7 ± 0.3	66.6 ± 3.9	61.3 ± 3.6
9	70.6 ± 3.9	70.1 ± 3.3	61.0 ± 3.0	63.1 ± 0.8	71.3 ± 0.8	70.3 ± 3.8	73.6 ± 0.8	69.7 ± 3.6	71.1 ± 0.7
10	73.1 ± 3.6	71.1 ± 0.7	61.1 ± 3.1	67.3 ± 1.1	76.1 ± 3.9	71.1 ± 0.3	71.1 ± 0.1	71.1 ± 3.1	73.7 ± 1.1
11	76.8 ± 1.1	73.7 ± 1.3	68.0 ± 0.1	69.1 ± 3.6	76.3 ± 3.6	73.7 ± 0.7	77.3 ± 3.3	73.7 ± 1.7	71.3 ± 3.1
13	71.3 ± 3.3	76.1 ± 0.6	70.3 ± 0.1	70.8 ± 3.1	77.6 ± 3.9	71.3 ± 0.3	78.9 ± 1.1	76.3 ± 3.6	76.3 ± 0.8

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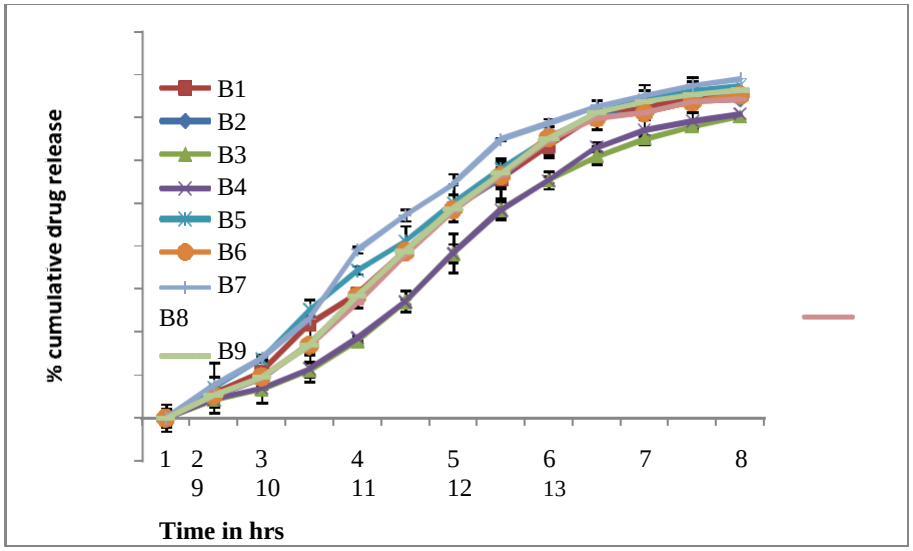

Fig. 5*In-vitro* release of drug from EC: HPMC (100 cps) microspheres

Table:- 13 *In-vitro* release of nateglinide from EC: HPMC (4000 cps) microspheres

Time (Hr)	Mean % drug released								
	C1	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	4.8 ± 0.4	4.1 ± 0.4	4.7 ± 1.4	4.8 ± 1.4	4.9 ± 0.7	4.8 ± 0.1	8.1 ± 0.6	4.7 ± 0.4	4.8 ± 0.1
2	7.8 ± 1.1	7.9 ± 0.9	7.4 ± 1.1	8.0 ± 1.4	8.1 ± 1.8	8.4 ± 0.9	9.1 ± 1.8	7.1 ± 1.1	7.4 ± 1.1
3	14 ± 0.6	14.8 ± 1.1	14.1 ± 0.6	14.1 ± 4.6	18.8 ± 1.6	14.8 ± 8.1	17.4 ± 4.1	14.4 ± 1.4	14.8 ± 0.7
4	11 ± 0.8	11.4 ± 4.1	10.1 ± 0.8	10.1 ± 1.1	18.1 ± 1.7	11.6 ± 4.8	18.8 ± 1.8	10.4 ± 4.4	11.6 ± 0.6
5	44 ± 1.6	40.1 ± 0.4	40.6 ± 1.4	19.4 ± 1.1	48.4 ± 0.8	41.1 ± 1.4	48.8 ± 0.8	18.8 ± 0.4	41.1 ± 1.4
6	49 ± 4.6	47.8 ± 0.8	46.1 ± 4.6	48.1 ± 4.4	40.1 ± 1.4	40 ± 0.6	48.6 ± 1.8	49.8 ± 1.1	48.4 ± 0.8
7	49.4 ± 4.8	48.4 ± 0.9	48.1 ± 1.9	48.8 ± 0.9	81.8 ± 4.6	49.4 ± 1.8	88.9 ± 4.1	47.4 ± 0.6	48.4 ± 0.7
8	87.4 ± 1.4	80.9 ± 4.8	80.4 ± 1.7	80.4 ± 0.8	60.1 ± 0.9	86.4 ± 4.1	64.4 ± 1.9	88.9 ± 0.7	88.4 ± 1.1
9	64 ± 0.6	86.1 ± 1.6	86.1 ± 0.9	88.1 ± 4.1	68.4 ± 1.8	64.1 ± 0.1	69.4 ± 0.4	60.7 ± 1.1	64.1 ± 4.4
10	67 ± 0.8	61.4 ± 1.8	60.4 ± 0.4	60.4 ± 0.4	68.4 ± 0.6	67.4 ± 0.7	71.6 ± 0.8	64.4 ± 0.8	67.4 ± 0.8
11	69.8 ± 1.0	66.4 ± 0.7	61.4 ± 0.4	61.8 ± 0.9	70.8 ± 0.9	68.9 ± 1.1	71.4 ± 1.4	68.8 ± 1.1	68.8 ± 0.1
11	71.1 ± 0.4	68.9 ± 0.9	64.4 ± 0.1	64.4 ± 0.4	71.4 ± 1.1	70.1 ± 1.4	74.1 ± 0.9	66.8 ± 0.6	70.8 ± 0.9

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It was found that formulations A7, B7 and C7 had the highest release rates, but had lower viscosity, buoyancy and percent yield values compared to formulations A2, B2 and C2. Based on all the consequences of A2, B2 and C2 negative behavior, the design was carefully chosen to compare the oscillation kinetics. Comparing the release of well-designed samples prepared from different viscosity levels ofHPMC, it can be seen that low viscosity HPMC exhibits good release compared to high viscosity HPMC. Drug release was found to be 83.2 > 74, respectively.

Formulations A2, B2 and C2 were 18% > 68.9%, respectively. Depending on the viscosity, as the density of the polymer matrix increases, the length of the diffusion path also increases, thus decreasing the drug release pattern from the polymer matrix (Ganesan et al., 2013). Products with high viscosity HPMC swell more slowly compared to low viscosity HPMC.

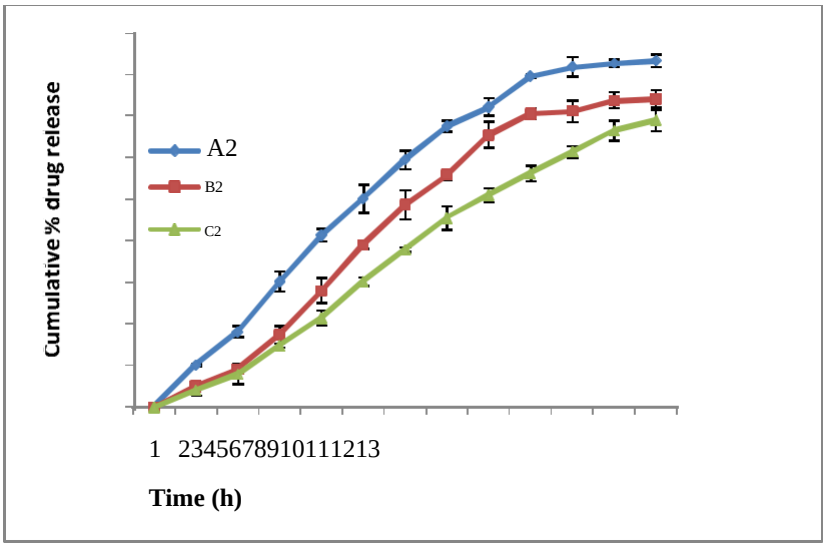

Fig. 6: Comparison of drug release of optimized A2, B2 and C2 formulations.

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Summary and conclusion:-

The aim of this study is to develop, characterize and evaluate NG floating microspheres, anti-inflammatory drugs for the treatment of type II diabetes. The plasma half-life of NG is approximately one hour. Due to its short half-life and easy absorption from the gastrointestinal tract (GIT), it is rapidly eliminated from the circulation, requiring frequent dosing. With repeated use of NG, some side effects may occur. Therefore, research efforts have focused on developing floating microspheres to overcome these problems.EC and HPMC are used to control the release and swellable polymers to induce drug release. Therefore, an attempt has been made to microencapsulate NG by the solvent evaporation technique to prevent gastrointestinal irritation and induce drug release. Floating microspheres coupled with EC alone as well as different levels (5, 100 and 4000 cps) HPMC were produced, showing good in vitro buoyancy and juice release. The aim of the experimental work performed bywas to create and grow floating microspheres with the best buoyancy and explosive properties. Four types of EC, EC: HPMC 5, 100 and 4000 cps formulations were developed, optimized and evaluated, respectively. The formulations are available in different sizes and have good in vitro compatibility. All formulations have high drug encapsulation efficiency and product yield. The drug-polymer ratio, spin rate, and emulsifier concentration affect the shape, size, and other parameters during operation. The short half-life allows rapid elimination of NG, making the delivery of the gastrointestinal tract more efficient.

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