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FORMULATION AND EVALUATION OF NATAGLINIDE MICROSPHERES

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Abstract:
The floating drug delivery system was first described by Davis (1968). Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems. FDDS are known as Hydro dynamically balanced systems or low-density system that has been made developed to increase the gastric transit time of drug [1]. Since the last three decades many drug molecules formulated as Gastroretentive Drug Delivery System (GRDDS) have been patented keeping in view its commercial success. Oral controlled release (CR) dosage forms have been extensively used to improve therapy of many important medications [2]. These microspheres are characteristically free flowing powders consisting of natural or synthetic polymers m.µand ideally having a particle size less than 200µm. Microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug [3]. Floating microspheres are one of the multiparticulate drug delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability and to target drug to specific sites.The present work described floating microspheres of Nateglinide was formulated and evaluated. In this present work attempt was being made for the preparation of various formulations (F1 to F4). The formulations were prepared with varying concentration of ethyl cellulose and HPMC & keeping Nateglinide concentration constant. The evaluation of all formulation were carried of its Floating ability, Micromeritic property, % drug content, Entrapment efficiency, SEM photography, FTIR drug – polymer interaction study, and in- vitro drug release study in triplicate. From this investigation it was concluded that the formulation F4 was a good formulation. Where the formulation was having 70% drug content, with controlled and zero order drug released kinetics observed up to 12 hour and having up to 24 hour of floating behaviour. From SEM studies the formulation was found in spherical nature. The loading efficiency was studied during the evaluation and found high in F4. The formulation was relatively stable, reproducible and ideal for the floating drug delivery. So, the formulation F4 is more effective in the treatment of Type-2 (non-insulin dependent) diabetes mellitus.

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INTRODUCTION:

The floating drug delivery system was first described by Davis (1968). Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems. FDDS are known as Hydro dynamically balanced systems or low-density system that has been made developed to increase the gastric transit time of drug [1]. Since the last three decades many drug molecules formulated as Gastroretentive Drug Delivery System (GRDDS) have been patented keeping in view its commercial success. Oral controlled release (CR) dosage forms have been extensively used to improve therapy of many important medications [2]. These microspheres are characteristically free flowing powders consisting of natural or synthetic polymers m.µand ideally having a particle size less than 200µm. Microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug [3]. Floating microspheres are one of the multiparticulate drug delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability and to target drug to specific sites. Floating microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency, and improving patient compliance [4]. Nateglinide is oral anti-diabetic drug used in type-2 diabetes (non-insulin dependent diabetes mellitus) that can acutely lower the blood glucose level in human by stimulation the release of insulin from the pancreas. Its short biological half-life (1-1.5 hours) necessitates that it be administrated in 2 or 3 doses of 60 to120mg of per day. Moreover, the site of absorption of nateglinide is in the stomach. Thus, the development of controlled-released microspheres would be eliminating the entire problem associated with drug.

MATERIAL AND METHODS:

Preparation of Floating Microsphere by double emulsion solvent diffusion method:

Microspheres containing Nateglinide as a core material was prepared by w/o/o double emulsion solvent diffusion method. The polymer Ethyl cellulose and hydroxy propyl methyl cellulose were dissolved in mixture of Acetonitrile and Dichloromethane (1:1). The core material Nateglinide was dispersed in the polymer solution with constant stirring to get a uniform mixing. By adding tabulated amount of double distilled water, to the drug-polymer solution w/o emulsion was formed. The w/o primary emulsion prepared was poured in a streamline to 100 ml of light liquid paraffin containing Span 80 as a surfactant with vigorous stirring at 1200 rpm by a mechanical stirrer using three bladed propeller type stirrer for 2 hr. Then the formulated microspheres was separated through vaccum filtration equipment and washed with n-hexane followed by petroleum ether till oil free microspheres achieved. Then collected microspheres were dried for 1 hr at room temperature and subsequently stored in desiccators for 24 hr [5].

Table 1: Formulation Composition of Floating Microsphere

Formulation Code Drug - Polymer Ratio	Composition offloatingmicrosphere formulations	Organic Solvent Ratio (Acetonitrile: Dichloromethane)
F1	1:0.5	1:1
F2	1:1	1:1
F3	1:1.5	1:1
F4	1:2	1:1

Size, shape and Surface Analysis:

Size distribution of the prepared microspheres was studied by optical microscope. Surface morphology of the microspheres was examined by Scanning electron microscopy (SEM).The coated microspheres were then, observed for morphological characteristics and to confirm the spherical nature of microsphere with a Scanning electron microscope.

Micromeritic properties:

Tapped density of the prepared microspheres was determined by using tap density tester and % carr'index and hausner'ratio was calculated. Angle of repose was assessed to know the flow ability of microspheres by a fixed funnel method.

Drug content of floating Microspheres:

About 100 mg of accurately weighed drugloaded microspheres were soaked in 100ml of 7.2 phosphate buffer. The resulting mixture was kept shaking on mechanical shaker for 24 hrs. Then after the solution was filtered, the drug content was estimated by UV-VIS double beam spectrophotometer (UV-1700 SHIMADZU) at 210 nm.

Buoyancy test:

In vitro evaluation of floating behaviour studies were performed by placing 50 nos of Microspheres into 250ml conical flask containing 7.2 phosphate Buffer containing 0.02% w/v tween 20 followed by agitation. At predetermined time interval (2, 4, 6, 8, 10, 12, 24hrs) no. of floating particles were counted.

In-vitro drug release study:

In this present study on prepared microspheres were introduced for in-vitro drug release analysis using USP standard basket type eight stage dissolution apparatus. An accurately weighed amount of prepared microspheres of different formulations (microspheres wt. equivalent to 100mg pure drug) were stirred in 900ml dissolution medium (7.2 Phosphate Buffer) maintained at 37 ± 1º C and 100rpm rotational speed of basket. Samples (10ml) were withdrawn at predetermined time interval and replenished immediately with the same volume of fresh medium to maintain sink condition. The withdrawal samples were analysed by UV-VIS double beam spectrophotometer.The drug release experiments were conducted in triplicates. From this, percentage drug release was calculated and plotted against function of time to study the pattern of drug release.

RESULTS AND DISCUSSION:

The mean particle size of the microspheres significantly increased with increasing polymer concentration. Particle size was in the range of 220.4 ± 3.7 to 261.9 ± 3.5 µm. Angle of repose for microspheres was between 27.8o and 33.1º, thus indicating good flow property for the microspheres. The findings were supported by Carr's (compressibility) index, which was <10 indicating good flow.

The production yield of floating microspheres was greater than 70 % for all the formulations. In the floatation test, more than 75 % microspheres remained floating at the end of 12 hr. The encapsulation efficiency of the prepared microspheres was in the range 72.8±3.7 to 94.2±1.4.

Scanning electron microscopy revealed pores on the microsphere as well as a hollow microsphere interior. The surface morphology and internal texture of microspheres were determined by scanning electron microscopy (SEM) as shown in Figure. The shape and surface topography was observed that fully spherical with nearly regular surface. SEM of formulation F-4 before and after dissolution was shown in the figure. From this figure it was observed that so many pores are formed due to drug release. Some pores are bigger in size and some are very small. It may be say that due to the blasting of drug, the drugs were released through this bigger pore and the controlled release of drug may be through the smaller pore. In vitro release studies of the floating microspheres were carried out using USP Standard 8 stage basket type dissolution test apparatus in 900ml 7.2 Phosphate Buffer, for a maximum period of 12 hr. The data tabulated as above. It was observed that all formulations have bursting effect of drug within first 1-2 hr.

Table 2: Micromeritic properties of various formulations

Formulation Code	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Packing Factor	Angle of Repose(0)
F1	0.46	0.50	7.98	1.08	31.40
F2	0.35	0.38	6.66	1.07	33.13
F3	0.33	0.36	7.69	1.08	32.21
F4	0.37	0.37	0 1	0 1	27.76

Table 3: Actual Drug content and % Drug Entrapment Efficiency of various formulations

Formulation Code	Mean Particle Size (µm)	Encapsulation Efficiency (%)	% Buoyancy
F1	251.0	72.8	75.7
F2	261.9	85.1	82.5
F3	232.0	87.7	84.4
F4	220.4	94.2	94.1

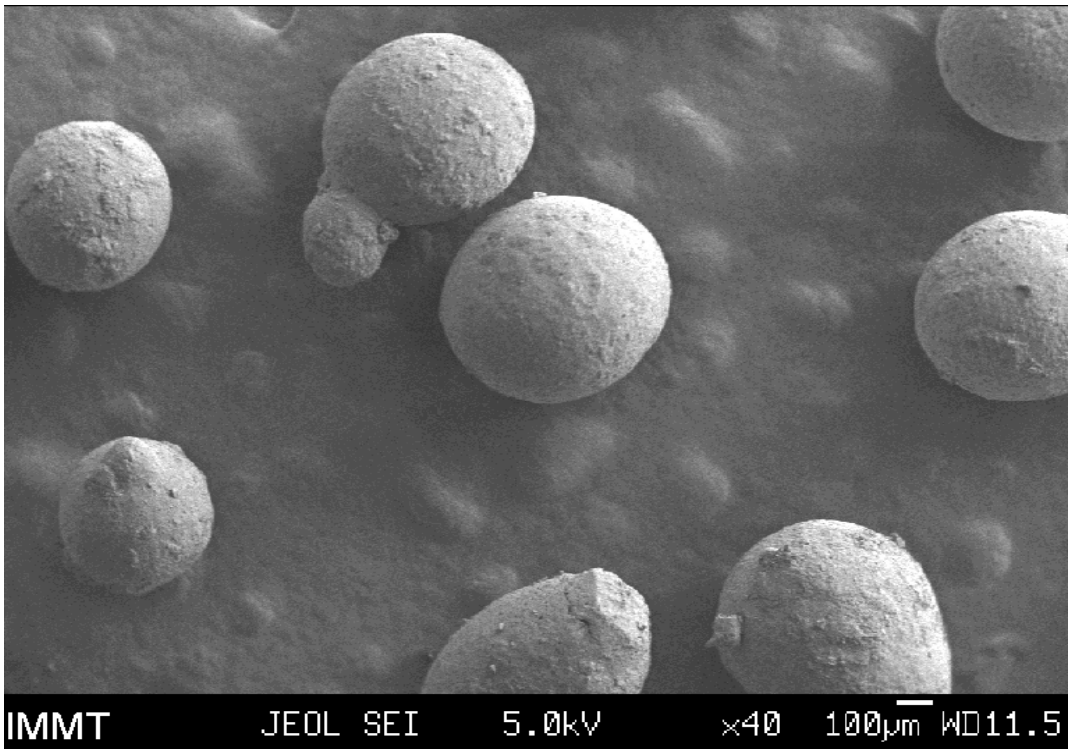

Figure 1: SEM photograph of microsphere

CONCLUSION:

The present work described floating microspheres of Nateglinide was formulated and evaluated. In this present work attempt was being made for the preparation of various formulations (F1 to F4). The formulations were prepared with varying concentration of ethyl cellulose and HPMC & keeping Nateglinide concentration constant. The evaluation of all formulation were carried of its Floating ability, Micromeritic property, % drug content, Entrapment efficiency, SEM photography, FTIR drug – polymer interaction study, and in- vitro drug release study in triplicate. From this investigation it was concluded that the formulation F4 was a good formulation. Where the formulation was having 70% drug content, with controlled and zero order drug released kinetics observed up to 12 hour and having up to 24 hour of floating behaviour. From SEM studies the formulation was found in spherical nature. The loading efficiency was studied during the evaluation and found high in F4. The formulation was relatively stable, reproducible and ideal for the floating drug delivery. So, the formulation F4 is more effective in the treatment of Type-2 (non-insulin dependent) diabetes mellitus.

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