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Evaluation of Repaglinide Loaded Floating Microspheres Prepared from Different Viscosity Grades of Hpmc Polymer

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ABSTRACT:
Repaglinide-encapsulated floating microspheres were developed and characterized during the investigation to extend the drug's residence period in stomach and subsequently boost its bioavailability. By using the emulsion solvent diffusion technique, floating microspheres of hydroxypropyl methyl cellulose (HPMC) and ethylcellulose (EC) (5 and 100 cps) were created. Numerous parameters, including the drug:polymer ratio, polymer ratio, emulsifier concentration, and stirring speed, were examined during process optimization. A few chosen optimal formulations were examined for drug release, kinetics, entrapment, and flying behavior. The microspheres ranged in size from 181.1 to 248 lm. For twelve hours, good buoyancy and entrapment were noted. The optimized formulation stayed buoyant for over six hours, as evidenced by the X-ray image. When compared to the pure medication treated group, the optimized formulation treated group exhibits a significant ($p < 0.01$) decrease in blood glucose levels. Repaglinide- loaded floating microspheres are anticipated to provide a new option for an affordable, safe, and more bioavailable formulation for NIDDM therapy.Abstract: Repaglinide-encapsulated foaming microspheres were developed and evaluated during the investigation to extend the drug's residence duration in gel and, consequently, boost its bioavailability. By using the emulsion solvent diffusion technique, floating microspheres of hydroxypropyl methyl cellulose (HPMC) and ethylcellulose (EC) (5 and 100 cps) were created. Many parameters were examined during process optimization, including the drug:polymer ratio, polymer ratio, concentration of emulsifier and stirring speed.

1. Introduction

These days, there is a lot of interest in oral dosage forms that can remain in the stomach for extended periods of time, prolonging the duration of drug administration (1). In pharmacological dosage forms, one of the key variables influencing the drug's bioavailability is the gastric resistance time (GRT) (2). The efficacy of administered doses may be eliminated due to partial drug release from the delivery mechanism above the absorption zone (stomach and upper portion of small intestine) caused by variable and short gastric emptying times (3). By extending GRT using a gastroretentive dosage form, such as the floating drug delivery system (FDDS), drug bioavailability can be sufficiently enhanced (4). By using a gastroretentive dosage form, such as the floating drug delivery system (FDDS), to prolong GRT, drug bioavailability can be sufficiently enhanced (5). The lower density of gastric and intestinal fluids than that of aqueous medium helps floating medicine delivery to stay buoyant over them. Single and multiple systems for fusing dosage forms have been created. Given that multiple unit dosage forms have been demonstrated to decrease both intra- and inter-individual variability in drug absorption and the likelihood of dose accumulation, they may present an appealing substitute for single unit dosage forms (6). Dosage forms that target the gastrointestinal system are ready to deliver the medication at the gastrointestinal location. There are various gastrointestinal target dose forms that have been created, such as the intragastric feeding system, high density system, mucoadhesive system, which adheres to the gastric mucosal surface to extend GRT, magnetic system, and unfoldable, extendible, or swellable systems. A floating drug delivery

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system can be helpful for a number of drug types that act locally in the stomach, are mostly absorbed in the stomach, have a small window of absorption, are poorly soluble in alkaline pH, are unstable in the intestinal or colonic environment, and so on

(7). Drugs that are soluble in acidic media and absorb better in the upper section of the intestine can be administered via the pharynx (8).Repaglinide is the first medication in the meglitinide class and an oral hypoglycemic drug used to treat type-2 diabetes mellitus.By attaching to a particular location on pancreatic b-cells, it inhibits the ATP-dependent potassium channel to promote the release of insulin (8). Due to its short half-life, repaglinide must be taken frequently before meals, which might cause side effects include headaches, skeletal muscle soreness, and git effects (9). Anti-diabetic medication-encapsulated microspheres improve the drug's efficacy and controlled release from polymeric membranes, extending the duration of its concentration. Because of its quick action, quick clearance, enzymatic stability, and all-around absorption, repaglinide is a good candidate for a gastroretentive dose form. The study's objectives were to lessen repaglinide's mentioned negative effects and boost its bioavailability. Additionally, the impact of various

viscosity grade HPMC on drug loading and in-vitro drug release was investigated, and an in-vivo X-ray research was conducted on the optimized formulation to determine its frying efficiency.

2. Materials and methods

2.1 Materials

We received a free sample of repaglinide from Torrent Pharmaceuticals in Ahmadabad, India. Himedia Chemicals, located in India, provided us with hydroxypropyl methylcellulose (5 and 100 cps) and ethylcellulose. Polyvinyl alcohol (PVA), dichloromethane, and ethanol of analytical grade were purchased from SD Fine Chemicals in Mumbai, India. Analytical grade chemicals were employed for all other purposes.

2.2 Preparation of microspheres

With a small modification, the solvent diffusion–evaporation approach was used to create microspheres with an anti-diabetic medication as the core material (10). In a 1:1 mixture of ethanol and dichloromethane, the drug, polymers, and 0.1% of PEG (as surfactant) were combined at room temperature. As an emulsifier, the slurry was gradually added to 80 milliliters of 0.46% w/v polyvinyl alcohol. For roughly an hour, the system was agitated using a propeller agitator to allow the organic phase to evaporate. The produced microspheres were placed in desiccators over fused calcium chloride after being cleaned three to four times with distilled water and dried for one hour at room temperature. During formulation optimization, a number of process variables were examined, including the drug:polymer ratio, the concentration of the emulsifier, the stirring speed, and the polymer ratio. Table 1 shows the optimum formulation conditions that were chosen based on the variables' results.

Formulation variables	Particle size	% Entrapment efficiency	% Buoyancy
Polymer ratio			
1:1	181.1 ± 1.5	58.5 ± 4.6	70.3 ± 1.1
1:2	192.5 ± 2.4	62.5 ± 3.2	77.2 ± 2.3
1:3	204.2 ± 3.5	63.2 ± 1.3	80.3 ± 3.3
Drug:polymer ratio			
1:1	179.6 ± 3.5	60.7 ± 2.3	70.4 ± 2.6
1:2	189.4 ± 4.5	64.8 ± 6.3.	78.1 ± 5.8
1:3	193.2 ± 7.2	66.6 ± 4.9	81.3 ± 6.4
Emulsifier concentration (% w/v)			

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0.46	208.1 ± 4.2	67.2 ± 5.3	84.3 ± 8.0
0.66	194.2 ± 1.1	64.3 ± 7.2	80.2 ± 6.1
0.86	182.3 ± 3.2	58.6 ± 6.2	79.4 ± 0.1
Stirring speed			
600	211.1 ± 0.3	65.2 ± 1.2	82.4 ± 4.2
900	201.2 ± 2.4	59.5 ± 2.6	78.1 ± 2.1

Table 1 Process variables for microspheres with HPMC (5 cps).

2.3. Characterization of floating microspheres

2.3.1. Surface morphology

Using a scanning electron microscope (SEM) (Jeol JSM-1600, Tokyo, Japan), the surface morphology was assessed.

2.3.2 Drug entrapment efficiency

The floating microspheres equivalent to 50 mg of repaglinide were weighed accurately and crushed. The powdered micro- spheres were placed in 10 ml of ethanol and kept for 12 h. The solution was then filtered through Whatman filter paper No. 44. The solution was diluted with fresh solvent and absor- bance was measured at 247 nm using UV spectrophotometer (Shimadzu 1700) and the percent drug entrapped was calculated as follows:

%Drug entrapment ¼ ðCalculated drug content=Theoretical drug contentÞ× 100

2.3.3. In-vitro evaluation of floating ability

A paddle-type, six-station dissolving test device (Veego, VDA-6DR, USP Std) was used to determine the drug release rate from floating microspheres. A weighed quantity of foaming microspheres, equal to 16 mg of medication, was stored in 0.1 N HCl (1.2 pH) with Tween 20 (0.02 w/v%) and held at 37 ± 0.5 °C while rotating at 100 rpm. The study's sink condition was maintained. At 30-minute intervals, 1 ml of the sample was taken out and run through a 5-lm membrane filter. and examined at 247 nm using spectrophotometric analysis. With pH 6.8 as the dissolving media, the same procedure was carried out once more. Every experiment was run three times.

2.3.4. In-vivo floating behavior

Weighting between 500 and 600 grams, healthy albino rats were given an optimum formulation and were observed using a modified radiological technique (11). The Shri Ram Institute of Pharmacy's Institutional Animal Ethics Committee, located in Jabalpur, Madhya Pradesh, accepted the study (Protocol No: SRIP/IAEC/2023/01). Individual animals were kept in polypropylene cages with normal lighting and temperature controls (12 hours of light and 12 hours of darkness; 25–30 °C). After a 12-hour fast, an X-ray was taken of the animals to make sure there was no radio opaque substance in their stomachs. Animals were not allowed to feed during the trial, but they were given unlimited access to water. 500 mg of barium sulfate was added to a polymeric solution to create radiopaque microspheres, and a similar process was used to create an optimal formulation. X-ray pictures of the stomach area (Siregraph-B, Siemens, Karlsruhe, Germany) were acquired at different intervals to observe the microspheres' floating behavior.

3. Results and discussions

3.1. Formulation and optimization of floating microsphere

Using ethylcellulose and HPMC (5 and 100 cps), the solvent-diffusion evaporation method was effectively used to create the floating microspheres. In order to investigate the impact of increasing polymer concentration on different described characteristics, formulations were created by altering the concentration of HPMC with a fixed ratio of EC. By adding a polymer and drug solution that had been produced in ethanol and dichloromethane to an aqueous PVA solution, microspheres were created. Ethanol spread out quickly into the surrounding aqueous phase, and a polymer film precipitated around the dichloromethane droplets. Cavities arise

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inside microspheres as a result of entrapped dichloromethane evaporating (Jain et al., 2005). This creates spherical, smooth-surfaced microspheres that can float above stomach fluid. The impact of viscosity on particle size was demonstrated using various HPMC viscosity grades. The findings displayed in Tables 1 and 2 demonstrate the strong influence that different formulation variables have on particle size, buoyancy, and entrapment efficiency. When HPMC concentration and viscosity rise at the same ratio, the mean particle size of microspheres also increases. The microspheres generated by HPMC (5 cps) and HPMC (100 cps) have particle sizes ranging from 181.1 ± 1.5–204.2 ± 3.5 lm and 221.2 ± 3.2– 236 ± 6.1 lm, respectively. Particle size rises with increasing HPMC concentration, resulting in the formation of bigger microspheres with HPMC (100 cps) compared to HPMC (5 cps). This is because a fixed volume of solvent has a significant rise in viscosity, which causes an increase in Microspheres diminish as the concentration of emulsifier rises. This could be because there are more PVA molecules covering the droplet surface, which will lessen the droplets' ability to prevent coalescence and lead to the production of tiny emulsion droplets. The size of the microspheres was determined by the size of the emulsion droplets, as they were generated from them after the solvent evaporated (12). The impact of stirring rate was also examined, and it was found that all batches had smaller particle sizes as the rpm increased from 600 to 900. Table 3 displays the optimized formula after the optimization results were combined.

3.2. Surface morphology

The surface morphology of the prepared microspheres was examined using a scanning electron microscope, as shown in Fig. 1.

3.3. Percent buoyancy and entrapment efficiency

The microspheres had a smooth and spherical surface. The percentage buoyancy of microspheres generated with HPMC 5 and 100 cps, respectively, ranged from 70.3–84.3% and 67.4–81.2% over the course of a 12-hour study. Microsphere foaming is influenced by the type of solvent used in formulation, the ratio of polymers, and the quantity of polymers utilized (13). Microspheres were continuously flooded, and it was discovered that the percentage of buoyancy increased as the polymer concentration increased. For every batch, entrapment efficiency was computed and found to be between 58.5 and 70.5%. Drug loading increases with increasing polymer concentration in the internal phase. This might be the result of an increase in internal phase viscosity, which lowers drug migration in the aqueous phase (14). Consequently, viscous polymer utilized in formulation hus, more entrapment is seen when viscous polymer is employed during formulation. However, as the stirring rate increased from 600 rpm to 900 rpm, the drug loading decreased. This could be because smaller microspheres generated at a faster rotational speed. Additionally, while washing microspheres, there is a greater loss of medication from the surface of small particles than from larger ones. While holding other parameters constant, the drug: polymer ratio of the microspheres was tuned. With a decrease in the drug polymer ratio up to 1:3, the drug entrapment initially rose for both batches, going from 60.7% to 66.6% and 61.8% to 68.6% (data not shown). Particle size and entrapment efficiency are influenced by a number of variables, including the size of the emulsion drop and the ultimate growth in particle size (14). The drug-polymer ratio and particle size ranges for the optimal formulations were 179.6 ± 3.5–193.2 ± 7.2 lm and 220.1

± 1.3–233.5 ± 1.8 lm, respectively, for increasing grades of HPMC utilized in the formulation process. It was also investigated how increasing emulsifier concentration affected particle size. The size of the particle was greater at low emulsifier concentrations and gets smaller as emulsifier concentration rises. Although % buoyancy drops somewhat with the amount of PVA used as an emulsifier, entrapment efficiency and particle size of the discharge of drugs has decreased. Thus, a 1:3 drug-to-polymer ratio was chosen as the optimal ratio.

3.4. In-vitro drug release study

Repaglinide release from microspheres was assessed for 12 hours in SGF. There is no burst effect in any of the formulations where the medication is released, suggesting a uniform distribution of the agent. Figure 2 compares the cumulative release of an optimal formulation made using various viscosity grades of

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HPMC and shows that it decreases as polymer concentration increases. For formulations comprising low viscosity HPMC (5 cps), drug release is higher (83.2%) than for HPMC (100 cps) (74.18%). The overall reduction in drug release is caused by the longer diffusional pathlength resulting from the increased density of polymer at higher concentrations.

3.5. In-vivo floating behavior

The EC:HPMC (5 cps) 1:2 ratio optimized floating microspheres were ultimately chosen for in-vivo feeding efficiency research using radiological techniques because they demonstrated improved drug release and strong in- vitro flotation capabilities. Figure 4 displays the radiographs taken at 0, 2, and 4 hours. It shows that the formulation was distributed uniformly over the stomach fluid and that it remained buoyant for more than 6 hours.

4. Conclusion

It was successful to formulate repaglinide-loaded EC and HPMC microspheres. The effectiveness of the formulation was assessed using a variety of formulation, characterization, in-vitro release study, and in-vivo assessments investigations. The suggested improved formulation shows how to extend medication release in a practical manner. The improved formulation demonstrated exceptional in-vivo feeding efficiency, with microspheres being kept in the rat stomach for an extended duration. Following the delivery of microspheres to healthy rats, good histological results were observed. The pharmaceutical business needs the created microspheres as a backup for efficient NIDDM control as they are safe.

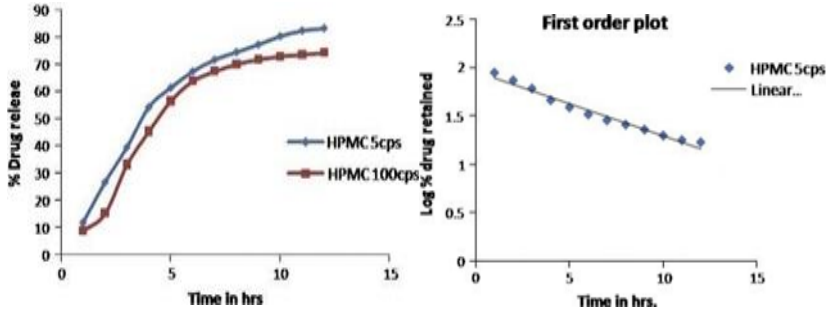

Figure 1 SEM photographs of microspheres prepared: (a) HPMC 5 cps and (b) 100 cps.

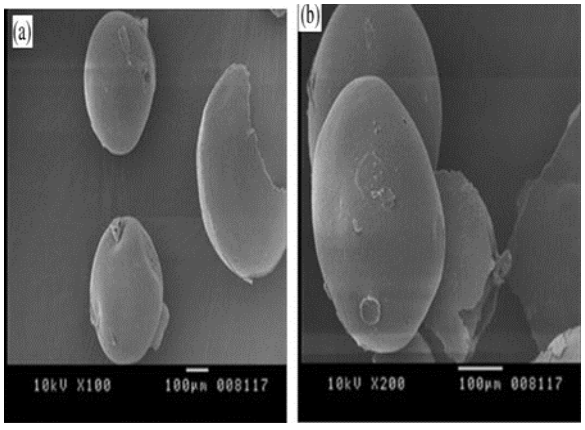

Figure 2 In-vitro release profile of optimized formulation of both the batches.

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