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DESIGN AND *IN VITRO* EVALUATION OF MULTIPARTICULATE FLOATING DRUG DELIVERY SYSTEM OF GASTROPROKINETIC DRUG

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ABSTRACT

Mosapride citrate is a 5-HT4 agonist and its action must be targeted to the esophagus and the upper part of the stomach. The present work relates to development of multiparticulate floating drug delivery system based on gas generation technique to prolong the gastric residence time and to increase the overall bioavailability. Modified release dosage form of mosapride citrate adapted to release over a predetermined time period, according to biphasic profile of dissolution. The system consists of mosapride citrate layered pellets coated with effervescent layer and polymeric membrane. The floating ability and in vitro drug release of the system were dependent on amount of the effervescent agent (sodium bicarbonate) layered onto the drug layered pellets, and coating level of the polymeric membrane (Eudragit® NE 30D). The system could float completely within 5 min and maintain the floating over a period of 12 h. The multiparticulate floating delivery system of mosapride citrate with rapid floating and modified drug release was obtained.

KEYWORDS : : Gastroprokinetic drug, Swelling index, Hydrodynamically balanced tablet.

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INTRODUCTION

Floating drug delivery system (FDDS) is one of the gastro retentive dosage forms which could prolong gastric retention time (GRT) to obtain sufficient drug bioavailability [1–4]. This system floats in the gastric fluid due to its lower bulk density compared to that of the aqueous medium. FDDS is desirable for drugs with an absorption window in the stomach or in the upper small intestine [5]. This system is also useful for drugs which act locally in the proximal part of gastrointestinal (GI) tract, such as antibiotic administration for Helicobacter pylori eradication in the treatment of peptic ulcer and for

drugs which are poorly soluble or unstable in the intestinal fluid [2]. Various approaches have been proposed to control the residence of drug delivery systems in the upper part of the gastrointestinal tract [6], like mucoadhesive systems, swelling/expanding systems, high density systems, magnetic systems, and floating systems. However, some of these systems seem to be less efficient and/or less recommendable than others. Mucoadhesive systems may be a potential cause of drug-induced injuries, which can range from local irritation to perforation depending on the ulcerogenic properties of drug. In the same way, accumulation of expandable gastroretentive dosage forms in the stomach might have serious implications for the patient. In this particular purpose, a fast biodegradation process would enhance the safety profile of such gastroretentive dosage forms [7]. Most of the floating systems previously reported are single unit systems such as tablets and capsules. A drawback of these systems is the high variability of the gastrointestinal transit time due to their all-or-nothing emptying processes [8–11]. On the other hand, the multiple-unit dosage forms may be an attractive alternative since they have been shown to reduce the inter- and intra-subject variabilities in drug absorption as well as to lower the possibility of dose dumping [12]. Recently, more emphasis is given on multiparticulate dosage forms because of their various advantages over single unit dosage forms demonstrated as flexibility during formulation development and therapeutic benefits for the patients [13]. There are many reasons for formulating a drug as a multiparticulate system for example, to facilitate disintegration in the stomach, or to provide a convenient, fast disintegrating tablet that dissolves in water before swallowing which can aid compliance in older patients and children. Multiparticulate systems show better reproducible pharmacokinetic behavior than conventional (monolithic) formulations. After disintegration which occurs within a few minutes often even within seconds, the individual subunit particles pass rapidly through the GI tract. If these subunits have diameters of less than 2 mm, they

are able to leave the stomach continuously, even if the pylorus is closed. These results in lower intra and inter individual variability in plasma levels and bioavailability [14,15].

In the present study, a new multiparticulate FDDS was designed and developed using bottom spray coating system (fluid bed processor). These forms are expected to remain lastingly buoyant on the gastric contents, without affecting the intrinsic rate of gastric emptying, as their bulk density is lower than that of the gastric fluids. The buoyancy principle providing floating dosage forms with a prolonged gastric residence time seems to offer a greater safety of use compared to the other approaches. The spherical coated pellets were prepared by coating of the drug layered sugar pellets with effervescent component (sodium bicarbonate) using hydroxypropyl methylcellulose (HPMC) as a binder and gas entrapped polymeric membrane (Eudragit® NE 30D). Mosapride citrate, which is absorbed in the upper part of gastrointestinal tract, was used as a drug. The effect of the preparative parameters, e.g., amount of the effervescent agent layered onto the pellets, and coating level of the gas-entrapped polymeric membrane, on the floating ability and drug release properties of the multiparticulate FDDS of Mosapride citrate were evaluated

MATERIALS AND METHODS

Materials

Mosapride citrate was supplied as a gift from Aurobindo Pharma, Hyderabad, India. Eudragit® NE 30D was provided by Degussa Evonik, India. Hydroxypropyl methylcellulose E5LV, sodium lauryl sulphate, polyvinyl pyrrolidone K30 (PVP K30) were obtained from Signet Chemical Corporation, Mumbai, India. Sugar pellets (# 25–30, ASTM) were provided by MB Sugars, Malegaon, India. Empty hard gelatin capsules (Size 0) was supplied as a gift from Associated Capsules Pvt. Ltd., Mumbai, India. All other chemicals and reagents used in the study were of analytical grade.

Drug layering

Mosapride citrate layered pellets were prepared by layering a drug-binder solution onto non-pareil sugar pellets using a fluidized bed coater (Pam Glatt, Glatt GmbH, Germany). Mosapride citrate was mixed with solution of polyvinyl pyrrolidone (PVP 30K) as a binder in 0.1 N HCl and HPMC in isopropyl alcohol (5%, w/w) with continuous stirring. Then talc was added as an anti-adherent. Sodium lauryl sulphate was used as a wetting agent. The composition of coating solution for drug layering is shown in Table 1. Drug-binder solution was sprayed onto the pellets using the bottom spray mode. The layering conditions were: batch size, 50 g; inlet temperature, 65–70 ◦C; product temperature, 33–36 ◦C; atomizing air pressure, 0.8–0.9 bar; spray rate, 0.5–1 g/min; fluidizing pressure, 0.5–0.6 bar; final drying at 40 ◦C for 30 min. The prepared pellets were then removed from the coating chamber and stored in a closed container for further experiments.

Coating of drug-layered pellets (effervescent layering)

The drug layered pellets were coated with two successive layers; an effervescent substance (sodium bicarbonate) as an inner effervescent layer and Eudragit® NE 30D dispersion (30%) as an outer gas-entrapped polymeric membrane. An effervescent agent (gas forming agent), sodium bicarbonate, was incorporated into HPMC solution plasticized with PEG 6000 (10%, w/w based on the solids content of HPMC) and then layered onto the drug layered pellets. On a dry solid basis, the ratios of sodium bicarbonate to HPMC were 2:8, 5:5 and 8:2 (w/w). The coating level of effervescent layer was 12% weight gain and the solids content of coating solution was kept constant at 12% (w/w). The composition for effervescent layering is shown in Table 1. The coating solution was then sprayed onto the drug layered pellets in a fluid bed coater (Pam Glatt, Glatt GmbH, Germany). The layering conditions were: batch size, 50 g; inlet temperature, 60–65 ◦C; product temperature, 30–

36 ◦C; atomizing air pressure, 0.9 bar; spray rate, 0.5–1 g/min; fluidizing pressure, 0.5–0.6 bar; final drying at 30 ◦C for 30 min. The effervescent layered (gas generating) pellets were then removed from the coating chamber and stored in a closed container for further experiments

Gas entrapped polymeric coating on effervescent pellets (modified release coating)

Eudragit® NE 30D dispersion (30%) was used as a modified release coating material to achieve a weight gain of 5, 10 and 15% (w/w) to obtain the complete multiple unit drug delivery systems. Eudragit® NE 30D can form film without the need of plasticizer and thus diluted with water without the incorporation of a plasticizer. Talc was added as glidant and an antiadherant in required portion of water and stirred it for 20 min. The composition of coating solution for modified release layering is shown in Table 2. The effervescent layered pellets were further subsequently coated with an aqueous colloidal dispersion of Eudragit® NE 30D. The coating conditions were as follows: batch size, 50 g; inlet temperature, 40 °C; product temperature, 23–26 °C; atomizing air pressure, 0.58 bar; spray rate, 0.5–1 g/min; fluidizing pressure, 0.45 bar; final drying at 30 °C for 30 min. The pellets were then removed from the coating chamber and stored in a closed container.

Evaluation of drug containing pellets Micromeritic properties

The micromeritic properties of pellets like bulk density, angle of repose, tapped density, Hausner's ratio were evaluated to check the flow properties of pellets [16,17].

Friability test

Friability of the pellets was determined by using USP friability test apparatus. Friability of the pellet formulations was determined as the percentage of weight loss after 200 revolutions of 10 g of the core

pellets in a friabilator (EF 1W, Electrolab, India) [18].

Scanning electron microscopy (SEM)

The surface morphology of the pellets was examined under a scanning electron microscope (JSM 6360A, JOEL, Tokyo, Japan). The pellets were mounted onto stubs using double sided adhesive tape. The mounted samples were sputter coated under an argon atmosphere with gold palladium and examined at 20 kV accelerating voltage.

Determination of the drug content

The drug content from the pellet formulations was determined by extraction with 0.1 N HCl. The effervescent layered pellets coated with gas-entrapped polymeric membrane (modified release pellets) of Mosapride citrate (100 mg) were accurately weighed, ground, and transferred into a volumetric flask and to it 0.1 N HCl was added and the mixture was sonicated for 30 min to ensure a complete extraction. The solution was filtered through a filter paper, diluted with appropriate amount of 0.1 N HCl and assayed spectrophotometrically at 270 nm (V-630, Jasco, Japan). The analysis was performed

Floating studies (*in vitro* buoyancy studies)

The *in vitro* floating study was carried out using USP dissolution apparatus II having 500 ml of 0.1 N HCl. The medium temperature was kept at 37 °C. The coated pellets (100) were spread over the surface of the dissolution medium and medium was agitated by paddle at 50 rpm. After agitation the pellets that floated over the surface of the medium were counted. The time to float and duration of floating (floating time) were measured by visual observation [19,20]. Three replicates were performed for each formulation. The percentage of floating was determined by following equation

$$\text{Floating pellets (\%)} = \frac{\text{Number of floating pellets at the measure time}}{\text{Initial number of pallets}} \times 100$$

Dissolution study (*in vitro* drug release study)

In vitro release of Mosapride citrate from pellet formulations was investigated by the USP apparatus II (paddle method – 37.0 ± 0.5 °C, 50 rpm, 500 ml, 0.1 N HCl, n = 3). The weight of pellets used was equivalent to about 20 mg of Mosapride citrate . At certain time intervals, 1 ml of sample was withdrawn and immediately same amount of fresh medium (37 ± 0.5 °C) was replaced. For the determination of Mosapride citrate amount, the absorbance of the samples was measured at 270 nm by UV spectrophotometer and total amount of Mosapride citrate released was calculated.

Stability studies

To assess the long-term stability, multiparticulate FDDS were stored at 40 °C/75% relative humidity (RH) for 3 months. After the first, second and third months, the formulations were observed for change in physical appearance, drug content and drug release profile. Stability studies were performed according to ICH guidelines [27].

Results and discussion

Fundamental design of multiparticulate floating drug delivery system the basic structure of multiparticulate floating pellets is schematically shown in Fig. 1. This system consisted of drug layered sugar pellets which are further coated with effervescent layer and gas entrapped polymeric membrane (modified release layer), respectively. In the effervescent layer, HPMC was used as binder, because sodium bicarbonate could not adhere onto the pellets. An ideal coating material for a floating system should be highly water permeable in order to initiate the effervescent reaction and the floating process rapidly. However, the wet or

hydrated coatings should also be impermeable to the generated CO_2 so as to promote and maintain the floating of the pellets. The polymeric coatings should be sufficiently flexible in wet state to be able to withstand the pressure of the generated gas and to avoid rupturing [28]. Hence in the present investigation, the higher flexibility polymer, an aqueous colloidal polymethacrylate dispersion (Eudragit® NE 30D), was chosen as a gas-entrapped polymeric membrane and modified release membrane. When such system comes in contact with the gastric fluid, the fluid permeates trough the outer polymeric membrane into effervescent layer. Then carbon dioxide was liberated and gets entrapped in the polymeric membrane. After that, the swollen pellets (like balloons) with a density less than 1.0 g/ml floated and maintained the floating and therefore, the drug was released from the system for a long time. The percentage drug release at the end of 12 hours from formulations 1, 2, 3, and 4 were found to be 90±0.2, 99.5±0.12, 94.9±0.15, and 98±0.13, respectively. The release profiles of the drug are shown in [Figure 2]

Evaluation of pellets

Physical characterization

The micromeritic properties of pellets like bulk density, angle of repose, tapped density and Hausner's ratio were evaluated to check the flow properties of pellets. The bulk density ranged from 0.79 ± 0.26 to 0.83 ± 0.21. The values obtained for angle of repose were 18.37 ± 0.41 to 24.15 ± 0.25 which indicates good flow properties of pellets. Hausner's ratio ranged from 1.01 ± 0.158 to 1.08 ± 0.258. The friability of the formulation was 0.15 ± 0.09%. This indicated that the pellets were quite hard and able to withstand the mechanical stresses during the subsequent coating process.

Determination of the drug content

Mosapride citrate content in the coated pellets was determined by using UV spectrophotometer. The

results showed that the content in any preparation was in a range of 96.2% and 102.1%. The results indicated that the multilayering also could produce the pellets with good reproducibility of drug content.

Floating studies (*in vitro* buoyancy studies)

The floating ability of the prepared pellets was evaluated in 0.1 N HCl as a dissolution medium. The time the pellets took to emerge on the medium surface (floating lag time) and the percentage of the pellets that floated on the dissolution medium surface were evaluated. Upon contact with an acidic medium the pellets swells and provides a gel barrier at the surface of the formulation. The sodium bicarbonate effervesced, releasing carbon dioxide and the released carbon dioxide is entrapped in the gel network producing buoyant formulation for prolonged periods. The system should float in a few minutes after contact with gastric fluid to prevent the dosage form from transiting into the small intestine together with food [29]. The floating capabilities of the pellets are guaranteed by the presence of both sodium bicarbonate, which generates CO_2 in a gastric acid medium (decreasing the density of the dosage form and allowing immediate buoyancy) and a swellable excipient (entrapping CO_2 bubbles and thus ensuring lasted buoyancy. It was observed that the entire pellets ascended to the upper one-third of the vessel within a short time, and remained floating until the completion of drug release. Most formulations performed satisfactory floating ability of which 70–90% of pellets remained floating up to 12 h. The buoyancy lag time for this system was in the range of 5–15 min. The *in vitro* floating test clearly showed that most of the pellets floated for around 12 h at the surface of the test fluid (Fig. 2). The pellets with the higher concentration of polymer were more floatable than those with lower concentrations of polymer. The time to float of the pellets decreased with increasing amount of effervescent agent and increased with increasing level of polymeric membrane coating. The higher amount of

effervescent agent caused faster and higher CO_2 generation [28]. This may be attributed to a decrease in density of pellets with an increase in polymer concentration.

Dissolution study (*in vitro* drug release study)

In-vitro release studies for the formulated mosapride beads were performed using USP Type II apparatus at 75 RPM. [31] The media was 900 ml of 0.1N HCl, which was maintained at 37±0.5 °C. pellets containing 20 mg of the drug were accurately weighed and placed into the dissolution apparatus. Samples were withdrawn at various time intervals, that is, 1, 2, 4, 6, 8, 10, 12, hours. The media was fully replaced during each sampling interval, because there could be chances of degradation of the drug. The samples were measured spectrophotometrically at 270 nm using a UV-spectrophotometer. The percentage drug release at the end of 12 hours from formulations 1, 2, 3, and 4 were found to be 90±0.2, 99.5±0.12, 94.9±0.15, and 98±0.13, respectively. The release profiles of the drug are shown in [Figure 2]. The release behavior of batches B1 to B4 changed due to the variation in the concentration of Eudragit® NE 30D in modified release layer, sodium bicarbonate and HPMC in the effervescent layer. As the concentration of Eudragit® NE 30D was increased the drug release was decreased. The drug release tended to increase with increasing amount of effervescent agent. However, no significant difference in drug release could be observed. A faster and higher CO_2 generation caused by increasing the level of effervescent resulted in higher swelling of polymeric membrane and subsequent drug release. Additionally, the higher level of effervescent agent was corresponded to the lower level of HPMC and this may lead to an increase of drug release according to the easier and faster water penetration through the pellets. The drug release decreased with increasing level of polymeric coating from low to high. The higher membrane thickness retarded water penetration, resulting in decreasing drug release [30].

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Stability studies

In any rationale design and evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection. During stability studies the product is exposed to accelerated conditions of temperature and humidity. However the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature for short period or time. The stability data of the coated pellets of Mosapride citrate is shown in Table 3. No macroscopical physical changes were observed during storage. The results obtained in the stability test showed that the drug content and *in vitro* drug release profile from the system stored at a temperature of 40 °C and a relative humidity of 75% was unchanged during a 3-month period of accelerated storage conditions. Drug content and *in vitro* drug release profile after 1, 2 and 3 months showed no significant differences (p > 0.05). This indicated that the pellet formulation was stable.

Conclusions

The multiparticulate floating system based on gas formation technique was designed and developed. The system consists of Mosapride citrate layered pellets coated with effervescent layer and polymeric membrane. The floating ability and *in vitro* drug release of the system were dependent on amount of the effervescent agent (sodium bicarbonate) layered onto the drug layered pellets, and coating level of the polymeric membrane (Eudragit® NE 30D). The system could float completely within 5 min and maintain the floating over a period of 12 h. The multiparticulate floating delivery system of Mosapride citrate with rapid floating and modified

drug release was obtained.

Table 1: Effervescent coating on drug layered pellets.

Ingredients (g)	A1	A2	A3	A4	A5	A6
drug layer pallets	50		50	50	50	50
HPMC 5 cps (% of pellets).	2.5	3.25	05	02	08	02
Sodium bicarbonate	2.5	02	05	08	02	08
PEG 6000	0.25	0.325	0.5	0.25	0.8	0.2
Isopropyl alcohol	35	55	80	30	110	30
Talc (%of polymer)	1.5	1.5	1.5	1.5	1.5	1.5
Water	39	50	80	112	35	112

Table 2: Gas entrapped polymeric coating on effervescent pellets (modified release coating).

Ingredients (g)	B1	B2	B3	B4
Effervescent layered pellets	50	50	50	50
Eudragit® NE 30D	10	16.5	33.3	50
Talc	01	02	04	06
Purified water	10	15	30	40

Fig. 1. Design of multiparticulate floating drug delivery system.
(Drug layered sugar pellets — Effervescent layer — Modified release layer)
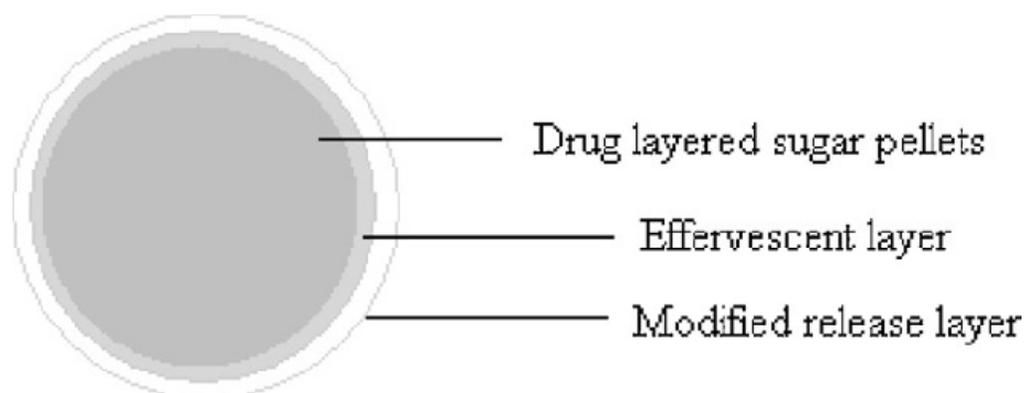
Table 3: Stability study results for coated pellets under accelerated condition.

Time/months	Appearance	Drug content*(%)	*in vitro* drug release at 12h
0	White	99.01±1.58	98.26±3.03
1	White	98.21±2.42	97.20±3.12
2	White	97.78±2.28	96.62±2.64
3	White	97.17±1.97	96.48±2.91

* n = 3; Mean ± S.D.

Figure 2: Release profile from B1, B2, B3 and B4 formulation
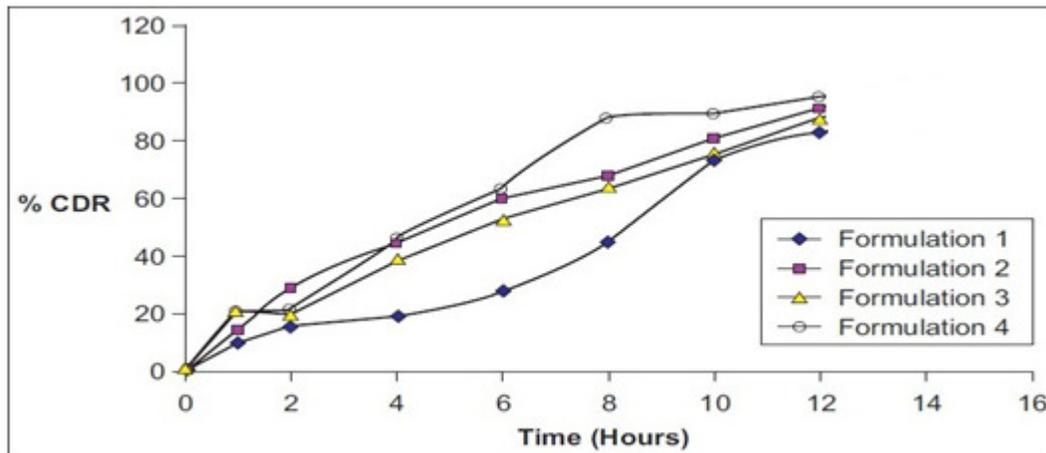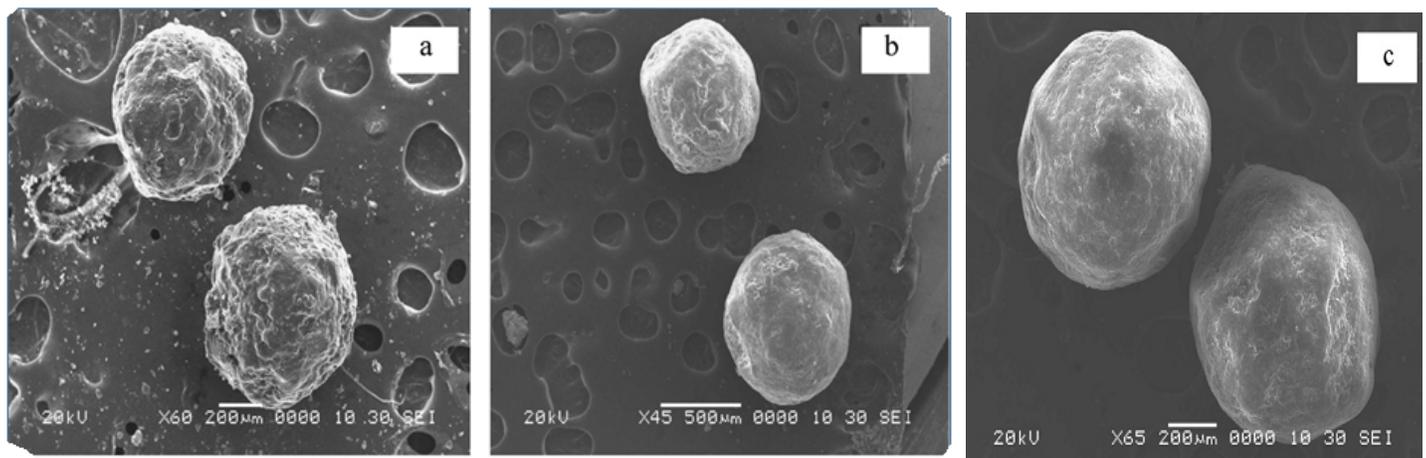

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Fig. 3: Scanning electron microphotographs of (A) drug layered pellets, (B) effervescent layered pellets, and (C) gas entrapped polymeric layered pellets..

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