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Development of novel floating mucoadhesive drug delivery system

Graduate School of Chosun University

College of Pharmacy

Prabhat Bhusal

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새로운 부유하는 점막점착성 약물전달체의 개발

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국문초록

새로운 부유하는 점막점착성 약물전달체의 개발

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위-잔류성 제형은 위장관 상부로의 약물 운반 방법으로 주목받고 있다. 이 연구의 목표는 새로운 형태의 위장관 잔류성 과립의 개발로 위장관 상부에서 부유할 수 있으며 위장 벽에 점착하여 강한 위-잔류성을 부여하는 것이다. 이 과립은 model drug로 사용 된 친수성 약물인 아세트아미노펜의 방출을 더 오랫동안 지연시켰다. 또한 약물의 방출에서 탄산수소나트륨의 역할도 평가되었으며, 약물 loading 정도에 따른 약물의 방출 양상 역시 관찰하였다. 5 w/w%의 탄산수소나트륨은 12시간 이상 과립을 부유시키는데 충분하였으며, 약물의 방출을 지연시키는데 최적의 과립 크기는 3-4mm 정도였다. 40 w/w%의 약물을 loading한 과립에서 충분한 점착성과 지연된 방출을 보였다. 따라서 점막점착성과 부력, 두가지 특징을 모두 가진 본 과립 제제는 오랜 시간 동안 위장관 상부에 머무를 수 있을 것으로 기대된다.

ABSTRACT

Development of novel floating mucoadhesive drug delivery system

Gastro-retentive dosage form is the topic of interest to deliver the drug in the GI tract. The aim of this study was to develop novel multiunit floating drug delivery devices, in the form of granules, which could float in the upper GI tract, and as well as adhere on the stomach walls thus imparting strong gastro-retentive properties. The granules was able to retard the release the hydrophilic model drug i.e. acetaminophen for the longer period. Effect of the Sodium bicarbonate on the release of the drug was also assessed. Various proportion of the drug loading was also done to see the release characteristics. 5 w/w% of the Sodium bicarbonate was sufficient to float the granules for more than 12 h in in-vitro conditions. The optimum size of the of the granule to retard the release of the drug was within the range of 3-4 mm. 40 w/w% drug loaded granules showed sufficient adhesion as well as sustained release property. Thus combining both properties of the mucoadhesion and buoyant properties in the granules is expected to reside in the upper part of the GI tract for longer period.

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1. INTRODUCTION

Absorption of the active pharmaceutical ingredients greatly depends upon the transit time of the drug in the intestine especially with the drugs having narrow absorption window. When the drug is allowed to stay in the upper part of the gastric region for a longer period, it results in prolonged contact time of the drugs with the gastrointestinal tract. This phenomenon leads to increment in bioavailability of the drugs. If such delivery system possesses controlled release property then it would lead to the higher absorption of the drugs. (Strubing et al., 2008). Knowledge of transit time of the drug allows drug delivery scientist to develop the time controlled release systems, which delivers the drug into specific location in the digestive system, which involves the use of the particular polymers or mixtures of polymers. Among all other gastro-retentive systems, stomach takes the advantage of several features of this organ particularly, the ones related to its physiology like low pH, motility or gastric emptying time. The following approaches have been tried in order to retain the dosage form in the stomach.

1.1 Floating system due to density

Buoyancy of the dosage form can be achieved by the entrapment of the air in a hydrogel network. Polymers such as hydroxypropyl methyl cellulose (HPMC), polyacrylates, sodium Alginate, corn starch, carrageenan, guar and arabic gums can be utilized for this approach. These hydrogels swell significantly in few min due to the water uptake by capillary wetting through interlocking pores (Pinto,

2010). Another approach to impart this property is development of microsphere with internal hollow structure. For example Lee et al. prepared internal hollow structure microspheres with smooth outer surface which was prominent when examined through scanning electron microscope (SEM). The hollow nature of the microsphere imparted floatation (Lee et al., 1999). Calcium silicate based, microspheres of repaglinide was prepared by Jain et al. using highly porous carrier material like calcium silicate and Eudragit® S as a polymer which is capable of floating on the gastric fluid and delivering the therapeutic agent over an extended period of time (Jain et al., 2005). Hollow porous calcium pectinate beads was also utilized by a recent study to develop floating pulsatile drug delivery which remain floated until 4 h, when observed via gamma scintigraphy, using rabbit as a animal model (Badve et al., 2007). Krogel and Bodmeier designed a multi-functional matrix drug delivery system, which was surrounded by an impermeable cylinder made of polypropylene with the tablet placed inside, which gave various extended drug release profiles with buoyant properties (Krogel and Bodmeier, 1999).

1.2 Floating System due to gas generation

Inclusion of the gas generator in an inert matrix is an alternative way to achieve floatation. This system is formulated in such as way that, they liberate CO_2 when they encounter the gastric acidic components (Arora et al., 2005). Gas forming agents are mainly carbon dioxide gas forming agents i.e., carbonate or

bicarbonate salts (Choi et al., 2002). Sodium bicarbonate based floating tablets showed less lag time for the floatation than that of the calcium carbonate based floating tablets as the later posses the lower efficiency for gas production (Tadros, 2010). Yang. et al. prepared triple layer tablets with the triple drug regimen (tetracycline, metronidazole and clarithromycin for the *H. Pylori* associated peptic ulcers. HPMC and polyethylene oxide (PEO) was used as the rate-controlling polymeric membrane, and gas-generating layer was prepared using sodium bicarbonate and calcium carbonate at the ratio of 1: 2, along with the polymers. Buoyant feature of this tablet prolonged the residence time of the system such that localized concentration of this drug in stomach was achieved (Yang et al., 1999). Similarly floating beads with gas forming agents was prepared by Choi et al. and the effect of the CO_2 generation on the properties, morphology and release rates was also characterized (Choi et al., 2002). Along with that, some ion exchange resin has also been reported by Atyabi et al. Sodium bicarbonate was loaded and coated with the semi-permeable membrane, which enabled exchange of the bicarbonate and chloride eventually leading to evolution of CO_2. The gas trapped within the membrane imparted floatation (Atyabi et al., 1996).

1.3 System acting by swelling

Swelling ability promotes the dosage form to localize in the stomach for the longer period. Eventually swelling leads to the decrease in the density and

promotes floating. Tablets containing hydroxypropyl cellulose, hydroxyethyl cellulose or hydroxylpropyl cellulose have visco-elastic structure, thus gel formed, was able to entrap air. When these type of system swells, they can withstand the peristaltic and mechanic contractility of the stomach thus prolonging the gastric residence time in the stomach (Deshpande et al., 1997). Swellable polymers undergo typical chain relaxation phenonmenon that resembles with the glassy rubbery transition. In this rubbery transition stage, the polymers may undergo swelling, dissolution and erosion or they also can form enduring gel barrier. Thus, this enduring barrier is responsible for controlling the release (Gazzanzia et al., 2008). Tablets containing the polymers like HPMC, hydroxyethyl cellulose have shown to possess visco-elastic gel structure in the outer layer, which promoted the air entrapment thus leading to the increase in the matrix volume (Baumgartner et al., 1998). Even salt like sucralfate with the combination of gellan gum has been utilized to prepare the gastro-retentive system as they have the tendency to form highly condensed viscous substance. In-situ gelling was achieved with the help of the sucralfate to prevent the degradation of the drug clarithromycin in the gastric environment (Rajnikanth et al., 2008).

1.4 Bioadhesion

Mucoadhesion to the gastric mucosa can lead to the prolonged retention of the dosage form to the stomach. Different bonds may arise to contribute mucoadhesion such as ionic, covalent, hydrogen, van-der-waals or

hydrophobic (Smart, 2005). Electronic theory, wetting theory, adsorption theory, diffusion theory, mechanical theory and fracture theory has been forwarded to explain the mechanism of mucoadhesion (Ahuja et al., 1997); (Mathiowitz et al., 1999). Contact stage between mucoadhesive materials and mucous membrane involves first and later in consolidation stage, various physicochemical interactions occur to consolidate and strengthen the adhesive joint. Intimate contact is precondition for the strong adhesive bond and it applies to all the adhesive system (Peppas and Sahlin, 1996). Polymers such as chitosan, Carbopol, thiolated chitosan, sodium alginate, carboxymethyl cellulose can be used as the mucoadhesive polymers. Among the entire above listed polymer, thiolated chitosan is believed to have strong mucoadhesion (Dhaliwal et al., 2008). Various mucoadhesive microspheres were prepared by the solvent diffusion method and interpolymer complexation method to retard the release of the hydrophilic model drug i.e. Acetaminophen (Chun et al., 2005). Antimicrobial agents were also incorporated in the mucoahhesive microspheres for the local action to treat the ulcers cause by *H. Pylori* (Chun et al., 2005). Cho and Choi. prepared mucoadhesive microsphere using chitosan and polyacrylic acid by solvent evaporation method as the interpolymer complexation of the above-mentioned polymer lead to decreased solubility of the complex, which eventually retarded the release of the drug (Cho and Choi, 2005).

1.5 Alternative System

The alternative system used for the stomach retention of the dosage form includes the approaches such as the programmable, controlled release capsules (Sakr, 1999), High-density system (Tadros, 2010) etc. Strussi et al. developed the various modules with various release characteristics, which were compressed by the compression machine using customized punches which was latter assembled to form the single shaped tablets. The module assemblage was accomplished using ultrasound. The outer modules disintegrated rapidly leaving only sustained release modules which eventually floats due to the void space present between the modules (Strussi et al., 2008). This system was even utilized with the two model drugs i.e. Clindamycin and Artensunate such that the assemblage system possesses multi-kinetic release at in-vitro conditions (Strussi et al., 2010).

When the delivery devices enter in the stomach, they are subjected to various movement cycles. Thus, for prolonged gastric retention the delivery system must be designed efficiently to overcome the extreme environment of the movement cycles. The physiology of the stomach and the factor affecting gastric retention must also be considered to design the appropriate drug delivery system. Anatomically the stomach consists of three main regions: fundus, body and antrum. The separation between stomach and duodenum is the pylorus. Fundus acts as a reservoir for undigested material, where the antrum is the main site for the mixing motion and the pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as feed states. During the

fasting state, an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2-3 h (Guyton, 1982). This is called interdigestive myo-electric cycle or migrating cycle (MMC). This can be further divided into four phases: Phases I also called basal phase lasts from 40-60 min., Phase II is also called pre-burst phase which lasts from 40-60 min. Phase III lasts for 4-6 min. It is associated with intense and regular contraction for short period. It is due to this wave that all the undigested material is swept out of the stomach, which is known as housekeeper wave. Last phase i.e. Phase IV lasts for 0-5 min is a transition period of decreasing activity until the cycle begins (Sauzet et al., 2009). Figure 1 depicts the probable site of the floating and non floating units during the course of residence time of dosage forms (Arora et al., 2005).

Studies have revealed that gastric emptying time of the dosage form in the feed state can also be influenced by size. Small sized tablets have high probability to reside in the stomach for the longer period that that of the large sized tablets. Size and the shape of the dosage form also effect the gastric emptying i.e. tetrahedron and ring shaped devices have better gastro-retentive property. Along with that diameter and the density of the system also influences the gastric residence time of the dosage form (Garg and Sharma, 2005). Therefore, multiple unit dose system are preferable rather than unit dose system as they have the advantage as they are not subjected to all or nothing gastric emptying nature of single unit system (Joseph et al., 2002). Various multi-unit floating

systems have been developed in different forms and with different principles of aiming the system to reside in the stomach for the longer period such as hollow microspheres (Nepal et al., 2007), low density foam powder (Streubel et al., 2002), beads (Gupta and Aggarwal, 2007), sustained release pills etc. (Sungthongjeen et al., 2006). A multiparticulate floating-pulsatile drug delivery system was developed using porous Calcium silicate (Florite RE) and sodium alginate for the time and site-specific drug release of meloxicam. The drug was adsorbed on the Florite RE (FLR) by fast evaporation of the solvent from the drug solution containing dispersed FLR. Floating time was controlled by density of beads hydrophobic character of drug (Roy et al., 2009). Ichikawa et al. also developed granule targeted to localize in the stomach, which consisted a core with drug, which was coated with the foaming layer i.e. gas-forming layer, by the use of the sodium bicarbonate (Ichikawa et al., 1989).

Contemplating the advantage of the multiunit floating device over unit floating devices, the attempt was made to develop the novel multiunit floating drug delivery systems. The units would be in the form of the granules such that the granules would not only float in the stomach but also attach on the mucosal walls of the stomach thus imparting strong gastro-retentive property. PVP (K-30) and Carbopol® 971 were used as the carrier such that they act as the reservoir for the drug and impart the mucoadhesive property to the Gastric mucosa. Sodium bicarbonate was used as the buoyant agent. The model drug used for this study was hydrophilic drug Acetaminophen. First, the ratio of the

Carbopol® and PVP (K-30) was determined based on the ability to float after the interval of 12 h, which was followed by the optimization of the possible minimum sized granules with sustained release characteristics. Then, minimum amount of the sodium bicarbonate required for floating was determined. Similarly, the effect of the drug loading on the release and adhesion time was also characterized. The optimized sized granule was also compared with the granules prepared dry granulation. Finally, SEM (scanning electron microscopy) study was carried out to examine the morphology of the granules at various conditions.

2. Materials and methods

2.1 Materials

Carbopol®971 (Lubrizol®) was generous gift from the United KOREA Ltd. PVP (K-30) (Kolloidon® 30) was received as gift sample from BASF Corporation. Acetaminophen (USP), Sodium bicarbonate (Junsei Chemical Company, Japan), Acetonitrile (Merck Chemicals, Germany) and other materials and reagents were of analytical grade and used as received without further purification.

2.2. Methods

2.2.1 Optimization of the ratio of the Carbopol® 971 and PVP (K-30)

Carbopol® 971 and PVP (K-30) were taken at various ratios, mixed and grounded in mortar and pestle along with the buoyant agent i.e. sodium bicarbonate (10 w/w %). The mixture was granulated with ethanol (0.400 mL/ 1.0

g mixture). After granulation, the mass was dried in the oven at 50 for 12 h. Then, the granules were separated between the sizes of 0.710 -0.250 mm. Then 250 mg of the granule was taken and introduced to 50 mL of pH 1.2 buffer and stirred at 100 rpm for 12 h. After 12 h, the floated portion was taken and dried at 80 °C overnight. Then, the floating efficiency was characterized by the formula:

$$\text{Floating}(\%) = \frac{\text{Initial Weight of the granules} - \text{Recovered Granule's Weight}}{\text{Initial Weight of granules}} \times 100$$

The weight of the Sodium bicarbonate was not accounted during calculation.

2.2.2 Optimization of the size of the granules

The dough was prepared by the method as describe in section 2.2.1. Then, the granules of various size ranges were prepared manually. For this dough was rolled down to form the rod. The rod was chopped with the help of knife and the granules were rolled between the fingers. After the preparation, the granules were separated within the size range of 2-3 mm, 3-4 mm, 4-5 mm and 5-6 mm respectively. The composition of the drug and sodium bicarbonate was kept fixed at 40 w/w% and 5 w/w% respectively. The granules were dried overnight in the oven at 50°C.The granules containing 60 mg equivalent amount of the Acetaminophen was taken and release study was characterized in the USP Dissolution apparatus (DST-810 and DS-600A, Labfine Inc., Suwon, Korea) at the paddle rotation speed of 50 rpm in 900 mL of pH 1.2 buffer. The temperature of the medium was kept at 37 °C.1 mL of the sample was withdrawn at the time interval of 15, 30, 60, 120, 240, 360, 480 and 720 min respectively. Then fresh 1

mL of pH 1.2 buffer was replaced immediately. The sample was centrifuged at 13,200 rpm for 10 min and supernatant was diluted suitably with methanol and analyzed by HPLC.

2.2.3 Optimization of the Sodium bicarbonate content

Sodium bicarbonate was loaded with 0, 2.5, 5, and 7.5 w/w% of the granule weight and the size of the granules were fixed around 3.5 mm. Drug loading was fixed at 40 w/w%. The manufacturing process of the granule was as same as the method described above. The floatation study was also characterized with the visual observation at the interval of 1 h. Then, release study was carried as method described previously.

2.2.4 Optimization of the Drug loading to the granules

Drug was loaded from 10 to 70 w/w% of the granule and the size of the granule was kept in the range of 3.5 mm. Sampling were done at 15, 30, 60, 120, 180, 240, 300, 360,420, 480, 600, 720 and 1440 min. The composition of sodium bicarbonate was kept same with all the types granules i.e. 5 w/w%. The release study and the adhesion time were determined to optimize the formulation.

2.2.5 Determination of the uniformity of size

Manually 10 individual granules were taken from the granules prepared by the wet granulation, and measured with the help of Digital Vernier Scale (Mitutoyo

Corporation. Japan).

2.2.6 Determination of the adhesion time of the granules

Polypropylene Plate method was used to determine the adhesion time as it closely correlate with the porcine mucosa (Chun et al. 2003). 6 cm X3 cm polypropylene plates were taken and 10 µL of the water was put on one end of the plate at three different places. Three granules were placed just above the drop of the medium and allowed to stand still for 10 min. Then, the plate with the attached granules was clamped to spatula and dipped in the dissolution apparatus maintained at 37° C. The position of the plate was fixed in such a way that the granule was half dipped in the medium. The volume of the medium was 900 mL of pH 1.2-buffer and rotation speed of the paddle was fixed at 150 rpm. The detachment time of the individual granule was noted visually in every 5 min time interval.

2.2.7 Analytical Method of Acetaminophen

The amount of Acetaminophen was determined by using a high performance liquid chromatography (HPLC) system (Shimadzu Scientific Instrument, MD, USA), consisting of a UV detector (SPD-10A), a pump (LC-10AD) and an automatic injector (SIL-10A). Samples were analyzed with the mobile phase consisting of Acetonitrile and Water in the ratio of 15:85 (v/v %) at the flow rate of 1.0 mL/min. The wavelength of the UV detector was 275nm and a reversed-phase column

(Gemini 5 μM, C18 110A, Phenomenex, USA) was used. The samples were analyzed at a column temperature of 30 ˚C.

2.2.8 Effect on the drug release of the optimized formulation prepared by various granulation methods

Granules containing 40 w/w% of Acetaminophen and 5 w/w % of sodium bicarbonate were prepared by wet granulation and direct compression method. Regarding direct compression, Carbopol® 971, PVP (K-30), sodium bicarbonate and Acetaminophen were mixed in the mortar and pestle for 15 min. Then, 650 mg of the mixture was taken and compressed using oblong punches in Pilot Press Tablet Machine (Chamunda Machinery Private Ltd. Ahemdabad. India). The tablets prepared, were again crushed in the mortar and pestle and the granules sized between 3-4 mm were separated using digital Vernier Calipers (Mitutoyo Corporation, Japan). The release study was characterized by the method mentioned above in the section 2.2.2.

2.2.9 Morphological examination of the granules

Scanning electron microscopy (S- 4700, Hitachi, Japan) was used to study the morphological study of the granules. Following kinds of samples were studied, i.e. granules prepared by dry granulation containing 40 w/w% of drug, 0 w/w% Sodium bicarbonate and 5 w/w% sodium bicarbonate without drug. To see the effect of sodium bicarbonate on the morphology during floating, the granules

containing 5 w/w% and 0 w/w% of sodium bicarbonate, were stirred in 900 mL of pH 1.2 buffer for 2 h. The granules were removed and dried in the oven at 80 °C for 12 h. Then, the morphology was characterized by mounting the sample onto an aluminum stub and sputter was coated for 120 s with platinum particles in argon atmosphere.

3. Results

3.1 Optimization of the ratio of the Carbopol® 971 and PVP (K-30)

It was found that, the recovery of the granules was maximum at the ratio of 1:1. Almost 95 % of the granules were recovered at the end of 12 h with thi s ratio. Considering the objective of the study the ratio was kept 1:1 in furth er experiments. The studies with other ratios were not carried out as the floa ting percentage decreased with the change in the ratios. The overall floating efficiency at various ratios is given in Table 1.

3.2 Optimization of the Size of the granules

It was found that the release of the hydrophilic drug Acetaminophen was dependent on the size. With smallest size granules i.e. within the range of 2-3 mm the release was maximum. Whereas the release rates were decreased with the increase in the size of the granules. The ranges of the granules of size 3-4 mm had the satisfactory profile to meet the objective of the study, further study were carried out with the granule having this size range.

3.3 Optimization of the Sodium bicarbonate Content in the granules

The floating behavior of the granules with various percentages of the sodium bicarbonate loading is depicted in Table 3. The granules without sodium bicarbonate floated until 2 h.Whereas, the granules containing 2.5 w/w % only float for 6 h. The granules containing 5 w/w % floated more than 12 h.

Regarding the release of the drug with the sodium bicarbonate concentration, it was found that the drug release increases with the Sodium bicarbonate concentration. Granules without sodium bicarbonate release approximately 45 % of the drug within the interval of 12 h, whereas, the release significantly increases with the increase in the sodium bicarbonate content.

3.4 Optimization of the Drug Content in the granules

The size of the granules taken for the various drug loading are given in Fig. 3. The granules were selected with minimum size variation. From the Fig. 4, we can observe that even with the 50 w/w% drug loading, granule is also able to release the drug in sustained manner. The release rate increase significantly beyond 50 w/w% of drug loading.

3.5 Adhesion time with various drugs loading

The adhesion time at various drug loading is depicted in Fig. 4. It was found that the adhesion time is not significantly different within the range of 40 w/w% of the drug loading. But, beyond 40 w/w% of the drug loading, the adhesion time got

significantly decreased.

The maximum adhesion time was found with the 10 % w/w drug load.

3.6 Effect on the release of the granules by wet and dry granulation methods

It was found that the granules prepared by the dry granulation releases the drug instantly whereas, the granules prepared by the wet granulation method release the drug in sustained manner. The release profile of the granules prepared by two different methods is depicted in Fig. 7. It shows more than 60 % of the drug is released within 2 h from the granules prepared by the dry granulation method.

3.7 Morphological Examination

Morphological examinations of the various types of the granules are portrayed in Fig. 8. The Fig. 8a and 8b shows the morphological properties of granules prepared by direct compression and wet granulation respectively. The granule prepared by direct compression consists of porous character. Whereas, the granules prepared by the wet granulation have compact appearance. Similarly, Fig. 8c and 8d shows the difference in the morphology of the granules containing 5 w/w % of Sodium bicarbonate before and after going into the pH 1.2 buffer. Before, the granule is compacted and devoid of the hollow pores but when it is in the buffer medium the hollow pores are generated on the surface. Fig. 8 e i.e. granule without Sodium bicarbonate shows the difference in the morphology with granule containing 5 w/w % Sodium bicarbonate when it is in

the buffer medium. It contains fewer amounts of hollow pores than that of the granules containing sodium bicarbonate.

4. Discussions

Table 2 shows the floating efficiency at various Carbopol® 971: PVP (K-30) ratios at fixed level of sodium bicarbonate content. Inter-polymer complexation between Carbopol® 971 and PVP (K-30) lead to formation of intermediate, which decreases the solubility of the polymer in the medium. Tan et al. also explained that the maximum inter-polymer complexation occurs at ratio of 1:1 between Carbopol® 971 and PVP (Tan et al., 2001). Thus, complex formation and buoyant feature contributed the higher fraction of the granules to float at the ratio of 1:1.

The size of the granule was extremely important for the retarding the release of the drug. The release profile with respect to various sizes ranges illustrated in Fig. 2 corroborated that the release of the drug is increased when the size of the granule is decreased. This may be due to the fact, that with small sized granules, the rapid penetration by the medium results rapid leaching of the drugs hence the smallest size granules will not be able to retard the release of the drug. Conversely when the size is increased the penetration of the medium to the inner core of the granules decrease thus resulting in less release as compared to small sized granules. Berkland et al. also demonstrated that size of the microspheres is primary determinant of drug release rates. As size increases, surface area: volume ratio decrease which decreases buffer penetration (Berkland et al., 2003)

and with small sized microspheres the surface area to volume increases buffer penetration eventually (Berkland et al., 2004). It was also found that the difference in release is prominent in the size range of 2–3 mm and 3–4 mm. However, the difference in the release gradually decreases with the increment in size. It might be due to the decrement in extent of the penetration of the buffer to the inner core of the granules with the granules having higher size range. Thus, granules having higher size range, the peripheral part of the granules may serve as the primary releasing site. However, with lower sized granules the release may be both from peripheral as well as inner core.

Table 3 shows the floating behavior of the granules at various percentage of the sodium bicarbonate loading. The granules floated with no lag time in every case except with the granules without sodium bicarbonate. When gas-forming agent is exposed to the pH 1.2 buffer, they immediately release CO_2 by the neutralization reaction. Thus, it results in the decrease in the specific gravity of the system, which causes it to float (Sing et al., 2000).

Granules without sodium bicarbonate floated with the lag time of 10–15 min and again sank after 2 h. The lag time for floatation of these granules may be due to the formation of air pockets in the granules during granulation process, which became only effective after the penetration by the medium. However, the pores formed may not be effective to sustain buoyancy with the course of time thus granules sank after 2 h. This is also can be explained by SEM image of the granules without sodium bicarbonate i.e. Fig. 8 e after 2 h stirring in pH 1.2

buffer where we could see fewer no. of pores.

Fig.3 illustrates the release of the acetaminophen at various sodium bicarbonate content. The release was dependent on the sodium bicarbonate concentration. It could be due to the generation of the pores by the gas forming agents at higher percentages. But, at lower percentages, the buoyant agent may not be able to produce enough pores due to lower amount of gas generation. Choi et al. also demonstrated that release of the riboflavin increased with increasing ratio of the sodium bicarbonate as the buoyant agents generates more pores due to the evolution of CO_2 (Choi et al., 2002). The SEM pictures in Fig. 8 can also explain the increment in release of the drug with sodium bicarbonate, where the number pores formed with and without sodium bicarbonate are significantly different. Thus, these pores formed; with the increment in the sodium bicarbonate concentration are responsible for the higher release rates of the model drug.

The release profile, illustrated in Fig. 5 confirms the retardation of the release of the drug. The retardation of the release rate can be explained by the formation of interpolymer-complexation behavior between the Carbopol® 971 and PVP(K-30). Interpolymer complexation was formed due to bonding of carboxyl group of Carbopol® and carbonyl group of the PVP (K-30). The release of the drug was significantly reduced from the complex due to strong hydrogen bonding between two groups. The bonding becomes strong at low pH as pKa of the polyacrylic acid is lower than pH of the medium and hence they hardly got dissociated (Chun et al., 2005). The release was higher as the drug loading was increased. It

could be due to the inability of the inter-polymer complex to prevent penetration of the buffer medium.

Fig. 6 portrays the adhesion time of the various types of granules with the polypropylene plates. The adhesion time was longest for the granules with 10 w/w% drug loading and it is decreased with the increase in drug load. The adhesion time of the granules with 20 and 40 w/w% drug loading was not significantly different. Hence, considering the release profile and the adhesion time the formulation containing 40 w/w% of the drug was chosen for the further experiments. The decrement in the adhesion time with the increase in drug load could be due to the replacement of the mucoadhesive sites by the drug itself. The adhesion period for more than 300 min and the floating property over 12 h could generate strong gastro-retentive property for granules. Whereas, the adhesion time was not significantly changed with the change in the sodium bicarbonate concentration in the granules. It might be because, the mucoadhesive site of the polymer and the complex is maintained with the higher concentration also. Moreover, due to the rapid neutralization of the Sodium bicarbonate in the simulated gastric pH buffer the active mucoadhesive site may not be blocked. At 5 w/w % of the Sodium bicarbonate loading was sufficient to make the granules to float over 12 h.

SEM image picture revealed that, the granules prepared by the direct compression lead to the formation of highly porous granules, which leads to the faster release rate than that of the granules prepared by wet granulation method

as depicted in Fig. 7. Due to compaction, the drug is embedded in the polymer or complex, thus the penetration by the medium is slower than the granules prepared by direct compression. Similarly, the difference in the morphology of the granules before and after introduction in the buffer medium, suggested that the pores were generated by the buoyant agent i.e. sodium bicarbonate. The pores were formed due to the production of CO_2 during neutralization reaction. The generated gas is expected to be entrapped inside the void space of the granules which results is prolonged floating of the granules. Accordingly, Fig. 8e shows that the granules without sodium bicarbonate possess significantly lower amount of pores than the granules with sodium bicarbonate. Because of the lesser amount of the hollow pores, the granules without Sodium bicarbonate sank after the experimental period of 2 h.

5. Conclusions

This experiment paved the path to explore further drugs in this drug delivery system, which are preferentially absorbed in the stomach or the upper part of the small intestine. Drugs having short absorption windows can be used further with this delivery device. In-vivo experiments can be done in order to ensure that the granules will be localized in the stomach for the prolonged period of time. Buoyant along with mucoadhesive property of the granules is expected to

provide strong gastro-retentive property in-vivo. The developed multi unit delivery system can also be compared with the unit floating devices in-vivo to demonstrate its superiority over the unit floating devices. The multi unit are thought to be efficacious over the unit devices because of the all or none probability of going down to lower GI tract.

The optimized formulation i.e. containing 40 w/w% of the drug seem to float more than 12 h maintaining shape which is demonstrated in Fig 9. Since it is able to retard the release the hydrophilic drug, sustained release of the partially hydrophilic to lipophillic drug is also confirmed.

The granules can be filled in the capsules for the convenient administration. Immediate release granules can be mixed with these granules and eventually filled in capsules to provide the multi-kinetic release.

The preparation method can be prepared with the spheronizer or other automated equipments in order to make the process simpler and feasible to scale up for large manufacturing.

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Table. 1 Lists of the drugs formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems (S. Arora et al., 2005).

Tablets	Chlorpheniramine maleate
	Theophylline
	Furosemide
	Ciprofolxacin
	Pentoxyfillin
	Captopril
	Acetylsalicylic acid
	Nimodipine
	Amoxycillin trihydrate
	Verapamil HCl
	Isosorbide di nitrate
	Sotalol
	Atenolol
	Isosorbide mono nitrate
	Acetaminophen
	Ampicillin
	Cinnarazine
	Diltiazem
	Florouracil
	Piretanide
	Prednisolone
	Riboflavin- 5´ Phosphate
Capsules	Nicardipine
	L- Dopa and benserazide
	hlordiazepoxide HCl
	Furosemide
	Misoprostal
	Diazepam
	Propanolol
	Urodeoxycholic acid
Microspheres	Verapamil
	Aspirin
	griseofulvin
	p-nitroaniline
	Ketoprofen
	Tranilast
	Iboprufen
	Terfenadine
Granules	Indomathacin
	Diclofenac sodium
	Prednisolone
Filims Drug Delivery devices	Cinnarizine
Powders	Several Basic Drugs

Table 2. Floating efficiency at various ratio of PVP (K-30): Carbopol® 971

PVP (K-30):Carbopol® 971	Floating percentage (%)
1:1	95.00±2.10
1:2	88.75±3.20
1:3	76.16±1.15
1:4	72.24±2.45
2:1	86.37±3.82
3:1	84.32±1.11
4:1	70.51±1.55

Table.3 Floating behavior of the granules at various loading of the Sodium bicarbonate Content

Sodium bicarbonate (% w/w)	Floating Duration Hours (h)
0	2
2.5	5
5	>12
7.5	>12

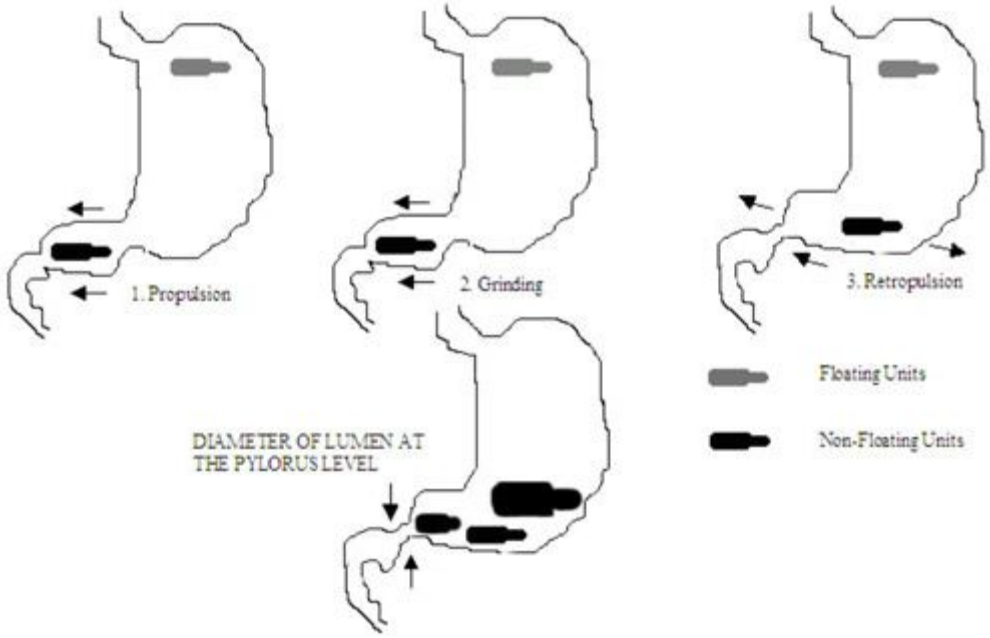


Fig.1. Intra-gastric residence positions of floating and nonfloating units (S. Arora et al., 2006).

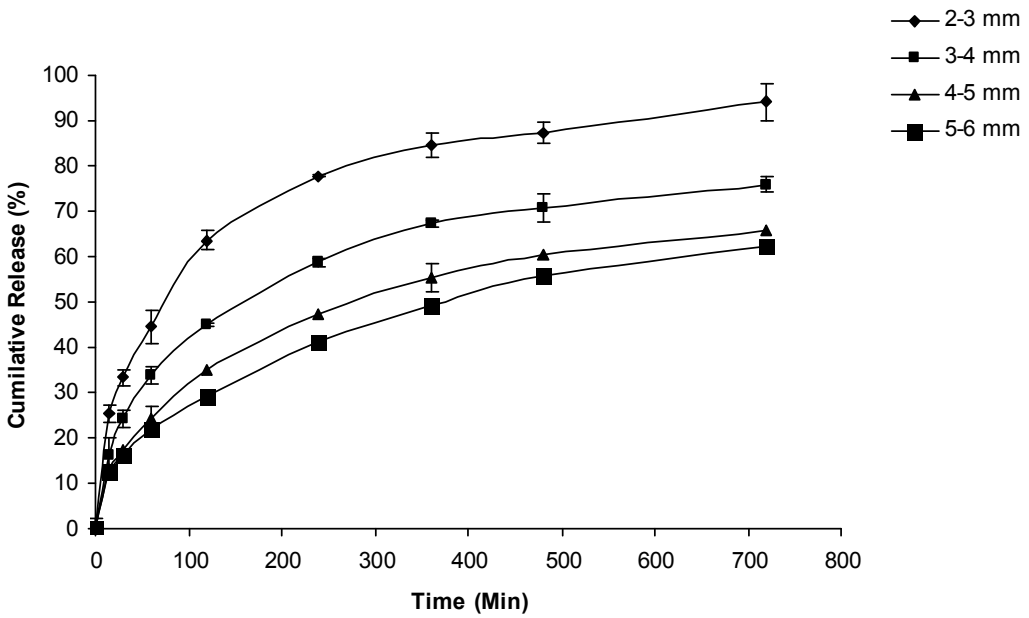


Fig. 2. Release of the acetoaminophen from the granules of various size range.

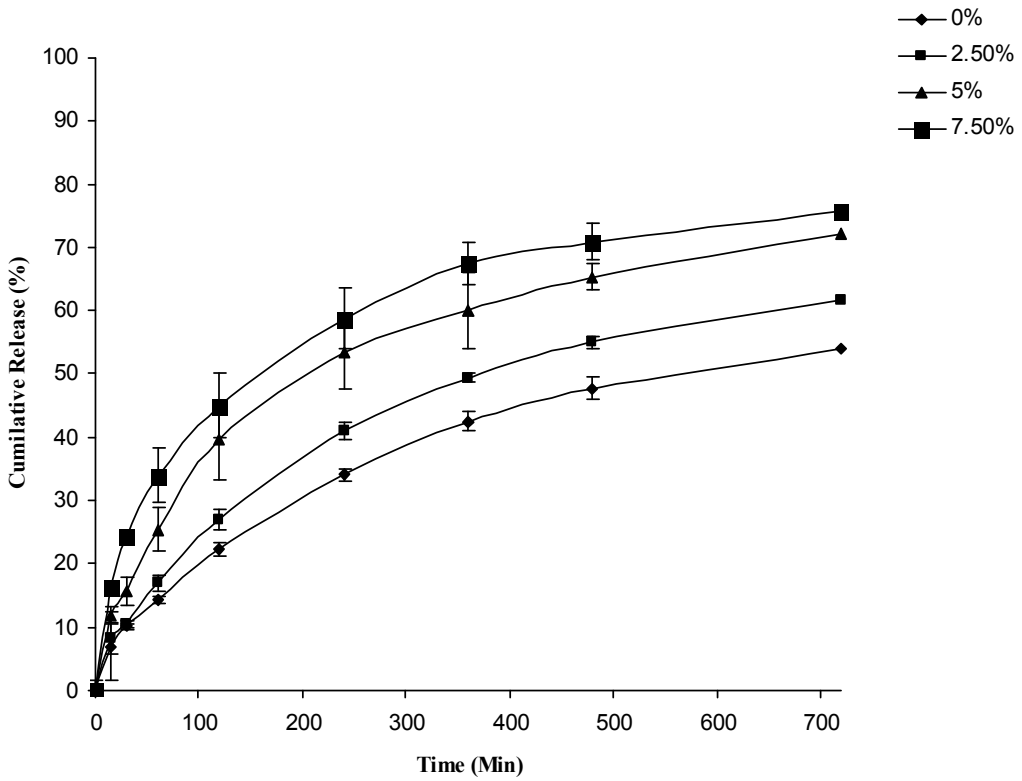


Fig. 3. Release of the acetoaminophen from the granules with various sodium bicarbonate content.

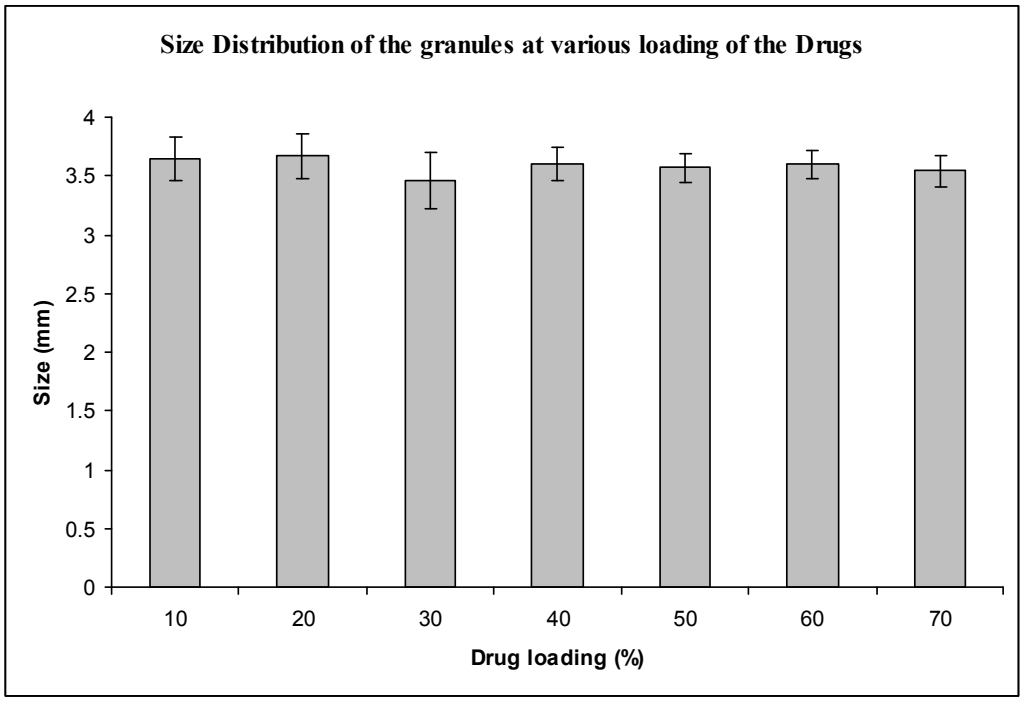


Fig.4. Size distribution of the granules.

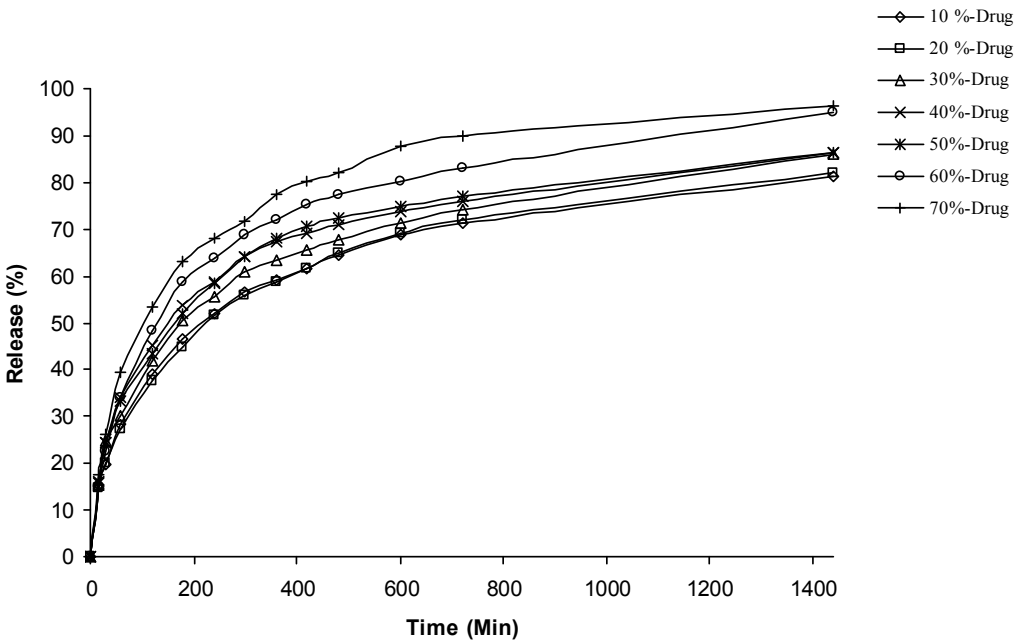


Fig. 5. Release of the acetoaminophen from the granules with various drug loading. Values are expressed as mean. (n=3)

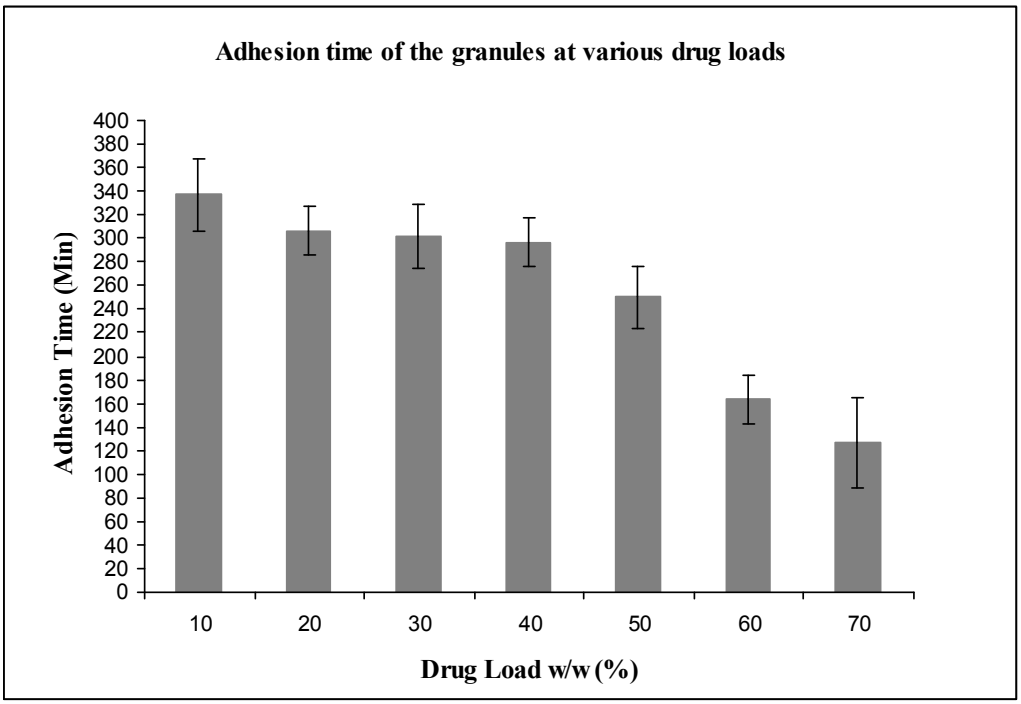


Fig. 6. Adhesion time of the granules at various drug loading

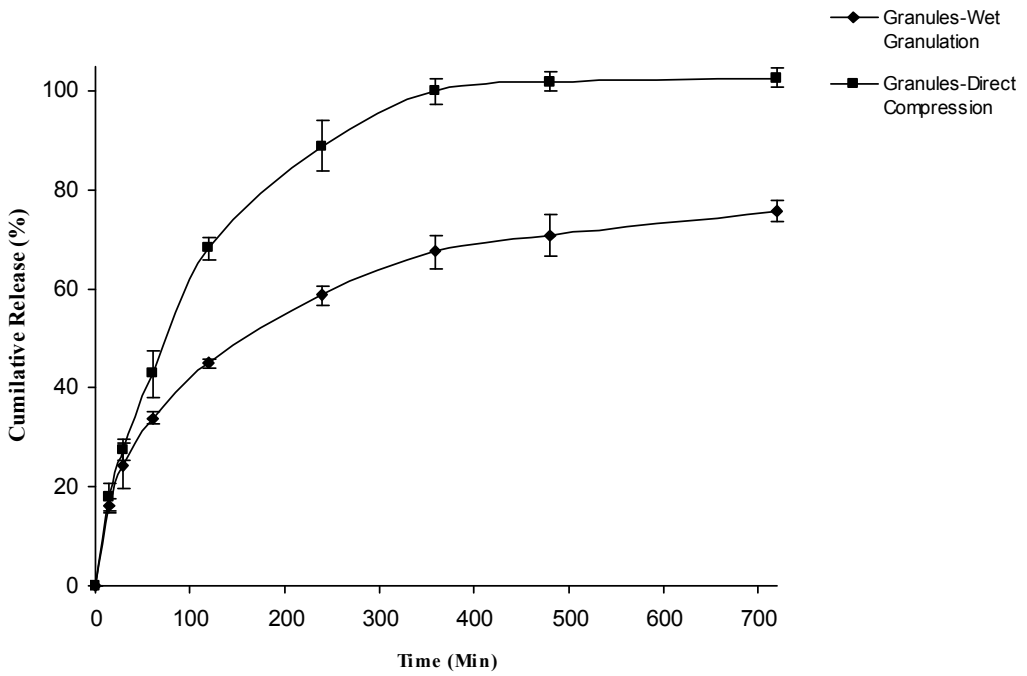
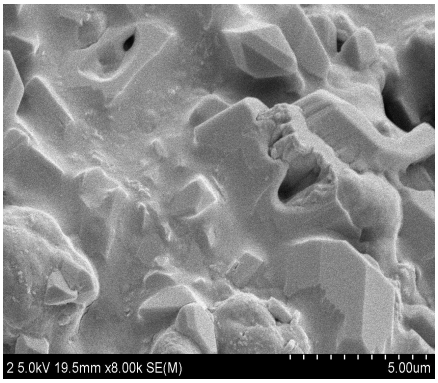
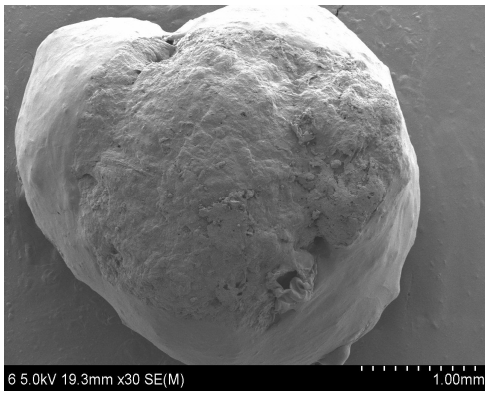


Fig.7. Release of Acetaminophen from the granules containing 40 w/w% Acetaminophen with different preparation method.

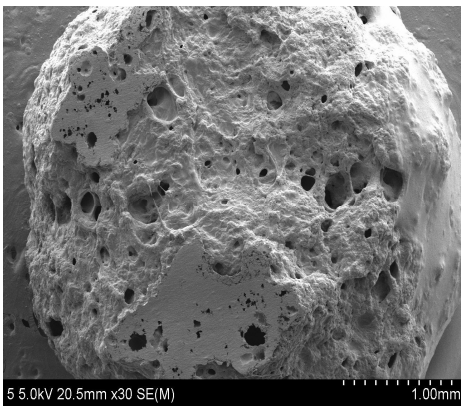
(a)



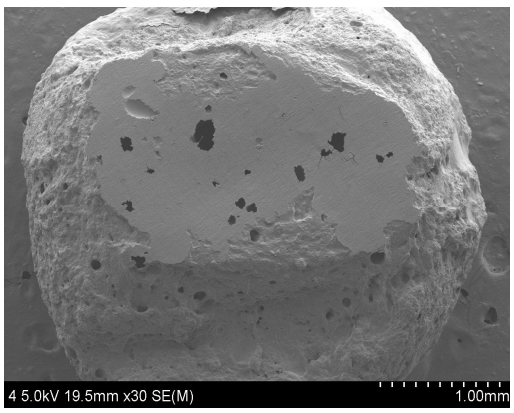
(b)



(c)



(d)



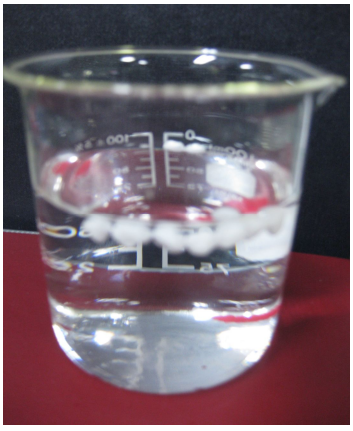
(e)

Fig.8. SEM Pictures of (a). Direct compression granules. (b). Wet granulated granules. (c). Granules containing 5 % Sodium bicarbonate. (d) & (e). Granules containing 5% and 0 % NaHCO3 stirred for 2 h in pH 1.2 buffer.

0 h

4 h

8 h



12 h

Fig.9. Floating behavior of the granules at various time interval

저작물 이용 허락서

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논문제목	한글: **새로운 부유하는 점막점착성 약물전달체의 개발**				
	영문: **Development of novel floating mucoadhesive drug delivery system**				

본인이 저작한 위의 저작물에 대하여 다음과 같은 조건아래 조선대학교가 저작물을 이용할 수 있도록 허락하고 동의합니다.

- 다 음 -

1. 저작물의 DB구축 및 인터넷을 포함한 정보통신망에의 공개를 위한 저작물의 복제, 기억장치에의 저장, 전송 등을 허락함.
2. 위의 목적을 위하여 필요한 범위 내에서의 편집과 형식상의 변경을 허락함. 다만, 저작물의 내용변경은 금지함.
3. 배포·전송된 저작물의 영리적 목적을 위한 복제, 저장, 전송 등은 금지함.
4. 저작물에 대한 이용기간은 5년으로 하고, 기간종료 3개월 이내에 별도의 의사표시가 없을 경우에는 저작물의 이용기간을 계속 연장함.
5. 해당 저작물의 저작권을 타인에게 양도하거나 출판을 허락을 하였을 경우에는 1개월 이내에 대학에 이를 통보함.
6. 조선대학교는 저작물 이용의 허락 이후 해당 저작물로 인하여 발생하는 타인에 의한 권리 침해에 대하여 일체의 법적 책임을 지지 않음.
7. 소속대학의 협정기관에 저작물의 제공 및 인터넷 등 정보통신망을 이용한 저작물의 전송·출력을 허락함.

동의여부 : 동의(O) 반대( )

2011년 2 월 25 일

저작자: 부살 프랍하트 (서명 또는 인)

조선대학교 총장 귀하

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Prabhat Bhusal
October 2010
Gwangju, South Korea.