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ORIGINAL ARTICLE

Flow, compressive, and bioadhesive properties of various blends of poly(ethylene oxide)

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Abstract

Background: Poly (ethylene oxide) (PEO) is nonionic, water soluble, and highly hydrophilic polymer with well-established applications in mucoadhesives, water-soluble films, rheology control agents and thickeners, and additives in pharmaceutical products. *Methods*: Different powder blends containing PEO in varying proportions were evaluated for their flow, compressive, and bioadhesive properties and subsequently compressed into gastroretentive tablets. Two optimized formulations, on the basis of above-mentioned examinations, were subjected to gamma scintigraphy studies on human volunteers. *Results*: The values of bulk and tapped densities, Hausner ratio and Carr index, angle of repose, loss on drying, total moisture content, and particle size distribution provided a fine estimation of flowability and compressibility of the powder blends. Further, apart from the routine pharmacopoeial assessments, the evaluation of compressed tablets for their surface pH in both acidic and basic environments nullified the possibility of any irritation to the membrane where it is intended to adhere. The measurement of swelling index and bioadhesive strength of tablets revealed that both the parameters were a direct function of the concentration of PEO in the tablet. The results of gamma scintigraphy indicated a fourfold increase in the gastric retention time of the optimized formulation vis-à-vis control formulation. *Conclusion*: The results indicate that PEO, in a concentration of 10–50% (w/w), can be successfully employed in manufacturing gastroretentive tablets.

Key words: *Bioadhesion; compression; flow properties; gamma scintigraphy; gastroretention; poly(ethylene oxide)*

Introduction

Several pharmaceutical processes including blending, transfer, storage, feeding, compaction and fluidization involve powder handling. The term powder applies to bulk solids, namely, granulations and granules either as single substance or as multicomponent blends. The flow of powder during manufacturing dictates the quality of the product in terms of its weight and content uniformity. Flow also affects manufacturing efficiency. During formulation development, the flow of a blend may affect excipient solution and may dictate whether direct compression is used or some form of granulation is required. A simple definition of powder flowability is the ability of a powder to flow[1,2]. Flowability can never be expressed as a single value or index. In fact, flowability is not an inherent material property. Flowability is the result of the combination of physical properties that affect material flow and the equipment used for handling, stirring, or processing of the material. Therefore, a more accurate definition of powder flowability is the ability of powder to flow in a desired manner in specific equipment.

This work focuses on the investigation of various powder flow and compressive properties of poly(ethylene oxide) (PEO) to ascertain its suitability for being compressed as gastroretentive tablets. PEO resins are made commercially by the catalytic polymerization of ethylene oxide in the presence of metallic catalyst systems[3]. Literature abounds in reports about the use of various grades of PEO and their blends as potential mucoadhesive drug delivery systems[4–7]. Apicella et al.[8] investigated water-soluble PEOs and their blends as potential mucoadhesive drug delivery systems. The authors reported that the mechanisms and rates of drug

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release were significantly affected by the polymer molecular weight characteristics, polymer swelling and dissolution rate, and drug diffusivity in the polymer gel surrounding the tablet. Park et al.[9] prepared thermosensitive mucoadhesive delivery systems composed of poloxamers and varying amounts of PEO and reported that mucoadhesiveness of the systems increased with the percent of PEO. Varma et al.[10] studied mucoadhesion, swelling, and drug release behavior of PEO and carbopol matrices using diltiazem hydrochloride. The authors concluded that PEO was more instrumental in providing mucoadhesive characteristics to the matrix than carbopol.

Prolonging the gastric retention of a delivery system by formulating it as a mucoadhesive system is desirable for achieving greater therapeutic benefit of the drug substance under certain circumstances[11]. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract (GIT)[12], and drugs that are less soluble in or are degraded by the alkaline pH may benefit from prolonged gastric retention[13,14]. Gastric retention provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example, treatment of peptic ulcer disease. Furthermore, improved bioavailability is expected for drugs that are absorbed readily upon release in the gastrointestinal tract. These drugs can be delivered ideally by slow release from the stomach[15]. Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption because of dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine[16].

Because PEO is a bioadhesive polymer, it was decided in this study to determine the effect of polymer concentration on the gastric transit time by scintigraphy studies in human volunteers. Further, the effect of polymer concentration on various flow, compressive, and bioadhesive characteristics is also examined.

Materials

PEO (Sentry™ Polyox™ WSR 301) was obtained from Union Carbide Corporation (Danburg, CT, USA). Spray-dried lactose (Flowlac®) was procured form BG Excipients and Technology (Wasserburg, Germany), while Aerosil® was provided ex gratis by Panacea Biotec Ltd. (Punjab, India). Microcrystalline cellulose (MCC) and magnesium stearate were procured from Hi Media Laboratories (Mumbai, India). The sulphocolloid and technetium (^{99m}Tc) for gamma scintigraphy were provided by Bureau of Radio Isotope Technology (Mumbai, India).

Methods

Preparation of powder blends

Nine powder blends were prepared by varying the concentration of PEO and Flowlac®. The concentrations of other ingredients, namely, magnesium stearate, MCC, and aerosil, were kept as constant. The ingredients were mixed well in geometric proportion for 5 minutes on a laboratory scale. The composition of the nine batches is described in Table 1.

Poured bulk density

Apparent or poured bulk density (ρ_o) was determined by pouring presieved (40 mesh) powder blend into a graduated cylinder via a large funnel and measuring the volume and weight[17]. Poured bulk density of the powder blend was calculated as described in Equation (1):

$$\text{Poured bulk density}\,(\rho_0) = \frac{\text{poured bulk volume}}{\text{weight of the powder blend}}. \quad (1)$$

Tapped bulk density

Tapped bulk density (ρ_t) was determined by pouring accurately weighed amount of the presieved (40 mesh)

Table 1. Composition of powder blends.

Code	Magnesium stearate (1%) (mg)	MCC (20%) (mg)	Aerosil (1%) (mg)	PEO (mg)	Lactose (mg)	Total weight of the tablet (mg)
P1	3	60	3	30 (10%)	204	300
P2	3	60	3	45 (15%)	189	300
P3	3	60	3	60 (20%)	174	300
P4	3	60	3	75 (25%)	159	300
P5	3	60	3	90 (30%)	144	300
P6	3	60	3	105 (35%)	129	300
P7	3	60	3	120 (40%)	114	300
P8	3	60	3	135 (45%)	99	300
P9	3	60	3	150 (50%)	84	300

powder blend into a graduated cylinder via a funnel and tapping the cylinder against a hard surface (500 times) till there was no change in the volume of the powder blend. Exact volume of the powder blend after tapping was recorded, and tapped bulk density was calculated as described in Equation (2)[18]:

$$\text{Tapped bulk density}(\rho_t) = \frac{\text{tapped bulk volume}}{\text{weight of the powder blend}}. \quad (2)$$

Hausner ratio and Carr index

Ratio of ρ_t to ρ_0 was expressed as Hausner ratio to give an index of flowability as expressed in Equation (3):

$$\text{Hausner ratio} = \frac{\rho_t}{\rho_0}. \quad (3)$$

Another explicitly used index of flowability, Carr Index, was also calculated as per Equation (4)[19,20]:

$$\text{Carr index} = \frac{\rho_t - \rho_0}{\rho_t} \times 100. \quad (4)$$

Angle of repose

To determine the angle of repose, the powder blend was poured from a funnel onto a horizontal surface to form a cone[21]. The height (h) and diameter (d) of the cone were measured accurately in triplicate. The angle of repose (α) was determined as described in Equation (5):

$$\alpha = \tan^{-1}\left(\frac{2h}{d}\right). \quad (5)$$

Loss on drying

The loss on drying (LOD) was determined on an IR moisture analyzer using approximately 1 g of the powder blend. The blend was placed on the aluminum plate of the balance of analyzer. The initial weight of the powder was recorded, and the sample was allowed to heat on the IR moisture balance at 105°C for 10 minutes. Final weight of the blend was recorded and percent LOD was calculated as described in Equation (6)[22]:

$$\%\text{LOD} = \frac{\text{weight of water in sample}}{\text{weight of dry sample}} \times 100. \quad (6)$$

Karl Fischer titration

Accurately weighed amount of the powder blend (1 g) was put into the reservoir of the instrument containing methanol. Care was taken not to lose any part of the sample on the side wall of beaker or on the electrode. Immediately after adding the sample, the stirrer was started. It took 15–20 minutes for the moisture in the sample to get extracted into methanol. After whole of the water in the sample was neutralized, the display showed the reading in milliliters of the Karl Fischer reagent required to neutralize the water in the sample. The reading obtained from the instrument was converted into percent using Equation (7):

$$\text{Moisture content}(\%) = \frac{\text{reading} \times A}{\text{weight of sample in mg}} \times 100, \quad (7)$$

where A is the factor that is determined before the analysis by using known amount of water instead of the sample.

Particle size analysis

The particle size distribution of powder blends was determined using Malvern Mastersizer 2000 particle size analyzer. Approximately 500 mg of the powder blend was dispersed into 10 mL of distilled water and sonicated for 2 minutes. Immediately after sonication, the sample was charged into the particle size analyzer and the instrument was allowed to stabilize for 2–3 minutes. The plots as obtained from the instrument were used to compare the particle size distribution of the powder blends.

Compression of powder blends

Direct compression method of tableting was used to compress the powder blends. The punches and die cavity were thoroughly polished and sterilized with methylated spirit. The powder blend was placed in die cavity between two round flat-faced punches, of 10 mm diameter, fitted in a single punch mechanical punching machine (DT F—4587, Dhiman Trading Corp., Nakodar, Punjab, India). The powder was compressed and hardness of the tablet was measured with hardness tester. The length of the upper punch was adjusted to get a hardness of 3–5 kg and final compression was carried out.

Physical evaluation of tablets

Hardness of tablets

The hardness of tablets was measured using Monsanto hardness tester. The tablet was placed in the cavity in

hardness tester and force was applied with the help of plunger of tester. The diametrically applied force required to break apart the tablet was recorded as a measure of hardness of tablet.

Friability of tablets

Six tablets were accurately weighed and placed in the plastic chamber of friabilator. The friabilator was allowed to revolve at 25 rpm, dropping the tablets a distance of 6 in. with each revolution. The apparatus was operated for 100 revolutions. The tablets were then dusted and reweighed. Percentage friability was calculated as per Equation (8):

$$\text{Percentage friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100. \quad (8)$$

Weight variation of tablets

Twenty tablets were weighed individually and their average weight was calculated. The percentage deviation was calculated and the results were evaluated in the light of the tolerance limits that USP allows for weight variation of uncoated tablets[17].

Surface pH determination

The tablets were placed in a flat bottom glass tube and 2 mL of 0.1 N HCl or phosphate buffer (pH 6.8) was added to each tube. The samples were allowed to equilibrate at 37 ± 0.5°C for 2 hours. After the stipulated time, a combined glass electrode was gently brought in contact with the soft swollen surface of the tablets and the pH was determined after 1 minute of equilibration. A set of three determinations were made for each compressed powder blend.

Swelling index

A modification of the method reported by Talukdar and Kinget[23] was adopted for the determination of swelling index (SI). Radial swelling of the tablets was monitored by immersing the tablet in a beaker containing 0.1 N HCl or phosphate buffer of pH 6.8 (250 mL, 37 ± 0.5°C). At predetermined time intervals, an increase in tablet diameter was determined over a period of 6 hours, the same being measured in two different axes perpendicular to each other and their mean values were taken. SI, expressed as a percent, was calculated as per Equation (9):

$$\text{SI at time } t\,(\%) = \frac{\text{diameter of tablet at time } t - \text{initial diameter}}{\text{initial diameter}} \times 100. \quad (9)$$

Bioadhesive strength

Bioadhesion measurement was based on the principle of recording force required to break the adhesive bond between a model membrane and the test formulation. Bioadhesive strength of the tablet was measured using a calibrated texture analyzer equipped with a 5-kg load cell. The tablet was attached to the probe and a cellophane sheet was attached to the lower plate of instrument. About 100 μL of 2% mucin solution in 0.1 N HCl was poured over the membrane. The membranes were kept in contact with the tablet sample for a period of 3 minutes, under a constant force of 10 g, to establish a proper contact between the membrane and the sample and to allow the formation of an adhesive bond. Force required to separate the two membranes was measured by the upper support of texture analyzer moving at a rate of 0.1 mm/s. Maximum force required to break the bond was measured as bioadhesive strength. For all the tablets, bioadhesive strength was determined in triplicate and the mean value calculated.

Gamma scintigraphy studies in human volunteers

Ethical considerations and subject selection

The ethical clearance for the conduction of in vivo studies in human volunteers was sought vide letter no. 2673 dated 10.07.07 from the Ethics committee of Post Graduate Institute of Medical Education and Research (Chandigarh, India). Six healthy male volunteers were recruited. All subjects were screened by the model questionnaire. Exclusion criteria included excessive tobacco and alcohol consumption, history of gastrointestinal disorders, and consumption of medication considered to influence the study outcome. All subjects were given written and verbal information, and informed consent was obtained prior to the study.

Preparation of test material

Compressed tablets of powder blends P5 (treatment 1) and P8 (treatment 2) were selected for the study along with a control formulation. For control formulation, powder blend containing aerosil, MCC, magnesium stearate, and spray-dried lactose in the same proportion as blends P5 and P8 were prepared. The single punch machine and the punch and die assembly were sterilized with methylated spirit and compression room was sealed 1 day prior to the test.

Radiolabeling of the test formulation

The radioisotope was provided by Bureau of Radio Isotope Technology located at Bhabha Atomic Research Center (Mumbai, India). ^{99m}Tc (chelated with sulfur colloid, 50 μL, equivalent to 8 millicurie of radioactivity) was compressed in between the powder blend on the test day.

The radioactivity of final formulation was confirmed by placing the formulation under gamma camera for 30 seconds. The radiolabeled formulation was then dried thoroughly, while stirring in a direct flow of warm air using a dryer, and consequently sealed in a water-proof envelope.

Stability testing of the test material

The stability of the radiolabel bound to the test materials was investigated before the study day over a 6-hour period in acid conditions to simulate the exposure to gastric juice during the in vivo study. The samples were incubated at 37°C and constantly agitated for 6 hours. Samples were taken at 2-hour intervals and filtered to remove any polymer residue. The activity in each sample was recorded using the gamma camera.

Design of the study

Crossover studies took place 7 days apart to allow for radioactive decay and biological clearance of each formulation. In a three-period, three-treatment study (treatment 1, treatment 2, and control), six volunteers were divided into three groups. Each volunteer received the formulation as mentioned in Table 2.

Procedure of the study

Subjects were fasted from the evening prior to the study. A single glass of water was allowed in the morning to prevent dehydration. The subjects were given one tablet of radiolabeled material, with one glass of water. Immediately, static images were taken and the images were repeated after every 0.5 or 1 hour depending upon the formulation. On the morning of each study day, anatomical markers were prepared, and they were used to locate the exact position of the tablet in gastrointestinal tract (GIT). They were used as points of reference to aid in data analysis. The images were acquired using an E-Cam gamma camera located in Department of Nuclear Medicine, Post Graduate Institute of Medical Education and Research, with a 48-cm diameter hexagonal field of view and a high-resolution general purpose collimater. Subjects were fed a standard test meal 4 hours after the initiation of the study.

Table 2. Design of gamma scintigraphy study.

Group	Volunteer	Day 1	Day 2	Day 3
1	1	Treatment 1	Treatment 2	Control
	2	Treatment 1	Treatment 2	Control
2	3	Treatment 2	Control	Treatment 1
	4	Treatment 2	Control	Treatment 1
3	5	Control	Treatment 1	Treatment 2
	6	Control	Treatment 1	Treatment 2

Data analysis

The images of each individual subject were analyzed by determining the location of the tablet at different time intervals and to assess the effect of polymer concentration on the location of the tablet in GIT. The time for the commencement and completion of disintegration was also determined.

Results and discussion

Poured and tapped bulk densities

The poured bulk density (sometimes called loose bulk density) of a bulk material is the weight per unit volume that has been measured when the sample is in a loose, noncompacted, or poured condition. A high bulk density is indicative of dense packing of powder with minimum air voids, whereas a low value of bulk density indicates large interparticle voids.

Another flowability characteristic is tapped bulk density, or simply tapped (tap) density, that is, the maximum packing density of a powder (or blend of powders) achieved under the influence of well-defined, externally applied forces. These are just two of the many parameters that are important in the overall tableting process.

The mean values of poured and tapped bulk densities, along with the respective SDs, are enlisted in Table 3. As the values of tapped density are significantly higher than the values of poured bulk density ($P < 0.01$), it can be concluded that the powders are easily compressible upon application of external pressure.

Table 3. Physical properties of powder blends.

Powder blends	Poured bulk density (g/L) ± SD	Tapped bulk density (g/L) ± SD	Hausner ratio	Carr index	Angle of repose (°)	LOD (%)	Total moisture content (%)
P1	461 ± 9.53	571 ± 5.56	1.23	19.2	24.65	2.96	5.33
P2	480 ± 15.14	571 ± 8.71	1.19	15.9	23.79	2.37	6.09
P3	500 ± 21.00	631 ± 4.58	1.26	20.7	25.96	1.19	5.29
P4	500 ± 19.69	631 ± 10.58	1.26	20.7	22.14	1.58	5.68
P5	500 ± 10.00	631 ± 11.53	1.26	20.7	22.64	1.42	5.47
P6	521 ± 4.35	666.6 ± 5.12	1.27	21.7	17.69	1.42	5.81
P7	500 ± 15.62	600 ± 17.32	1.2	16.66	26.24	1.55	4.42
P8	480 ± 8.18	571 ± 10.53	1.19	15.9	23.02	1.46	4.12
P9	469 ± 8.54	586 ± 3.61	1.25	19.9	28.15	3.1	4.90

Hausner ratio and carr index

Hausner ratio and Carr index are based on the ratio of ρ_t and ρ_o, and they provide a measure of compressive and flow properties of the powder blend. Table 3 provides an insight on the calculated values of Hausner ratio and Carr index for the powder blends. The value of Hausner ratio varies from 1.2 for a free flowing powder to 1.6 for cohesive powders. On the same heels, a powder can be termed as having good flowability if its Carr index varies between 12 and 16.

Angle of repose

The frictional forces in loose powder can be measured by the angle of repose. This is the maximum possible angle between the surface of a pile of powder and the horizontal plane. The angle of repose measurements are particularly sensitive to changes in particle size distribution and to moisture content, and they provide a rapid means of monitoring significant batch-to-batch differences in these respects[24]. As the angles of repose, enlisted in Table 4, of all powder blends (except one blend) were between 20° and 30°, it can be concluded that all powder blends possessed good flow properties.

Loss on drying

The moisture in a solid can be expressed on a wet-weight or dry-weight basis. On a wet-weight basis, the water content of a material is calculated as a percentage of the weight of the wet solid, whereas on the dry-weight basis, the water is expressed as a percentage of the weight of the dry solid. In pharmaceutical sciences, the term *loss on drying* is an expression of moisture content on a wet-weight basis[24]. Table 3 comprehends the LOD of the powder blends calculated on wet-weight basis. As shown in Table 5, powder blends P3, P4, P5, P6, P7, and P8 possess LOD values in the range 1–2, which makes them ideal for direct compression.

Karl Fischer titration

The Karl Fischer titration is a widely used titrimetric method for water determination in various substances. Table 3 enlists the total water content of powder blends. This titration provides the total water content (both bound and unbound) of a powder. The determination of water is important to check the product quality[25] and to assure even chemical and physical properties of the product[26]. In the pharmaceutical industry, a stable water content is important for intermediate powders that are formed to tablets. When the powder is too dry, the tablets crumble, and when it is too wet, the tablets will stick to the blister foil.

Particle size analysis

The flow of a powder system is largely affected by particle size and size distribution[27,28], particle shape and shape distribution, surface chemistry, density, and the

Table 4. Relative positions of tablets at various time intervals.

Treatment	Volunteer	Position of the formulation	Time (hours)
Control	GS 1	Distal part of small intestine	1
	GS 2	Distal part of small intestine	1
	GS 3	Distal part of small intestine	1
	GS 4	Distal part of small intestine	1
	GS 5	Distal part of small intestine	1
	GS 6	Distal part of small intestine	1
Treatment 1	GS 1	Distal part of small intestine	5
	GS 2	Distal part of small intestine	5
	GS 3	Distal part of small intestine	5
	GS 4	Distal part of small intestine	5
	GS 5	Distal part of small intestine	5
	GS 6	Distal part of small intestine	5
Treatment 2	GS 1	Between stomach and duodenum	5
	GS 2	Duodenum	5
	GS 3	Duodenum	5
	GS 4	Distal part of duodenum	5
	GS 5	Distal part of small intestine	5
	GS 6	Duodenum	5

Table 5. Time for commencement and completion of disintegration of tablets during gamma scintigraphy studies.

Treatment	Volunteer	Time of commencement of disintegration (hours)	Time of completion of disintegration (hours)
Control	GS 1	0.5	1
	GS 2	0.5	1
	GS 3	0.5	1
	GS 4	0.5	1
	GS 5	0.5	1
	GS 6	0.5	1
Treatment 1	GS 1	3	5
	GS 2	2.5	5
	GS 3	2	5
	GS 4	2	5
	GS 5	1.5	5
	GS 6	3	5
Treatment 2	GS 1	4	5
	GS 2	3.45	5
	GS 3	3.45	5
	GS 4	4	5
	GS 5	3.45	5
	GS 6	3.45	5

surrounding medium. As the size of a particle decreases, the ratio of its surface area to volume increases. The particle size of all the powder blends varied between 30 and 40 μm. All the powder blends possessed unilobed particle size distribution, which is indicative of the uniformity of particle size in the powder blends. This uniformity of particle size is required in tableting[29] as this will result in a better filling of the die cavity and hence better compression. This reduces various problem of tablet stability, namely, capping and lamination.

Physical evaluation of tablets

Representative tablets tested from each batch possessed hardness values between 3 and 5 kg, which is indicative of adequate hardness required to prevent friability losses[30] and at the same time provide good tablet disintegration and dissolution profiles. All the tablets tested from each batch possessed friability values between 0.5% and 1% that are generally considered acceptable as per official compendia. The variations on the weights of all tablets tested were not more than 7.5%, indicating that all batches had passed the weight variation test[17].

Surface pH

It is the pH of the surface of the tablet, rather than the pH of the medium, upon which depends the extent of ionization of the polymer, which in turn will determine whether a complex between polymer and excipients will be formed. This complex could be formed in situ in the tablet because of acidity of polymer, independent of the pH of the dissolution medium, at least during the initial stages. The mean surface pH of tablets in 0.1 N HCl and phosphate buffer (pH 6.8) varied between 1.60–1.75 and 6.85–6.95, respectively.

The pH of the surface of mucoadhesive tablet was determined to rule out the possibility of any irritation to the membrane where it is intended to adhere. The tablets were tested in 0.1 N HCl (pH inside the stomach) and phosphate buffer of pH 6.8 (pH inside the intestine). Apart from mucosal irritation, the stability of drug substances inside the polymer matrix is also affected by the surface pH of the tablet. However, no tablet showed any sign of sudden change in pH on being exposed to both pH conditions, indicating the polymer matrix as an effective mucoadhesive drug delivery system[31].

Swelling studies

The SI of tablets compressed from the powder blends was measured in radial direction in 0.1 N HCl and in phosphate buffer (pH 6.8). SI of a tablet is directly related to its bioadhesive property. The more the water uptake, the more is the bioadhesion[32,33]. The results of swelling studies are represented graphically in Figures 1 and 2. The relatively earlier dissolution of tablets P1, P2, P3, and P4 may be attributed to the lower PEO and higher lactose content of these tablets. As the concentration of PEO increases, the water carrying capacity of the matrix also increases. Thus, it can be concluded that more is the concentration of PEO, the more is the water uptake, hence more is the mucoadhesion.

Bioadhesive strength

Bioadhesive formulations are required to exhibit adhesion to mucosal surfaces[34,35] as this will decrease their clearance time and hence improve clinical efficacy[36]. The method to measure bioadhesion was based on the principle of measuring the force required to break the adhesive bond between cellophane membrane and the test formulation using texture analyzer. Figure 3 presents a graphical comparison of bioadhesive

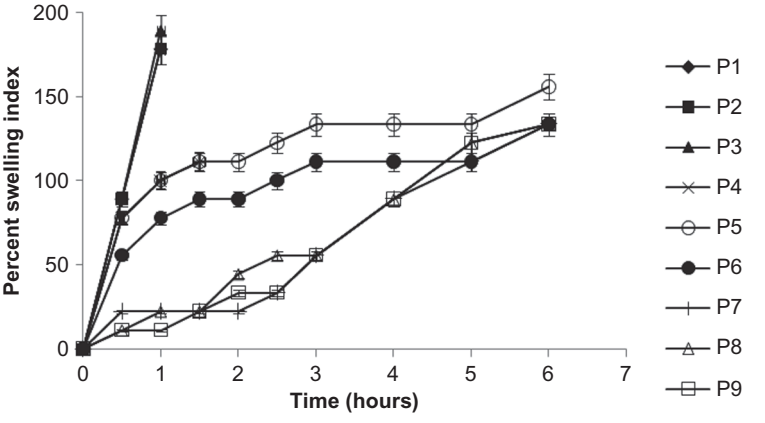

Figure 1. Graph between percent swelling index and time for 0.1 N HCl.

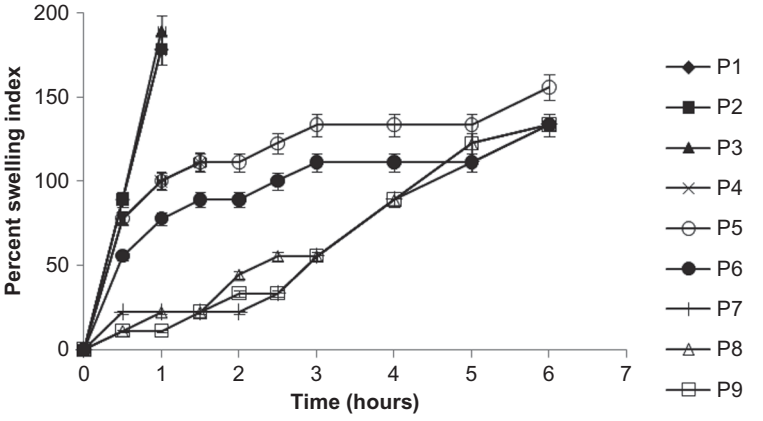

Figure 2. Graph between percent swelling index and time for phosphate buffer (pH 6.8).

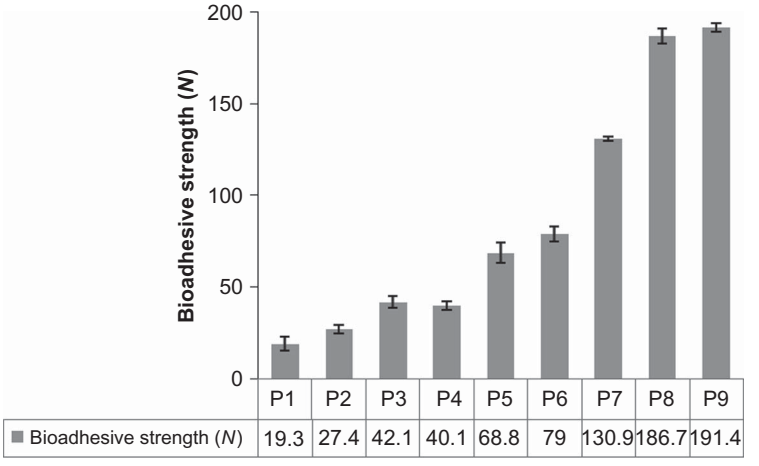

Figure 3. Comparison of bioadhesive strength of tablets.

strengths of different formulations. It can be deciphered from Figure 3 that bioadhesive strength is a direct function of the amount of PEO present in the formulation, further strengthening the fact that PEO can be regarded as a polymer of choice for formulating bioadhesive tablets.

Gamma scintigraphy studies in human volunteers

The selection of formulations to be subjected to gamma scintigraphy studies was based on the following observations:

- The Carr index values were found to be the best for formulations P2, P7, and P8.
- The Hausner ratio and angle of repose values of these powder blends also indicated their free flowing nature.
- The SI values indicated that the formulation containing highest concentration of PEO (formulation P8) will possess maximum water uptake capacity resulting in maximum mucoadhesion.
- This observation was further strengthened by the results of in vitro bioadhesion studies in which formulation P8 showed maximum bioadhesion.
- Thus, formulation P8 was selected along with formulation P5 (containing 30% PEO) to observe the effect of concentration of PEO on in vivo mucoadhesion in human volunteers.

The tablets were visualized for their gastric retention in terms of the time taken by each tablet to get completely dispersed in the GIT and their position in the GIT. The location of the formulation in human digestive tract at different times after their administration is given in Table 4. A representative image of gamma scintigraphy was obtained in volunteer 3 in control, treatment 1, and treatment 2 and is shown in Figures 4–6.

The scintigraphs showed that all the formulations were intact in the physiological environment of stomach and small intestine in all the three groups indicating that PEO is capable of protecting the core from being released. The tablets in control group disintegrated in 1 hour, releasing the tracer throughout the

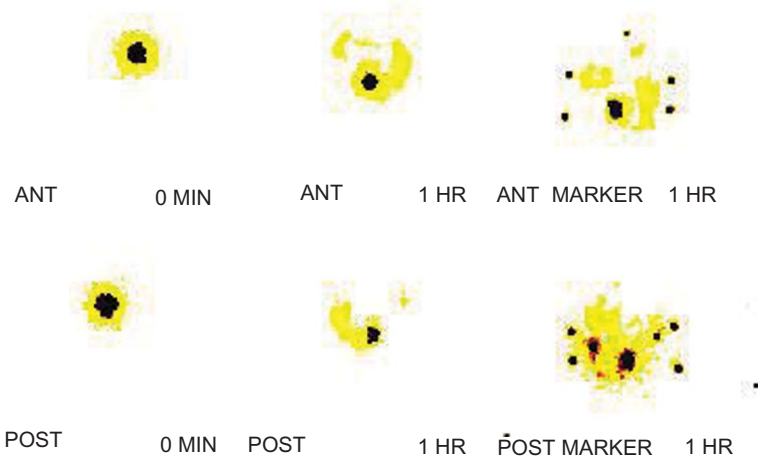

Figure 4. In vivo gamma scintigraphy image of volunteer 3 in control group.

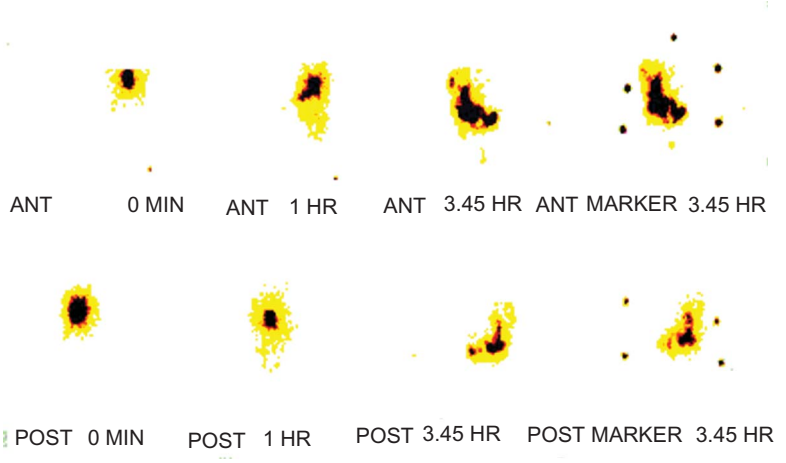

Figure 5. In vivo gamma scintigraphy image of volunteer 3 in treatment 1.

GIT. However, the tablets in treatment 2 group had not started to disintegrate even after 5 hours in the GIT (Figure 6). The tablets in treatment 1 group also remained intact after 5 hours of administration, but they reached the distal part of small intestine by this time. On the contrary, tablets in treatment 2 group stayed in stomach or duodenum in all volunteers (except one volunteer). The results show that as the concentration of polymer increases in the formulation, the time taken by formulation to pass through the GIT also increases, that is, gastric retention is a direct function of the polymer concentration.

The commencement and completion of disintegration of tablets in the volunteers in the each group is shown in the Table 5. It is evident from the Table 5 that an increase in the polymer concentration was able to increase the time of commencement of disintegration as well as the time of completion of disintegration. So, it can be concluded that the PEO matrix tablets can be used to prolong the release into the surrounding medium as well as provide bioadhesive characteristics to the tablets.

Conclusions

Flowability can never be expressed as a single value or index. During formulation development, the flow of a blend may affect excipient selection and may dictate whether direct compression is used or some form of granulation is required. The significantly higher values of tapped density than poured bulk density ($P < 0.01$) indicate that the powders are easily compressible upon application of external pressure. The values

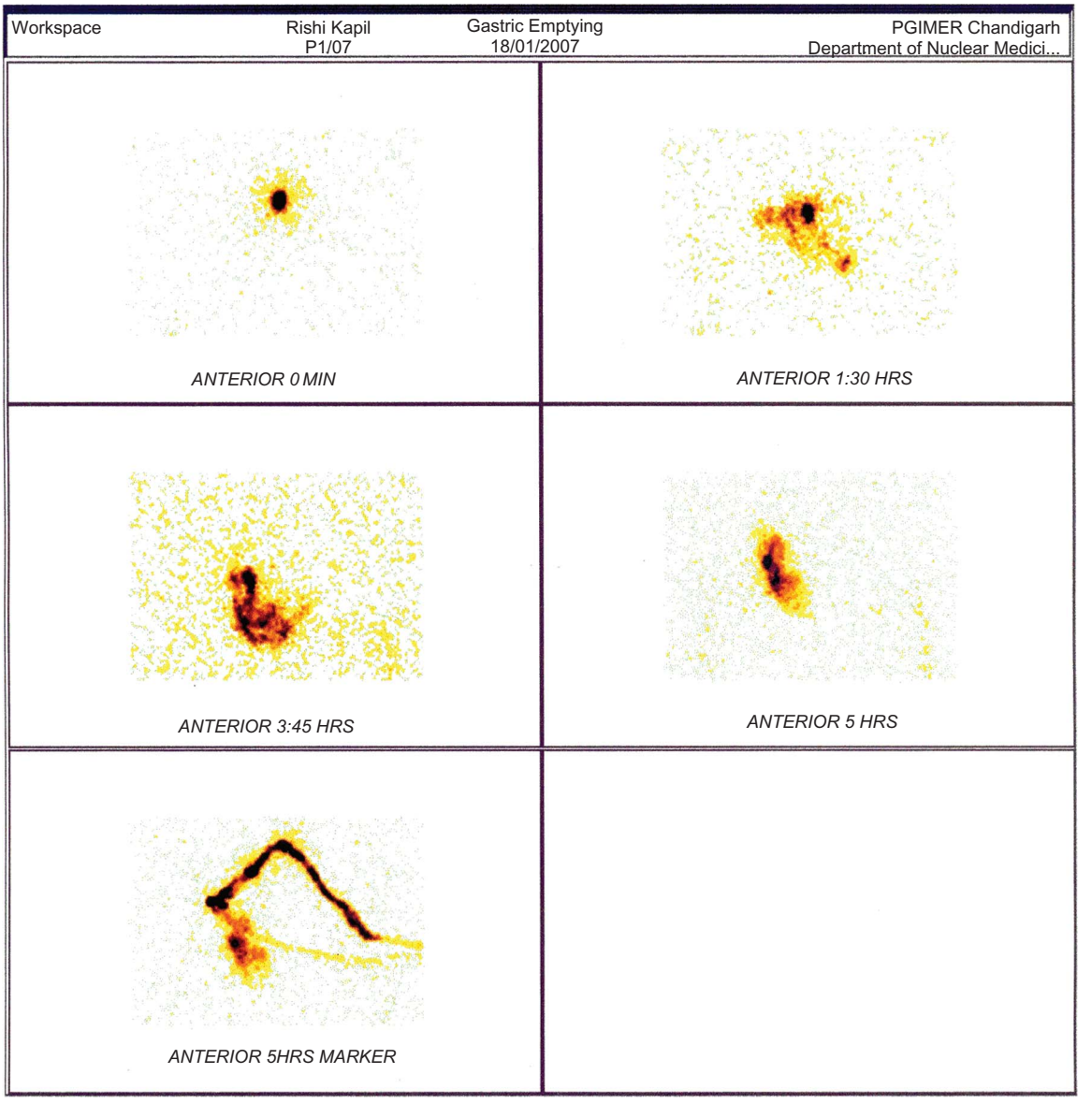

Figure 6. In vivo gamma scintigraphy image of volunteer 3 in treatment 2.

of Carr index and Hausner ratio for the powder blends P2, P7, and P8 signified good flowability of these blends. Also, the favorable values of angle of repose and uniformity in particle size distribution of these blends ratified the absence of massive frictional forces that could hamper the flow of powder from hopper to die cavity. The low values LOD and total moisture content make these powder blends directly compressible into a physically stable product. The absence of sudden change in surface pH of tablets on being exposed to both pH conditions (0.1 N HCl and phosphate buffer, pH 6.8) indicated that the polymer matrix is an effective mucoadhesive drug delivery system. The bioadhesive strength of tablets increased with an increase in the concentration of PEO. Gamma scintigraphy studies showed that all the formulations were intact in the physiological environment of stomach and small intestine in all the three groups, indicating that PEO is capable of protecting the core from being released. Further, the results indicated that as the concentration of polymer increases in the formulation, the time taken by the formulation to pass through the GIT also increases, that is, gastric retention is a direct function of the polymer concentration.

Declaration of interest

The authors report no conflicts of interest.

References

1. Carson JW, Pittenger BH. (1998). Bulk properties of powders. In: Eisen WB, ed. ASM handbook vol. 7—powder metal technologies and applications. Materials Park, OH: ASM International, 287–301.
2. Amidon GE. (1999). Physical test methods for powder flow characterization of pharmaceutical materials: A review of methods. Pharma Forum, 25:8298–305.
3. Dhawan S, Varma M, Sinha VR. (2005). High molecular weight poly(ethylene oxide) based drug delivery systems. Part I: Hydrogels and hydrophilic systems. Pharm Technol, 29:72–80.
4. Needleman IG, Martin GP, Smales FC. (1998). Characterisation of bioadhesives for periodontal and oral mucosal drug delivery. J Clin Periodontol, 25:74–82.
5. Dhawan S, Singla AK. (2004). Composition and method for maintaining blood glucose level. US patent 6,703,045.
6. Dhawan S, Dhawan K, Varma M, Sinha VR. (2005). High molecular weight poly(ethylene oxide). Part II: Applications to drug delivery systems. Pharm Technol, 29:82–96.
7. Dhawan S, Singla AK. (2008). A method of maintaining blood glucose level by employing the hydrophilic matrix based oral controlled release antidiabetic composition. Indian patent IN212066.
8. Apicella A. (1992). Poly(ethylene oxide) (PEO) and different molecular weight PEO blend monolithic devices for drug release. Congr Int Tecnol Pharm, 4:15–24.
9. Park SJ, Kim KS, Kim SH. (2005). Effect of poly(ethylene oxide) on the release behaviors of poly(epsilon-caprolactone) microcapsules containing erythromycin. Colloids Surf B Biointerfaces, 43:238–44.
10. Varma M, Singla AK, Dhawan S. (2004). Release of diltiazem hydrochloride from hydrophilic matrices of polyethylene oxide and carbopol. Drug Dev Ind Pharm, 30:545–53.
11. Talukder R, Fassihi R. (2004). Gastroretentive delivery systems: A mini review. Drug Dev Ind Pharm, 30:1019–28.
12. Rouge N, Buri P, Doelker E. (1996). Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int J Pharm, 136:117–39.
13. Matharu RS, Sanghavi NM. (1992). Novel drug delivery system for captopril. Drug Dev Ind Pharm, 18:1567–74.
14. Fell JT. (1996). Targeting of drugs and delivery systems to specific sites in the gastrointestinal tract. J Anat, 189:517–9.
15. Rocca JG, Omidian H, Shah K. (2003). Progresses in gastroretentive drug delivery systems. Drug Deliv (Oral) Business Briefing, Pharm Tech, 152–156.
16. Hwang SJ, Park H, Park K. (1998). Gastric retentive drug-delivery systems. Crit Rev Ther Drug Carrier Syst, 15:243–84.
17. USP. (2004). United States Pharmacopoeia. Rockwille, MD: The United States Pharmacopoeial Convention, Inc.
18. Kumar V, de la Luz Reus-Medina M, Yang D. (2002). Preparation, characterization, and tabletting properties of a new cellulose-based pharmaceutical aid. Int J Pharm, 235:129–40.
19. Carr RL. (1965). Evaluation of flow properties of solids. Chem Eng, 72:163–8.
20. Schroder K, Schmid K, Lobenberg R. (2007). Influence of bulk and tapped density on the determination of the thermal conductivity of powders and blends. AAPS PharmSciTech, 8:E78.
21. Shah RB, Tawakkul MA, Khan MA. (2008). Comparative evaluation of flow for pharmaceutical powders and granules. AAPS PharmSciTech, 9:250–8. Epub 2008 Feb 2015.
22. Chrzanowski F. (2008). Preformulation considerations for controlled release dosage forms. Part I. Selecting candidates. AAPS PharmSciTech, 9:635–8.
23. Talukdar MM, Kinget R. (1995). Swelling and drug release behaviour of xanthum gum matrix tablets. Int J Pharm, 120:63–72.
24. Lachman L, Lieberman HA, Kanig JL. (1991). The theory and practice of industrial pharmacy. 3rd ed. Bombay: Varghese Publishing House, Hind Rajasthan Building, Dadar.
25. Young PM, Edge S, Staniforth JN, Steele DF, Traini D, Price R. (2007). Effect of moisture on the compressibility and compactibility of sodium starch glycolate. Pharm Dev Technol, 12:217–22.
26. Bravo-Osuna I, Ferrero C, Jimenez-Castellanos MR. (2007). Influence of moisture content on the mechanical properties of methyl methacrylate-starch copolymers. Eur J Pharm Biopharm, 66:63–72.
27. Kaerger JS, Edge S, Price R. (2004). Influence of particle size and shape on flowability and compactibility of binary mixtures of paracetamol and microcrystalline cellulose. Eur J Pharm Sci, 22:173–9.
28. Picker-Freyer KM, Durig T. (2007). Physical mechanical and tablet formation properties of hydroxypropylcellulose: In pure form and in mixtures. AAPS PharmSciTech, 8:E92.
29. Uribarri E, Laguna A, Sierra R, Ricardo Y. (2002). Physicomechanical characterization of policosanol, a novel hypocholesterolemic drug. Drug Dev Ind Pharm, 28:89–93.
30. Patel VM, Prajapati BG, Patel HV, Patel KM. (2007). Mucoadhesive bilayer tablets of propranolol hydrochloride. AAPS PharmSciTech, 8:E77.
31. Patel VM, Prajapati BG, Patel MM. (2007). Formulation, evaluation, and comparison of bilayered and multilayered mucoadhesive buccal devices of propranolol hydrochloride. AAPS PharmSciTech, 8:22.
32. Nafee NA, Ismail FA, Boraie NA, Mortada LM. (2003). Mucoadhesive buccal patches of miconazole nitrate: In vitro/in vivo performance and effect of ageing. Int J Pharm, 264:1–14.
33. Nafee NA, Ismail FA, Boraie NA, Mortada LM. (2004). Mucoadhesive delivery systems. II. Formulation and in-vitro/in-vivo evaluation of buccal mucoadhesive tablets containing water-soluble drugs. Drug Dev Ind Pharm, 30:995–1004.
34. Adhikary A, Vavia PR. (2008). Bioadhesive ranitidine hydrochloride for gastroretention with controlled microenvironmental pH. Drug Dev Ind Pharm, 34:860–9.
35. Singh B, Pahuja S, Kapil R, Ahuja N. (2009). Formulation development of oral controlled release tablets of hydralazine: Optimization of drug release and bioadhesive characteristics. Acta Pharm, 59:1–13.
36. Singh B, Chakkal SK, Ahuja N. (2006). Formulation and optimization of controlled release mucoadhesive tablets of atenolol using response surface methodology. AAPS PharmSciTech, 7:E1–10.