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Original Article

MULTIPLE UNIT PELLET SYSTEM (MUPS) BASED FAST DISINTEGRATING DELAYED-RELEASE TABLETS FOR PANTOPRAZOLE DELIVERY

SANDIPKUMAR A. PATEL[1], NRUPA G. PATEL[2], ABHIJEET B. JOSHI[3*]

[1]National Institute of Pharmaceutical Education and Research (NIPER), Ahmedabad, India, [2]Product Development, Teligent Pharma Inc., New Jersey, USA, [3]Centre for Biosciences and Biomedical Engineering, Indian Institute of Technology, Indore, India
Email: abhijeet.joshi@iiti.ac.in

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ABSTRACT

Objective: The rationale for the study was to develop multiple unit pellet system (MUPS) of delayed release pantoprazole with desired physical properties and unaltered drug release profile from pellets even after compression into a fast disintegrating tablet.

Methods: In the presented study, delayed release pellets of pantoprazole were developed by two methods, i.e. extrusion-spheronization and drug layering techniques, coated using enteric polymer and subsequently compressed in to tablet. In drug layering technique, pantoprazole was loaded on Celphere®102 (microcrystalline cellulose spheres) as well as on Suglet® (sugar spheres) in fluid bed processor. Acid resistant polymer Eudragit ND 30D was subsequently coated on each type of drug loaded pellets. Suitable tableting excipients were prepared such as soft pellets, Ceolus® (fibrous grade of microcrystalline cellulose) granules, Ludipress® (compressible lactose composition), Avicel® PH 200 and different combination of them. Various factors like property of pellets to be compressed, coating level, the composition of tableting excipient and ratio of drug-loaded pellets to tableting excipients were identified and optimized.

Results: MUPS with delayed releasing pellets of pantoprazole proved to provide sufficient hardness, rapid disintegration property, and unaltered release profile after compression. Delayed release pantoprazole pellets prepared by drug layering on celphere® 102 followed by coating with Eudragit® NE 30D showed better compressibility to withstand the drug release properties. The combination of Ceolus® granules and Ludipress (in 1:1 ratio) was found to be suitable tableting excipient that helped compression of pellets without rupturing polymeric coat. Pellets to excipients ratio at 1:3 was found optimum.

Conclusion: Compaction behaviour of pantoprazole delayed-release pellets without loss of original delayed release profile was achieved by formulating as MUPS based tablet of pantoprazole delayed release pellets using celephere® 102 was developed which was found suitable for desired release profile and physical properties.

Keywords: Multiple Unit Pellet System (MUPS), Ceolus, Celphere, Delayed Release Pellets, Pellet Compression, Extrusion-Spheronization, Drug Layering

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INTRODUCTION

Gastro esophageal reflux disease (GERD) and related complications such as erosive esophagitis, esophageal stricture, and Barrett's esophagus are some of the digestive disorders that are caused by gastric acid flowing from the stomach into the esophagus [1-2]. GERD is very common in infants, though it can occur at any age. It is the most common cause of vomiting during infancy. In certain complication, the esophageal path becomes extremely narrow, i.e. erosive esophagitis, esophageal stricture and Barrett's esophagus [3].

The drug should be targeted to a specific site in GIT (absorption window) such as the stomach, intestine, colon [4-6] in order to get absorbed. Proton pump inhibitors (PPI) are acid sensitive which need to be administered to deliver in the intestine by enteric coating [7-8]. Various approaches have been proposed for stability enhancement of pantoprazole [9]. For the treatment of GERD, delayed release pantoprazole is given orally as tablets or delayed release granules are administered via nasogastric tube for patients who are not able to swallow tablets and capsules but frequent clogging of a nasogastric tube is a major issue. Uniform pellets with a spherical shape for film coating, good flowability, low friability and narrow particle size distribution is a better option [10-11]. Coated pellets can be compressed into fast disintegrating tablets [12-13] as a final dosage form. Fast disintegrating tablets are the choice of the formulation when it is to be given to geriatric patients [14-16]. Several advantages reported for pellets containing dosage forms are improved appearance of the formulation products, larger surface area and better dissolution [17]. Chemically incompatible drugs can be formulated in separate pellets as multiparticulates and combined in the single dosage form. Pellets have good flow properties and provide flexibility in the formulation development and manufacturing [12]. Drugs having different sites of release can be incorporated as multiparticulates in the same formulation [18]. Pellets decrease the chances for dose dumping of controlled release formulations. Delayed release multi-particulate formulations are reliable for intestinal drug delivery system to avoid dose dumping and lower variability in dosage in each patient. Current research aims at developing delayed release pantoprazole pellets which can be compressed into a MUPS fast disintegrating tablet formulation. Pellets prepared by extrusion-spheronization and drug layering were subjected to compression. Tableting excipients suitable for compression of pellets were identified to make MUPS formulation with desired properties and unaltered release profile.

MATERIALS AND METHODS

Materials

Pantoprazole sodium was received as a gift from Cadila Pharmaceuticals, Ahmedabad (India) and Ranbaxy Laboratories, New Delhi, India. Avicel®(microcrystalline cellulose (MCC)) and Ac-Di-Sol®(croscarmellose sodium) were procured from FMC Biopolymer (USA), Kollidone® 90 (polyvinylpyrrolidone), Kollidone VA64 CL (vinylpyrrolidone-vinyl acetate copolymers) and Ludipress®(co-processed excipient of lactose, povidone and crospovidone) were procured from BASF (Germany), Celphere® (MCC spheres) and Ceolus®(compressible grade MCC) were procured from Asahi kasei (Japan), Suglet®(sugar spheres) and

Ethocel® E5 LV (ethyl cellulose) were procured from Colorcon Asia Pvt Ltd. (Mumbai, India), lactose monohydrate (LMH) procured from Meggle (USA), Aerosil® 200 (colloidal silicon dioxide) procured from Degussa (Germany), magnesium stearate was procured from Lobachemie (India), PEG 400 from Thrien enterprise, Ahmedabad (India), low substituted hydroxypropyl cellulose (L-HPC) LH 32 from Shin-Etsu polymer (Japan). Other chemicals such as isopropyl alcohol, methanol, acetonitrile and hydrochloric acid were procured from Qualigens fine chemicals. Triethyl citrate was procured from Sigma Aldrich (India). Potassium dihydrogen phosphate procured from HiMedia laboratory (India).

Methods

Preparation of pantoprazole core pellets by extrusion and spheronization

Extrusion and spheronization method was used to prepare pellets containing 10% (w/w) of pantoprazole.

All powder ingredients described in table 1 were mixed in rapid mixing granulator (Kevin, India) for 10 min.

After mixing, water was added as granulating fluid and granulated for 5 min.

Table 1: Composition of pantoprazole core pellets prepared by extrusion and spheronization

Ingredients	Quantity (%w/w)	Function
Pantoprazole sodium	10%	Active Ingredient
Avicel® PH 101	50%	Diluent, extrusion aid
Lactose monohydrate	9%	Diluent
Magnesium oxide	20%	Stabilizer
Kollidone® K 90	3%	Binder
L-HPC LH 32	5%	Disintegrant, extrusion aid
Talc	1%	Anti-tacking agent
Ac-Di-Sol®	2%	Disintegrant

(L-HPC: Low substituted hydroxypropyl cellulose)

The wet mass was extruded from gravity fed cylinder extruder (R. R. Enterprises, India). Extrudates were spheronized for 10 min at 1000-1200 rpm in spheronizer (R. R. Enterprises, India). spheronized pellets were dried in the fluid-bed processor (FBP) for 10 min at 40^{0}C. Dried pellets were passed through sieve #16 (1190 µm) and retained on sieve #25 (700 µm).

Preparation of pantoprazole core pellets by layering on sugar seeds and MCC sphere

Pantoprazole was loaded **on sugar seeds by** wurster technique using fluid bed processor (FBP). 10% w/v of pantoprazole dispersion in methanol: water (80:20) using HPMC E5 LV (1.5%w/v by solvent used) as a binder. Polyethylene glycol 400 (10% w/w by the amount of HPMC E5 LV) was added as a plasticizer. Talc (1%w/w of total solid) was used as the anti-tacking agent. Pantoprazole was loaded to get 20% weight gain. Experimental parameters were pre-warming of core pellets at 45°C for 10 min; atomizing air pressure at 1 bar; spray nozzle diameter of 1 mm; air flow rate 60-70 m^3/h; inlet air temperature of 50-55 ^{0}C; product temperature 38-40 ^{0}C; spray rate of 2 ml/min; post drying at 55^{0}C for 15 min in FBP.

Enteric coating of pantoprazole core pellets and evaluation of coated pellets

Pantoprazole loaded core pellets were coated by 10% dispersion of Opadry AMB (Aqueous moisture barrier coat of HPMC and other excipients from Colorcon Asia Pvt. Ltd.) up to 5% weight gain as seal coat. These pellets were subsequently coated with Eudragit NE 30 D (30% dispersion of polymethacrylic acid from Evonic, India) up to 20% weight gain (Beckert *et al.*, 1998). Seal coating and enteric coating were done in the fluid-bed processor (Niro-Aeromatic, Switzerland) at 1 ml/min flow rate of coating dispersion, 1 bar atomizing pressure, 55^{0}C inlet temperature and 70-80 m^3/h air flow. Post drying was done at the same temperature for 10 min. Coated pellets were evaluated using dissolution study.

Drug-excipient compatibility study

Differential scanning calorimetry is one of most useful technique reported for drug-excipient compatibility study for various formulations, either it is solid dosage form or semi-solid dosage form filled in capsule [19-21]. For the present study, drug-excipient compatibility was evaluated by differential scanning calorimetry (DSC) [22]. The physical mixtures of Pantoprazole with lactose monohydrate, Avicel® PH 101, Kollidone® K 90 and L-HPC LH 32 in the proportion of 1:1 were prepared by triturating in a dry mortar for 2 min. The samples were heated in the sealed aluminium pan under nitrogen flow (50 ml/min) at scanning rate 10 °C/min from 10 °C to 270 °C. An empty aluminium pan was used as a reference.

Characterization of delayed release pantoprazole pellets

Enteric coated pantoprazole pellets were characterized by complete release profile using dissolution USP Type II apparatus at 50 rpm at 37±0.5^{0}C. 0.1 N HCl (750 ml) and 0.2 M Tribasic Sodium Phosphate (250 ml) were used as dissolution media. Sampling was done at the end of 1 h and 2 h for acid stage and 15 min, 30 min and 45 min for buffer stage respectively. Method B of dissolution test given in USP was used. All dissolution samples were analyzed by the UV-Visible spectroscopic method. A mean of six determinations was taken into consideration for each run of dissolution. Minimum 20 pellets were taken from the pellets retained on sieve #25 (700 µm) for testing mechanical crushing force. The diametric crushing force was measured using digital tablet hardness tester (EH-01, Electrolab, India) [23, 24]. The physical property of enteric coated pantoprazole pellets was measured in terms of size (µm), shape (pellips), bulk density (gm/l), tapped density (gm/l), Carr's compressibility index and angle of repose (θ).

Development and characterization of tableting excipients

Cushioning pellets support the compression behavior of drug loaded pellets. These dummy pellets have the deforming ability, hence they are also known as "soft" pellets [25]. Cushioning pellets were made by extrusion and spheronization. Barium sulfate, 55% w/w; glyceryl monostearate (GMS), 20% w/w, microcrystalline cellulose, 23% w/w and Kollidone® K 30, 2% w/w were used in the preparation [26]. Granules to be added with pellets before compression was made by wet granulation in rapid mixing granulator (Kevin, India). Mannitol (60% w/w) and Ceolus KG-1000 (40% w/w) were granulated using water as granulating fluid and 2% w/w Kollidone® K 90 as a binder. Excipients for the direct compression were added with the pellets to be compressed. Avicel PH 200 (granular grade MCC), Ceolus® KG-1000 (compressible MCC) and Ludipress®were used as dry blend tableting excipients in the ratio of 1:1.

Different combinations were made to enhance the flow property as well as compressibility of the excipients. Each combination was characterized to determine the desired property of tableting excipients i.e. bulk density, tapped density, carr's index and angle of repose of dry blend; hardness, friability and disintegration property of compressed tablet with the delayed release (DR) Pantoprazole tablet to assess cushioning the effect of each excipient.

Characterization of MUPS using selected excipients in different ratio

Three types of pellets i.e. pellet prepared by extrusion and spheronization, layering on sugar sphere and layering on MCC sphere, were compressed with a screened excipient in different ratio. The ratio of drug loaded pellets to tableting excipient was taken in 1:1, 1:2 and 1:3 ratios. Compressed tablets were characterized by dissolution test, mechanical crushing strength, friability test, disintegration test, average weight, weight variation test and content uniformity test.

Development and characterization of MUPS tablet from pantoprazole (DR) pellets

Prepared pantoprazole (DR) pellets were compressed into tablet dosage form using previously developed tableting excipients. For the optimization, different approaches were used. Compression of pantoprazole (DR) was done initially using 40% of each kind of pellets, i.e. prepared by extrusion and spheronization, layering on sugar sphere and layering on MCC sphere, with Ceolus granules and compressed to assess the comparative compressibility of pellets.

Pellets prepared by different methods were taken about 40% with Ceolus granules: Ludipress (1:1) and compressed into a tablet. The dissolution behavior shows the compressibility of each type of pellet. Influence of tableting material was checked by taking 40% delayed release pantoprazole pellets with different tableting excipients, and the drug release profile was checked.

Dissolution study of pantoprazole delayed-release MUPS

Prepared MUPS was characterized by dissolution behavior, measuring friability, disintegration time, hardness, weight variation and content uniformity test. Dissolution was carried out in 750 ml 0.1 N HCl for 2 h and subsequently adding 250 ml of 0.2 M tribasic sodium phosphate and adjusting pH 6.8 by 2 N NaOH and 2 N HCl.

Scanning electron microscopy (SEM)

Cross section of MUPS tablet was evaluated for physical observation under scanning electron microscopy at different magnification (Make: JOEL, Model: JSM-7600F). Pellet was further assessed to observe intactness of core and coat.

Table 2: Composition of MUPS prepared from pantoprazole delayed release (DR) pellets

Ingredients	Quantity (%w/w)
Pantoprazole (DR) pellets	40
Ludpess: Ceolus granules	50
Ac-Di-Sol®	9
Magnesium stearate	0.5
Talc	0.5

Table 3: Physical properties of uncoated pantoprazole pellets prepared by extrusion and spheronization

Test parameter	Result (mean±SD)
Friability (%), n=3	0.642±0.026
Mechanical crushing force (N), n=20	14±3
Active ingredient content (% w/w), n=3	98.76±0.57
Size, n=6 (mm)	1.085±0.087

Data given in this table is presented as mean±SD

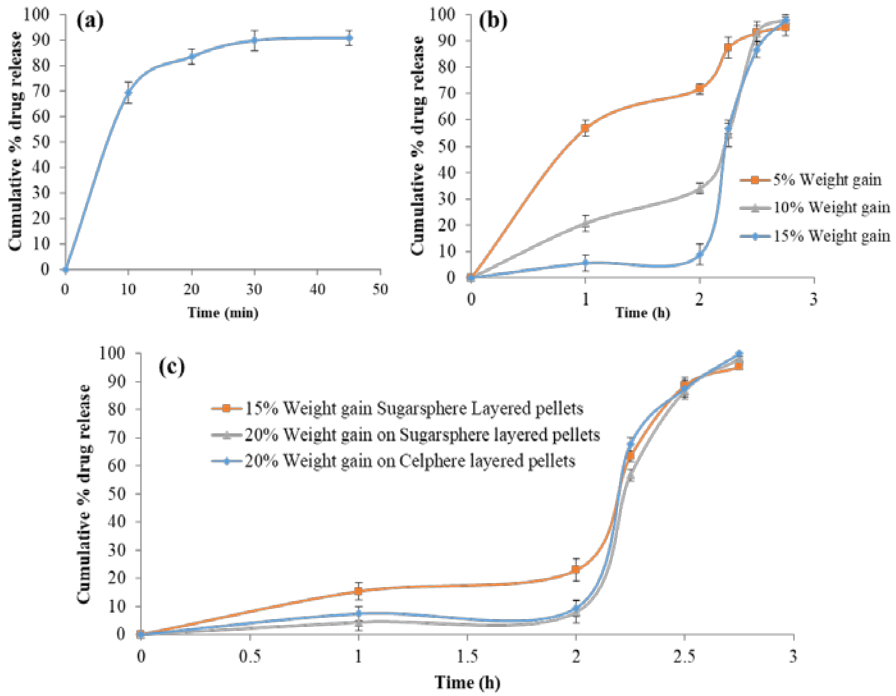

Fig. 1: (a) Dissolution of uncoated drug loaded pellets of pantoprazole prepared by extrusion and spheronization, (n=6) (b) Dissolution of enteric coated pantoprazole pellets prepared by extrusion and spheronization, (n=6) (c) Drug release study of delayed-release pantoprazole pellets prepared by layering, (n=6)(data given in mean±SD)

RESULTS AND DISCUSSION

Development of delayed release pantoprazole pellets using extrustion-spheronization and drug layering

Core pellets were characterized using dissolution method as presented in fig. 1 and for their physical properties as shown in table 3. The values clearly indicate that the pellets have suitable properties. fig. 1(a) shows the dissolution behaviour of uncoated Pantoprazole pellets in 0.1 N HCl and results indicated almost 90% drug was released in 45 min. So it was further coated with enteric polymer Eudragit NE 30 D. Enteric coating was done at different levels of weight gain and characterization was done by dissolution study. fig. 1(b) shows the dissolution behavior of three different levels of weight gain using Eudragit NE 30 D. Pellets coated with 5% weight gain of Eudragit NE 30 D cannot delay the release of Pantoprazole as seen in fig. 1(b). Even pellets coated with 10% weight gain released up to 30% drug in 2 h. So, 15% weight gain was optimum to avoid the release of pantoprazole (<10% drug released in 2 h) which was further used for compression.

Pantoprazole was successfully layered on sugar spheres and celphere 102. Characterization of uncoated pellets was done by dissolution study. Then pellets were coated with Eudragit NE 30 D at two level of weight gain, i.e. 15% and 20% as shown in fig. 1(c) for delayed release. In fig. 1(c) it was observed that 15% weight gain on sugar spheres layered pellets released more than 10% drugs 2 h.

This could be due to higher surface area of sugar sphere pellet than pellets prepared by extrusion and spheronization. Hence additional 5% weight gain (total 20%) in coating was done to achieve desired release profile in sugar sphere pellets. Similarly, celphere layered pellets showed the desired release profile at 20% weight gain.

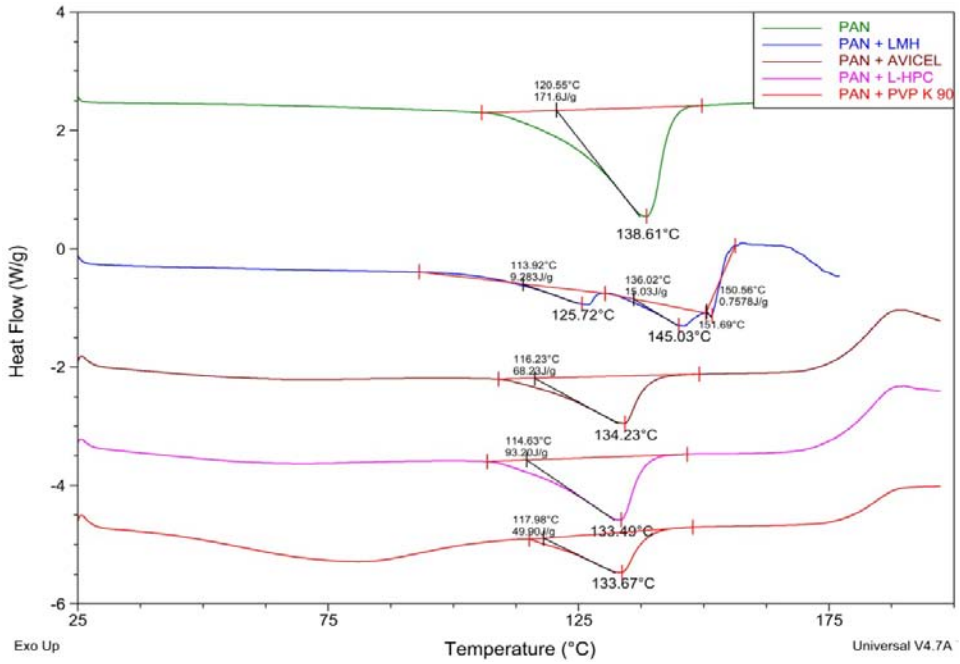

Fig. 2: Drug-excipient interaction study of pantoprazole (PAN) with lactose monohydrate (LMH), avicel PH 101, L-HPC and PVP (polyvinylpyrrolidone) K 90

Drug-excipient interaction

The possible interaction of pantoprazole with various excipients used in formulation development was studied using differential scanning calorimeter (DSC). DSC study revealed that pure pantoprazole exhibited melting endothermic peak between 125-146^{0}C shown in fig. 2. These observations indicated the absence of any interaction between pantoprazole with their excipients making them suitable for formulation of a multiunit pellet system (fig. 2).

Combination and characterization of tableting excipients

Different tableting excipients were prepared and characterized to assess suitability for pellet compression. Disintegration time was measured by compressing a tablet using tableting excipient (84%w/w), Ac-Di-Sol (10%w/w), Kollidone VA64 CL (5%w/w), Magnesium stearate (0.5%w/w) and Talc (0.5%w/w). Table 4 shows the physical characterization of tableting excipients. It was observed that Ceolus granules had lowest bulk density but were most useful excipients among all of the above as it retarded the segregation when mixed with other pellets or excipients. The results showed that Ceolus granules alone did not have good flow property as shown in table 4. Soft pellets were made up of barium sulfate which had disintegration property and glyceryl monostearate (GMS) which produced cushioning effect [26]. But results showed that soft pellets had a high bulk density which resulted in segregation. The combination of soft pellets and Ceolus granules resulted in proper flow property but could be used only for the compression of pellets of larger size. However, larger pellets such as made by extrusion and spheronization were observed to break during compression. Combination of Avicel PH 200 and Ceolus granules had good disintegration property and was used successfully for the preparation of MUPS. The bulk density of this combination was found lower, and angle of repose was not good as compared to the combination of Ludipress and Ceolus granules.

The combination of Ludipress and Ceolus granules was found to be suitable as a tableting excipient for the preparation of MUPS. A possible reason can be explained by the mechanism of compressibility. Avicel PH 200 is granular grade MCC which was directly compressible but was not water soluble.

However, Ludipress is co-processed excipient with a granular grade of lactose, crospovidone and polyvinylpyrrolidone. It was fragmented primarily during compression and subsequently underwent deformation, so helped during the disintegration of the tablet which was not observed with Avicel PH 200 [27-28].

Table 4: Characterization of tableting excipients

Type of excipients	Bulk Density (g/cm^3), (n=3)	Tapped Density (g/cm^3), (n=3)	Hausner ratio (n=3)	Carr's Index, (n=3)	Angle of Repose, (n=3)	Disintegration time (seconds), (n=3)
Ceolus Granules	0.26±0.03	0.34±0.04	1.31±0.01	23.68±0.23	28.37±1.23	87±5
Soft Pellets	1.14±0.02	1.20±0.02	1.05±0.02	4.76±0.07	9.43±0.56	253±13
Soft Pellets+CeolusGranules	0.49±0.07	0.57±0.08	1.17±0.05	14.29±0.57	29.12±2.54	157±6
Avicel PH 200+Ceolus granules	0.31±0.01	0.42±0.01	1.36±0.06	26.67±1.27	23.54±2.31	53±7
Ludipress+Ceolus granules	0.38±0.01	0.47±0.01	1.24±0.06	19.05±0.87	21.60±1.23	36±3

Data given in this table is presented as mean±SD

Development and characterization of MUPS tablet from pantoprazole (DR) pellets

Results showed that pellets prepared by extrusion and spheronization were not able to retain its release property during compression. With attaining similar mechanical properties only pellets prepared by layering on celphere could withstand compression forces.

Fig. 3(a) shows the characterization of MUPS prepared by different types of pantoprazole (DR) pellets. MUPS prepared from pellets (by extrusion and spheronization) showed 78% dissolution (in 0.1 N HCl for 2 h) which indicated rupturing of pellet's coat during compression. Pellets prepared by layering on MCC sphere had better tendency to retain its coat during compression and hence showed lesser dissolution (3.5%). In fig. 3(b) and (c), scanning electron microscopy of a cross-section of MUPS tablet (left) and pellet (right) can be observed showing intact pellet after compression.

The SEM images clearly indicate that the morphology of the pellets is maintained even after compression and can provide an unaltered release profile.

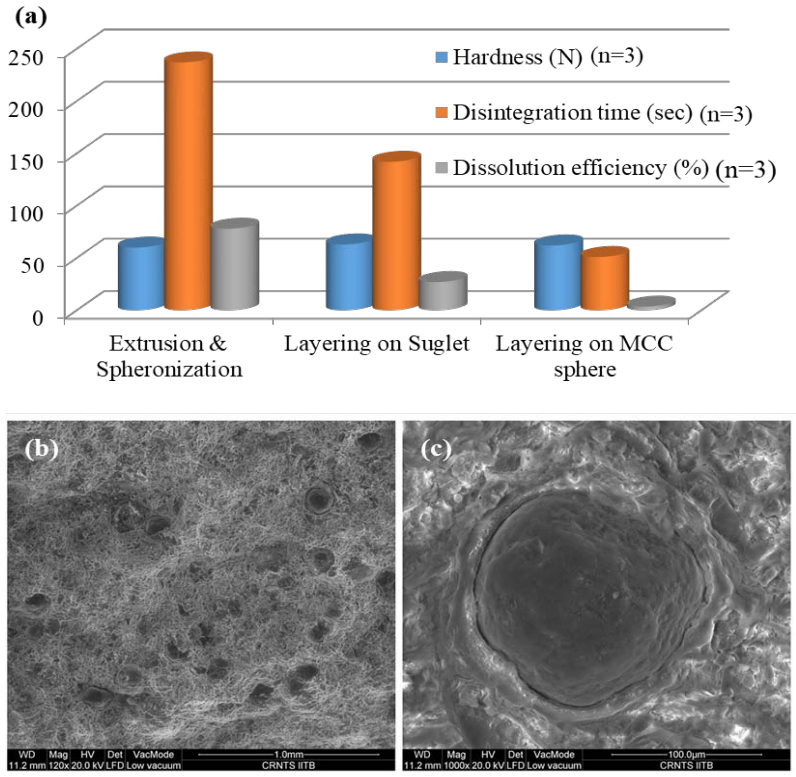

Fig. 3: (a) Characterization of MUPS prepared by different types of Pantoprazole (DR) pellets (n=3) (data in this fig. **is presented as mean) (b) Scanning Electron Microscopy (SEM) of MUPS tablet and (c) SEM image of pellet prepared using Pantoprazole delayed release pellets**

Influence of level of coating for the compression of pellets

Beside the other properties, coat applied on pellets must have enough flexibility in order to modify the release properties of the drug from the formulation [29]. Eudragit NE 30 D produced the very flexible film. A major problem encountered during coating was the tackiness. The film-forming temperature of Eudragit NE 30 D is 5^0C, so it forms a film at room temperature causing tackiness. This problem can be solved by adding up to 30% (w/w of dry solid) talc [30], but it reduces the plasticity of the film due to solid nature of talc. Such harder film could break/rupture during compression by erosion and cracking that would reduce the delay time [31].

So glyceryl monostearate (5% w/w of dry solid, in the form of 0.2% emulsion with 0.08% aqueous solution of Tween 80) was added which solved the problem.

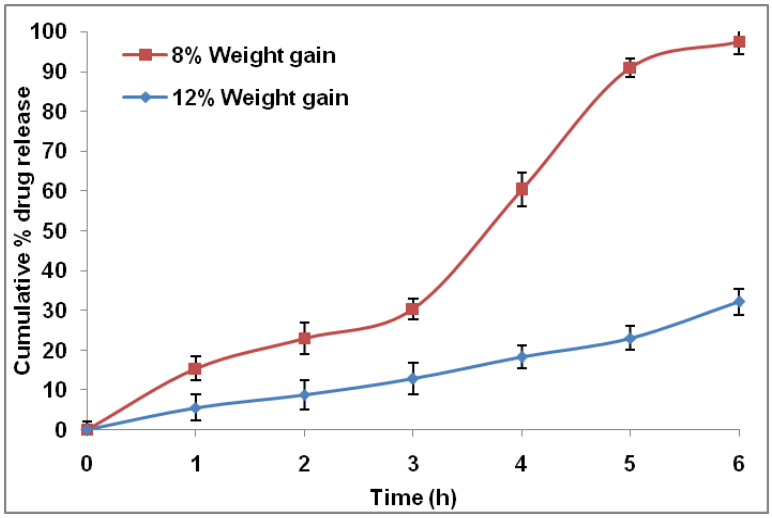

Fig. 4: Effect of weight gain of Eudragit NE 30 D coat on pantoprazole pellets to delay the drug release, (n=6)(data given in mean±SD)

Fig. 4 shows the effect of weight gain of Eudragit NE 30 D coat on pantoprazole pellets to delay the drug release in acid media. Eudragit NE 30 D was loaded on pantoprazole pellets at 8% and 12% weight gain. Dissolution was continued for 6 h in 0.1 N HCl. It was observed that pellets with 12% weight gain could delay the release effectively than the pellets with8% weight gain.

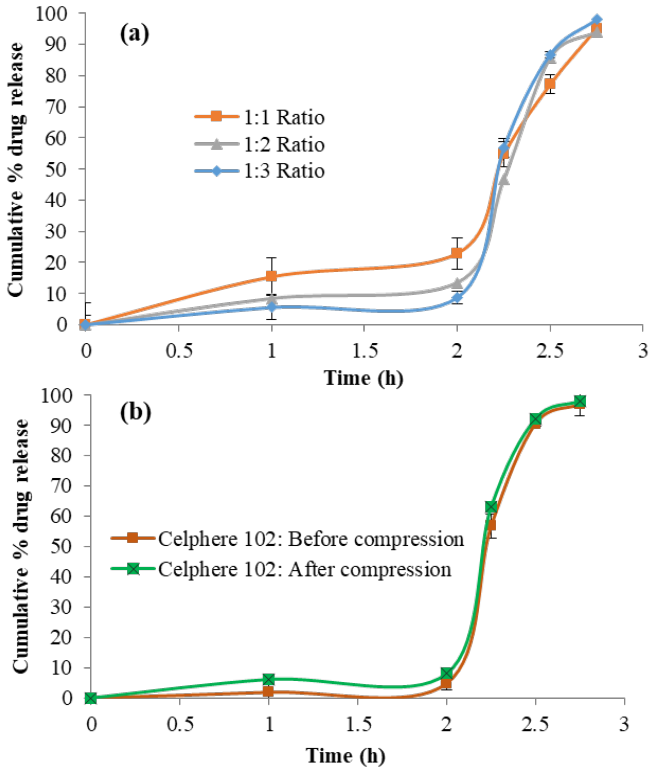

Fig. 5: (a) Effect of ratio of delayed release pantoprazole loaded celphere 102 to tableting excipient (n=6) (c) Dissolution of delayed release pantoprazole pellets before and after compression with ludipress: ceolus granules, (n=6) (data given in mean±SD)

Influence of ratio of drug loaded pellets to tableting excipients

As concluded from table 4, a mixture of ceolus granules and ludipress was used as tableting excipients for pellet compression. Ludipress has several advantages such as the low degree of hygroscopicity, good flowability, tablet hardness independent of machine speed [32]. The ratio of drug loaded pellets to tableting excipients was an important parameter optimized to compress the pellets into tablet form [33]. fig. 5(a) suggested that 1:3 ratio of drug loaded pellets to tableting excipients was optimum for pellet compression. fig. 5 (b) shows dissolution profile of pantoprazole MUPS, prepared from Celphere 102 compressed with Ludipress and Ceolus granules.

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. f_2 factor for the comparison of dissolution profile of celphere 102 loaded pellets before and after compression was 71 which complied with the dissolution criteria ($50<f_2>100$).

CONCLUSION

The core of three types of delayed release pantoprazole pellets was prepared using different techniques like extrusion and spheronization, drug layering on sugar spheres and drug layering on MCC spheres. Pellet formulation of pantoprazole prepared by extrusion and spheronization and subsequently coated with Eudragit NE 30 D were not able to withstand compression and failed to delay the drug release. These pellets were larger in size which had higher tendency to break/rupture during compression. The surface of such spheronized pellets was relatively uneven and difficult to coat uniformly with more chances of coat rupture. Pellets prepared by drug layering on suglet (sugar sphere) also failed in delaying the drug release. However, drug release of pellets prepared by layering on Celphere 102 (MCC sphere) found the better control to delay the release of pantoprazole. Celephere 102 spheres were harder and smaller than sugar spheres which can provide enough support to pellet coat during compression. The combination of Ceolus granules and Ludipess (1:1 ratio) was found suitable tableting excipient for pellet compression. Ceolus is a fibrous grade microcrystalline cellulose which protects pellets during compression by deformation mechanism. Celphere 102 layered pantoprazole pellets compressed with tableting excipients in the ratio of 1:3 provided MUPS fast disintegrating tablet with better control for delayed drug release. The developed MUPS showed enough hardness, rapid disintegration property and unaltered release profile. MUPS of delayed release pantoprazole was successfully developed that could be used for GERD and its complication.

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AUTHORS CONTRIBUTIONS

Experimental design, execution, data generation and writing of manuscript were done by first author Sandipkumar A. Patel. Support to draft manuscript design, data interpretation and corrections were done by second author Nrupa G. Patel. The design, guidance for the work and manuscript review was done by Abhijeet B. Joshi.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Rang H, Dale M, Ritter M, Flower R. Rang and dale's pharmacology. 6th ed. Churchillivingstone, New York; 2003. p. 386-93.
2. Frye J, Vaezi M. Extraesophageal GERD. Clin Gastroenterol 2008;37:845-58.
3. Richter J. Extraesophageal manifestation of GERD. Gastro-enterology 2013;145:691.
4. Sarang M, Padhi S. Colon targeted drug delivery system-an approach for treating colonic ailments. J Crit Rev 2015;2:12-8.
5. Ikasari E, Utomo A, Setyopuspito A, Adhityaasmara D, Setyowati H. Evaluation of antiulcer activity of mucoadhesive-microgranules containing ranitidine hydrochloride in experimental rats. Int J Curr Pharm Res 2017;9:45-9.
6. Etman M, Mahmoud E, Galal S, Nada A. Floating ranitidine micro particulates: development and *in vitro* evaluation. Int J Appl Pharm 2016;8:1-9.
7. El-Garhy O. An overview of the azoles of interest. Int J Curr Pharm Res 2015;7:1-6.
8. Formulation development and evaluation of the novel fixed-dose combination of s (-) Pantoprazole and Mosapride citrate by tablet in capsule approach. Asian J Pharm Clin Res 2015;8:224-8.
9. PM A, Rathnanand M CM. Stability enhancement of proton pump inhibitor in the stomach: Formulation and *in vitro* evaluation of stabilized proton pump inhibitor. Asian J Pharm Clin Res 2017;10:88-92.
10. Bianchini R, Bruni G, Gazzaniga A, Vecchio C. Influence of extrusion-spheronization processing on the physical properties of d-Indobufen pellets containing pH adjusters. Drug Dev Indian Pharm 1992;18:1485-503.
11. Varshosaz J, Kennedy R, Gipps E. Use of enteric polymers for the production of microspheres by extrusion-spheronization. Pharm Acta Helv 1997;72:145-52.
12. Bodmeier R. Tableting of coated pellets. Eur J Pharm Biopharm 1997;43:1-8.
13. Patel N, Patel S, Joshi A. Multiple unit pellet system (MUPS Technology) for development of modified release fast disintegrating tablets: a review. J Pharma Sci Innovation 2017;6:50-6.
14. Masih A, Kumar A, Singh S, Tiwari A. Fast dissolving tablets: a review. Int J Curr Pharm Res 2017;9:8-18.
15. Movva B, Kumar D, Ravi Kumar K. Formulation and evaluation of fast dissolving tablets of ranitidine hydrochloride by HOLE technology. Asian J Pharm Clin Res 2013;6:143-7.
16. Balaji V, Sathisha A, Geetha S, Swetha E. Drug utilization pattern among geriatric patients admitted in medical intensive care unit of a tertiary care teaching hospital. Asian J Pharm Clin Res 2017;8:281-3.
17. Abdul S, Chandewar A, Jaiswal S. A flexible technology for modified-release drugs: multiple-unit pellet system (MUPS). J Controlled Release 2010;147:2-16.
18. Ghanam D, Hassan I, Kleinebudde P. Compression behaviour of κ-carrageenan pellets. Int J Pharm 2010;390:117-27.
19. Prajapati HN, Patel DP, Patel NG, Dalrymple DD, Serajuddin AT. Effect of difference in fatty acid chain lengths of medium-chain lipids on lipid-surfactant-water phase diagrams and drug solubility. J Excipients Food Chem 2011;2:73-88.
20. Patel N, Dalrymple DM, Serajuddin AT. Development of solid SEDDS, III: Application of acconon® C-50 and Gelucire® 50/13 as both solidifying and emulsifying agents for medium chain triglycerides. J Excipients Food Chem 2012;3:83-92.
21. Patel N, Prajapati HN, Dalrymple DM, Serajuddin A. Development of solid SEDDS, II: application of acconon® C-44 and Gelucire® 44/14 as solidifying agents for self-emulsifying drug delivery systems of medium chain triglyceride. J Excipients Food Chem 2012;3:54-66.
22. Bosan J, Vranic E. Basic principles of drug--excipients interactions. Bosn J Basic Med Sci 2004;4:56-8.
23. Sousa J, Sousa A, Podczeck F, Newton J. Factors influencing the physical characteristics of pellets obtained by extrusion-spheronization. Int J Pharm 2002;232:91-106.
24. Newton J, Pinto M, Podczeck F. The preparation of pellets containing a surfactant or a mixture of mono-and di-gylcerides by extrusion/spheronization. Eur J Pharm Sci 2007;30:333-42.
25. Debunne A, Vervaet C, Mangelings D, Remon J. Compaction of enteric-coated pellets: influence of formulation and process parameters on tablet properties and *in vivo* evaluation. Eur J Pharm Sci 2004;22:305-14.
26. Pinto J, Podczeck F, Newton J. Investigations of tablets prepared from pellets produced by extrusion and spheronisation. II. Modelling the properties of the tablets produced using regression analysis. Int J Pharm 1997;152:7-16.
27. Johansson B, Alderborn G. Degree of pellet deformation during compaction and its relationship to the tensile strength of tablets formed of microcrystalline cellulose pellets. Int J Pharm 1996;132:207-20.
28. Johansson B, Nicklasson F, Alderborn G. Effect of pellet size on the degree of deformation and densification during compression and on compactability of microcrystalline cellulose pellets. Int J Pharm 1998;163:35-48.
29. Shimizu T, Nakano Y, Morimoto S, Tabata T, Hamaguchi N, Igari Y. Formulation study for lansoprazole fast-disintegrating tablet. I. effect of compression on dissolution behavior. Chem Pharm Bull 2003;51:942-7.
30. Dashevsky A, Wagner K, Kolter K, Bodmeier R. Physicochemical and release properties of pellets coated with Kollicoat® SR 30

D, a new aqueous polyvinyl acetate dispersion for extended release. Int J Pharm 2005;290:15-23.

31. Celik M. Compaction of multiparticulate oral dosage forms, multiparticulate Oral Drug Delivery, Marcel Dekker, New York; 1994. p. 181–215.
32. Patel H, Gohel M. A review on development of multifunctional co-processed excipient. J Crit Rev 2016;3:48-54.
33. Beckert T, Lehmann K, Schmidt P. Compression of enteric-coated pellets to disintegrating tablets. Int J Pharm 1996; 143:13-23.