Original Article

TIPS Trends in Phramaceutical Sciences 2016: 2(2): 151-158.

Preparation of Enteric Coated Pellets Containing Lansoprazole Using Extrusion/Spheronization Technique

Tavakol Heidari Shayesteh[1], Mina Abbasnia[2], Reza Mahjub[2,*]

[1]Department of Medicinal Chemistry, School of Pharmacy, Hamedan University of Medical Sciences, Hamedan, Iran.
[2]Department of Pharmaceutics, School of Pharmacy, Hamedan University of Medical Sciences, Hamedan, Iran.

Abstract

Lansoprazole degrades rapidly in an aqueous solution at low pH values. Degradation rate increases at pH values below 4 .The aim of this study was development of enteric coated pellets containing Lansoprazole by an extrusion/ spheronization technique. Eight different formulations based on lactose and six different formulations based on mannitol, consisting of different portions of other excipients including sucrose, hydroxy propyl methyl cellulose, magnesium carbonate, and sodium lauryl sulfate have been prepared. Feret diameter, shape factor, and amount of drug released were determined for each formulation. Among different formulations, F14, which consists of mannitol, sucrose, HPMC, talc, magnesium carbonate, and lansoprazole, is considered to be the best formulation. Six other different formulations for the preparation of enteric coatings based on Eudragit S100, Eudragit L100, triethyl citrate, and talc were prepared and coating procedure on pellets (F14) was performed using coating pan. In vitro drug release tests in acidic media (pH=1.2) and buffer media (pH=6.8) were performed for pellets, coated with each coating formulation and dissolution profile for each formulation was prepared. The pellets coated by formulation F.C 4, consisting of Eudragit L 100, triethylcitrate, and talc, showed a proper in vitro drug release profile. Accelerated stability tests were performed on coated pellets according to USP, and data suggested that pellets will be stable for 2 years.

Keywords: Coated Pellets, Extrusion/ Spheronization Technique, Lansoprazole, Filler, Enteric Coating.

1. Introduction

The formulation of multi-particulate pharmaceutical dosage forms as pellets is of great interest, and extensive studies have been done on this area recently. Spherical pellets have many advantages, such as low surface area to volume ratio, good flow properties, and uniform packing. Pellets can be coated for several purposes, including protection of active components from harsh environments and also creation of the sustained release pattern for the release of active components (1,2).

Among different methods for preparation of pellets, extrusion/ spheronization technique is widely studied, and several successful commercial products have been produced by this technique (3, 4). This process involves two steps. In the first step called extrusion, wet mass consisting of filler and binder with or without an active ingredient is converted to thin and long rods called extrudates by means of an extruder. In the second section, called spheronization, extrudates produced by the first step is sphronized by means of a spheronizer, to produce uniform spherical pellets. In most cases, microcrystalline cellulose (MCC) is used in pellet formulations produced by extrusion/ spheronization, because of facility in granulation and ability to keep water on its spongy structure. Different binders, such as sucrose, hydroxyl propyl methyl cellulose (HPMC) , hydroxy propyl cellulose

Corresponding Author: Reza Mahjub, Department of Pharmaceutics, School of Pharmacy, Hamedan University of Medical Sciences, Hamedan, Iran.
Email: r.mahjoub@umsha.ac.ir

Recieved:06/05/2016; Accepted:27/05//2016

(HPC), polyvinyl pyrolidon (PVP), sodium alginate are also used in combination with MCC (5,6).

Pellets containing drug is produced by two methods. In the first method, called matrix pellet preparation, the active ingredient is incorporated to wet mass in combination with different excipients and homogenously distributed throw a pellet sphere (7), the second method, called coating procedure, the spherical pellets without active ingredients, called non-pareil seeds (NPS) are prepared and then the active ingredient is coated with the spherical pellets by different methods of coating, such as pan coating and fluid bed coating (8, 9, 10, 11, 12).

Lansoprazole is classified as a proton pump inhibitor (PPI) and has a benzimidazole structure, which is used for acid-peptic disorders, such as duodenal ulcer, gastric ulcer, GERD, Zollinger-Ellison syndrome, erosive esophagitis, and eradication of *Helicobacter pylori* (13,14). Lansoprazole is sensitive to acidic media and is degraded in the acidic pH of stomach. Therefore, it is formulated as enteric coated granules (15). Studies have shown the structural changes in Lansoprazole upon exposure to acidic media (16).

The aims of this study are: 1) Production of a suitable formulation for matrix pellets containing Lansoprazole as an active agent, 2) Investigation of the formulation variables, such as type of filler, type of binder, amount of binder on prosperities of pellets, and 3) Development of a suitable coating formulation for the enteric coating of pellets.

2. Materials and Methods

2.1. Materials

Lansoprazole USP was obtained from Sigma-Aldrich Co. (U.S). Hydroxy propyl methyl celloluse (HPMC) was purchased from Samsung fine chemical co. (S. Korea). Lactose monohydrate was supplied from Meggle Co. (Germany); pharmaceutical grade Talc from Fujian Sannong Co. (China); Eudragit S100 & L100 from Rohm Pharma (Germany); mannitol from Helm AG (Germany); microcrystaline cellulose (Avicel PH 102) from FMC biopolymer (Belgium); sucrose from NP Pharm (France); sodium lauryl sulfate from Rohm Pharma (Germany); and magnesium carbonate from Lehmann & Voss Co. (Germany).

All other materials were of pharmaceutical and analytical grade and were used as received.

2.2. Preparation of pellets

Different formulations of pellets containing 10 %(w/w) of lansoprazole were prepared by extrusion/ spheronization technique. Pellets were categorized to two groups based on their formulations: the first, formulations based on lactose and the second, formulation based on mannitol . Other excipients were mixed with lactose or mannitol on a planetary mixer. Then, a solution containing suitable amount of sodium lauryl sulfate (SLS) and hydroxy propyl methyl cellulose (HPMC) in deionized water, as the granulation liquid, was added to the powder blend and mixed until a cohesive plastic mass was obtained. Then, resulting wet mass was processed in an extrusion/ spheronization equipment. Table 1 and Table 2 show the eight formulations (F1-F8) based on lactose and six formulations (F9-F14) based on mannitol. In these formulations, mannitol and lactose act as fillers. On the other hand, microcrystalline cellulose and HPMC are considered to be binders. Because of low solubility of lansoprazole in aqueous media, sodium lauryl sulfate (SLS) was added to the formulation as a solubility enhancer. Previous studies have shown the effect of SLS on the enhancement of bioavailability and drug release in insoluble drugs (17-19). Since lansoprazole is considered to be an instable agent, magnesium carbonate was added to the formulation as an alkaline stabilizer. Previous studies have shown improvement of stability of enteric granules containing lansoprazole by magnesium carbonate (15).

The extrusion/ spheronization process were as follows:

1) Extrusion of wet mass in an extruder (WLS Gabler Gum & pharma equipment, Germany) equipped with perforations of 1.5 mm in diameter.

2) Spheronization of extruded mass in a spheronizer (WLS Gamler Gum & pharma equipment, Germany) for 10 minutes.

Wet mass was dried on a tray, in an air dryer at 50 °C for 1 hour. Different methods of drying such as fluid bed drying and microwave were reported in the literature (20).

2.3. Characterization of pellets

PPellets produced by extrusion/ spheronization technique were characterized using image analysis (21), connected to a black and white camera. Feret diameter and shape factor were also determined. Shape factor, indicating degree of roundness, was calculated according to the formula (n=10 for each formulation) (Eq. 1).

$$\text{Shape factor} = \frac{4\pi A}{P^2} \qquad \text{Eq. 1}$$

Where:

A: area of particle.

P: perimeter of particle.

Different pellet formulations were tested for the amount of release in phosphate buffer medium (pH=6.8) in 45 minutes (n=10 for each formulation). After 45 minutes, a sample of supernatant related to each pellet formulation was collected and assayed for the amount of lansoprazole by HPLC.

According to the data achieved in this step, the best formulation for non-coated lansoprazole pellets was obtained.

2.4. Statistical analysis

Statistical analysis for determination of differences in the measured properties-i.e. Feret diameter, shape factor, and amount of drug released in 45 min-between different pellet formulations were accomplished by one-way analysis of variance, performed with SPSS® ver.11.5. Differences were considered to be statistically significant when P value<0.05, then different groups were identified by LSD post hoc test, performed by SPSS® Ver.11.5.

2.5. Particle size analysis

Particle size analysis was accomplished for the best pellets (F.14) by sieving method. The pellets were sieved throw a nest of sieves of different aperture sizes to give a progression from 280µm to 2800 µm. 150 g of non-coated pellets were applied to the nest of sieves and agitated for 10 min via a shaker. After 10 minutes, the sieves were taken apart and weighted. By subtracting the final weight of each sieve from tare weight, the amount of sample entrapped in each sieve was obtained.

2.6. Preparation of coating solution and coating procedure

Lansoprazole is an acid sensitive agent and maybe degraded in acidic pH of stomach. Therefore, lansoprazole pellets should be enteric coated. Eudragit S 100 and Eudragit L 100 as enteric coating polymers were used in this study. Eudragit L 100 may dissolve in media with pH values above 6, but Eudragit S 100 will dissolve in pHvalues above 7 (22, 23). Because of degradation of the drug in pellets due to the interaction between acidic carboxylic groups of Eudragit and lansoprazole, a sub-coat formulation containing hydroxy propyl methyl celloluse (HPMC) 2% (W/W) in a suitable amount of ethanol, were applied on pellets (F14) by pan coating equipment.

After subcoating, six different formulations were prepared for main coating, based on

Table 1. Formulation and measured properties of pellets prepared based on lactose.

No.	Lactose (%)	Avicel (%)	Sucrose (%)	HPMC (%)	SLS (%)	$MgCO_3$ (%)	Lanzoprazole (%)	Mean Feret diameter (mm±SD)	Shape factor±SD	Release in 45 min±SD (%)
F1	64	20	5	--	--	1	10	1.699 ±0.437	0.82 ±0.13	12.28±0.06
F2	66	20	3	--	--	1	10	0.725 ±0.480	0.71±0.21	18.63±0.12
F3	56	30	3	--	--	1	10	0.848 ±0.690	0.61 ±0.22	34.72±0.07
F4	69	20	--	--	--	1	10	0.421±0.493	0.52 ±0.26	28.54±0.14
F5	59	30	--	--	--	1	10	0.402±0.464	0.39 ±0.20	32.48±0.10
F6	65.5	20	2	1	0.5	1	10	0.811±0.474	0.86 ±0.12	37.12±0.05
F7	65.5	20	1	2	0.5	1	10	0.729 ±0.409	0.72 ±0.18	45.92±0.12
F8	65.5	20	--	3	0.5	1	10	0.703 ±0.492	0.54 ±0.13*	57.39±0.06

Table 2. Formulation and measured properties of pellets prepared based on manitol.

No.	manitol (%)	Avicel (%)	Sucrose (%)	HPMC (%)	SLS (%)	$MgCO_3$ (%)	Lanzoprazole (%)	Mean Feret diameter (mm±SD)	Shape factor±SD	Release Rate±SD
F9	63.5	20	5	--	0.5	1	10	1.836 ±0.455	0.87 ±0.11	(%)
F10	65.5	20	3	--	0.5	1	10	0693±0.420	0.78±0.2	51.17±0.09
F11	55.5	30	3	--	0.5	1	10	0.890±0.531	0.66 ±0.17	62.56±0.06
F12	68.5	20	--	--	0.5	1	10	0.414 ±0.434	0.47 ±0.19	60.94±0.14
F13	65.5	20	2	1	0.5	1	10	0.749±0.418	0.83 ±0.10	65.17±0.11
F14	65.5	20	1	2	0.5	1	10	0.736±0.409	0.85 ±0.12	87.32±0.08

Eudragit S 100 and Eudragit L 100, also triethylcitrate and talc as plasticizer and glidant, respectively. The details of each formulation are shown on Table 3.

2.7. HPLC analysis

An isocratic HPLC method have been established for determination of lansoprazole in pellets.

Samples were analyzed using HPLC-UV at 285 nm.

Chromatography was based on USP 30/NF 25. Briefly, isocratic elution was performed using a mixture of water, acetonitrile, and triethylamine (60:40:1) adjusted with phosphoric acid to pH value of 7.

The column used was a C18 stainless steel column (4.6 mm*25 cm that contained 5µm packing). The flow rate and injection volume were 1ml/min and 20 µl, respectively. Lansoprazole was detected at the retention time of 8.1 min.

2.8. Method validation

According to ICH guidelines, the validation of an analytical method consists of selectivity, accuracy, precision, LOD and LOQ determination, linearity and range. Selectivity was evaluated by comparing chromatograms of 3 blank samples from three different sources to make sure there were no significant interfering peaks at retention time at LOQ of the lansoprazole. The within-run precision and accuracy were determined by analysis of a set of samples (n=3) for all five concentrations in calibration curve. The between–run precision and accuracy were studied on a set of set of samples (n=3) at 3 consecutive days at five points of the calibration curve. The assay precision was evaluated by determining of the RSD. Accuracy was evaluated by the relative error (mean calculated*100/concentration spiked). For lansoprazole, a r2 value greater than 0.99 was found, in the range of 5-25 µg/ml. LOD and LOQ was defined using ICH guidelines based on signal to noise by injection of spiked plasma samples. The concentrations related to signals greater than 3 and 10 times of noise, were considered as LOD and LOQ, respectively.

2.9. In vitro drug release studies

In vitro dissolution tests were performed according to the USP basket method using a dissolution tester (Erweka, Germany).

For determining the resistance of coated pellets in acidic media, the coated pellets were

Table 3. Formulations for enteric coating of pellets prepared by F14.

Coating Formulation No.	Eudragit L 100 (%)	Eudragit S 100 (%)	Triethylcitrate (%)	Talc (%)	Ethanol (%)	Solid content (%)
F.C.1	4.5	--	0.93	0.75	93.82	6.18
F.C.2	8.5	--	1.76	1.4	88.34	11.66
F.C.3	12.5	--	2.5	2	83	17
F.C.4	15.5	--	3.1	2.51	78.89	21.11
F.C.5	--	4.5	0.93	0.75	93.82	6.18
F.C.6	--	8.5	1.76	1.4	88.34	11.66

studied for drug release in 900 ml of HCL 0.1 N with pH 1.2, at 37 °C as dissolution medium. The basket was rotated at 100 rpm. The condition was set as in a sink condition. After 2 hrs, the medium was changed and pellets were transferred to 900 ml phosphate buffer pH 6.8, at 37 °C for 45 min. The basket was rotated at 100 rpm.

For determination of drug release, samples were collected at 30, 60, 120, 125, 130, 135, 145, 155, and 165 minutes and an equal amount of fresh medium was replaced to the media at each sampling point. Samples were analyzed by HPLC for determination of lansoprazole. This experiment was done in triplicate for each coating formulation.

3. Results and Discussions

3.1. Preparation and characterization of pellets

Two different types of pellets-i.e. lactose based and mannitol based-with different amounts of excipients and a constant amount of lansoprazole (10% w/w) were prepared, and their Feret diameters and shape factors were determined.

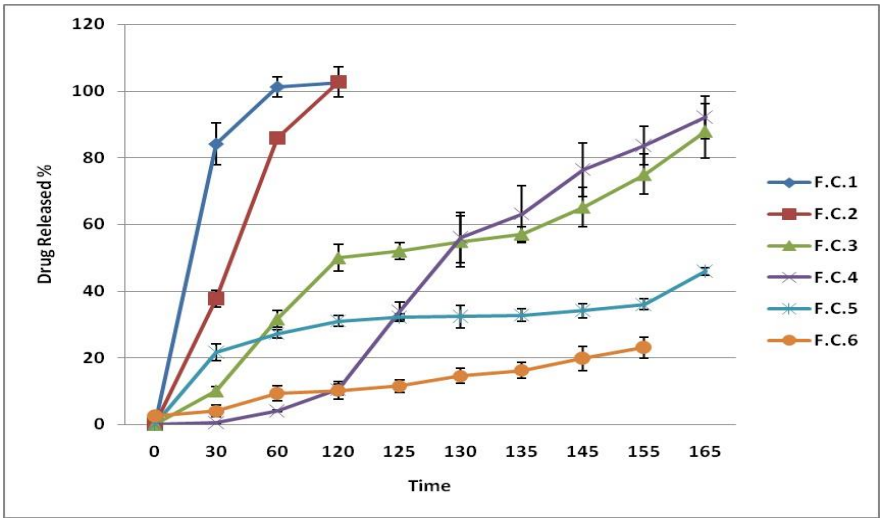
Table 1 and Table 2 show the properties of pellet formulations. As predicated, the amount of release is increased when SLS was added to the formulation of lansoprazole. As shown in the tables, the mean amounts of drug release are higher in pellets based on mannitol. We suppose that this phenomenon has occurred due to the higher solubility of mannitol in aqueous media compared to lactose, so mannitol can be the better candidate for improvement of dissolution of insoluble drugs such as lansoprazole. Further discussion about the obtained results will be found in the below.

3.2. Statistical analysis

A statistical analysis was performed for the measured factors of different formulations (F1-F14). The results show that Feret diameters of F1 and F9 is not statistically different from all of the other formulations (P value>0.05) but shape factor for F1 and F9 are statistically higher than F2 and F10, respectively (P value<0.05). In accordance to our results, studies have reported that a higher concentration of binder does not influence the size of pellets (24). We suppose that an increase in the sphericity of pellets in formulations containing a high proportion of microcrystalline cellulose maybe due to a high binding capacity of formulation.

On the other hand, the results indicated that F4, F5, and F12 had significant small Feret diameters compared to the other formulations (P value<0.05). Moreover, the pellets produced by these formulations have been easily crushed. These pellets were also dumbbell shaped and showed a significant reduction on shape factors (P value<0.05). These properties maybe justified by a low binding capacity.

Microcrystalline cellulose (MCC), as filler and binder, facilitate the granulation process due to creation of a spongy structure (6), but a high amount of MCC in the formulation cause



an increase in spheronization time, production of dumbbell shaped pellets, and also a reduction in size (25, 26). These are the reasons for the lower shape factor of F5 compared to F4. Moreover, as indicated in previous studies, the amount of water required for granulation is linearly increased with an increase of MCC content in the formulation due to the development of spongy structures.

Hydroxypropyl methylcellulose (HPMC) was added to the formulation as binder and solubility enhancer. Formulations that contained HPMC (F6,F7,F8,F13, and F14) showed significant higher amounts of release compared to the other formulations. Higher amounts of HPMC in the formulation cause increases in the drug release (P value<0.05). Although F8 showed the highest amount of release among lactose-based pellets, it had a low sphericity due to the low binding capacity resulted from lack of sucrose in the formulation.

Based on the data that are shown in Table 2 and 3, F14 was considered to be the best formulation, so further studies were accomplished on F14.

3.3. Particle size analysis

F14 was considered as the best pellet. Its particle size analysis was done by sieving method. The results are shown in Table 4. For this test, different sieve sizes were used (from 280 µm to 2800 µm) and the amount of sample in each sieve size, the percentage of sample that was entrapped in each sieve size and the cumulative percentage over size were reported. As seen in the table, all pellets fell in a size range between 280-1400 µm, and most of the pellets were entrapped in the sieve No.4 (710-1000 µm), which was in accordance with the mean Feret diameter reported for F14.

3.4. Method validation

Table 5 indicates the precision and accuracy of the method for within-day and between-day assays of all 5 concentrations used for calibration. As indicated, the highest RSD% for within-day assays was 2.98% that belonged to the concentration of 25 µg/ml of lansoprazole. Moreover, the highest RSD% for between-day assays were 4.20% that belonged to the concentration of 20 µg/ml of lansoprazole. The calibration curve showed a linear relationship between peak area and concentration. The equation that was used for determination of concentrations have been derived from Microsoft Excel and is as follows: Y=0.0139X+0.0069, where Y is the peak area of lansoprazole and X is the concentration of lansoprazole, LOD and LOQ were calculated to be 0.25 µg/ml and 0.83 µg/ml, respectively.

The concentrations of lansoprazole were investigated in real analytical samples and were shown to be in the range of 4.67-9.25 µg/ml. Therefore, all real samples were in the calibration line curve. Considering LOD and LOQ, this method has sufficient sensitivity for determination of lansoprazole in real samples.

3.5. In vitro drug release studies

Pellets formulated by F14 and coated with different coating formulations, were studied for *in vitro* drug release. Data are shown on Figure 1. As shown in the figure, F.C.1 and F.C.2 released all of their active agents in the acidic media because of insufficient amount of Eudragit L100 as enteric coating polymer. F.C.3 released 50% of its active agent in the acidic medium. F.C.5

Table 4. Results of particle size analysis by sieve method for un-coated pellets prepared by F14.

No.	Sieve Size (µm)	Amount of sample in each sieve (g)	Cumulative percentage oversize(%)
1	<300	21.77	100
2	300-500	4.95	85.47
3	500-710	8.5	82.17
4	710-1000	75.64	76.51
5	1000-1400	39.14	26.09
6	1400-2000	0.00	0.00
7	2000-2800	0.00	0.00

Table 5. Accuracy and precision of HPLC method.

Concentration added (µg/ml)	Error%	CV%	Concentration Found (Mean±SD; µg/ml)	Concentration added (µg/ml)	Error%	CV%	Concentration Found (Mean±SD; µg/ml)
whithin-day (n=3)5	2.4	1.75	5.12 ±0.09	Between-day (n=3)5	-0.8	1.20	4.96±0.06
10	2.5	2.73	10.25±0.28	10	1.5	1.37	10.15±0.14
15	-2.46	2.87	14.63±0.42	15	-0.86	1.34	14.87±0.2
20	2.35	4.2	20.47±0.86	20	0.75	1.93	20.15±0.39
25	-2.16	2.69	24.46±0.66	25	1.72	2.98	25.43±0.76

and F.C.6 released a few amount in the acidic media, but due to the incorporation of Eudragit S100 that dissolves in pH values above 7, less than 50% of active agent was released in buffer medium. Eudragit S100 may be considered as a suitable polymer for colon targeted drug delivery (20, 27). Among all these coated formulations, F.C.4 seems to be the best enteric coating formulation that has a few release in acidic media with pH value of 1.2 and suitable release in buffer media with pH value of 6.8.

4. Conclusion

Among different pellet core formulations, that have been studied in this research, F14, contains mannitol (65.5% W/W), microcrystalline cellulose (20% W/W), sucrose (1% W/W), HPMC (2% W/W), SLS (0.5% W/W), magnesium carbonate (1% W/W), and lansoprazole (10% W/W) seems to be the best formulation and poses proper shape, size and amount of release.

Among different enteric coating formulation, F.C.4, which contains Eudragit L100 (15.5% W/W), triethylcitrate (3.1% W/W), and talc (2.51% W/W), seems to be the best formulation with a proper dissolution profile. Accelerated stability studies indicate that this formulation is stable for 2 years.

Acknowledgment

This study was made possible by financial supports of deputy of Research, Hamedan University of Medical Sciences.

Conflict of Interest

None declared.

5. References

1. Koo OM, Heng PW. The Influence of Microcrystalline Cellulose Grade on Shape and Shape Distributions of Pellets Produced by Extrusion-Spheronization. *Chem Pharm Bull (Tokyo)*. 2001;49:1383-7.
2. Abbaspour MR, Sadeghi F, Afrasiabi Gharekani H. Design and study of ibuprofen disintegrating sustained-release tablets comprising coated pellets. *Eur J Pharm Biopharm*. 2008;68:747-59.
3. Podczeck F, Knight P. The Evaluation of Formulations for the Preparation of Pellets with High Drug Loading by Extrusion/Spheronization. *Pharm Dev Technol*. 2006;11:263-74.
4. Tomer G, Podczeck F, Newton JM. The influence of model drugs on the preparation of pellets by extrusion/spheronization: II. Spheronization parameters. *Int J Pharm*. 2002;231:107-19.
5. Gherbre Sellasie Issac. (2005).Pharmaceutical pelletization technology. New York, US: Marcel Dekker.
6. Fielden KE, Newton JM, Rowe RC. Movement of liquids throw powder beds. *Int J Pharm*.1992;79:47-60.
7. Piao J, Lee JE, Weon KY, Kim DW, Lee JS, Park JD, Nishiyama Y, Fukui I, Kim JS. Development of Novel Mucoadhesive Pellets of Metformin Hydrochloride. *Arch Pharm Res*. 2009;32:391-97.
8. Dietrich R, Brausse R. Validation of the pellet coating process used for a new sustained-release theophylline formulation. *Arzneimittelforschung*. 1988;38:1210-9.
9. Kramar A, Turk S, Verecer F. Statistical optimisation of diclofenac sustained release pellets

coated with polymethacrylic films. *Int J Pharm.* 2003;256:43-52.
10. Kablitz CD, Harder K, Urbanetz NA. Dry coating in a rotary fluid bed. *Eur J Pharm Sci.* 2006;27:212-19.
11. el-Mahdi IM, Deasy PB. Tableting of coated ketoprofen pellets. *J Microencapsul.* 2000;17:133-44.
12. Ganesan M, Pal TK, Jayakumar M. Pellet coating by air suspension technique using a mini-model coating unit. *Boll Chim Farm*. 2003;142:290-4.
13. Sachs G, Shin JM, Howden CW. Review article: The clinical pharmacology of proton pump inhibitors. *Aliment Pharmacol Ther*. 2006;23:2-8.
14. Michael R. Riley. 2000). Drug facts and comparisons. Missouri, US: facts and comparisons®
15. Tabata T, Makino T, Kikuta J, *et al*. Manufacturing method of stable enteric granules of a new antiulcer drug (Lansoprazole). *Drug Dev Ind Pharm.* 1994;20:1661-72.
16. Tutunji MF, Qaisi AM, El-Eswed B, Tutunji LF. An *in vitro* investigation on acid catalyzed reactions of proton pump inhibitors in the absence of an electrophile. *Int J pharm*. 2006;323:110-16.
17. Deasy PB, Law FML. Use of extrusion-spheronization to develop an improved oral dosage form of indomethacin. *Int J Pharm.* 1997; 148:201-9.
18. Sheng JJ, Kasim NA, Chandrasekharan R, Amidon GL. Solubilization and dissolution of insoluble weak acid, ketoprofen: effects of pH combined with surfactant. *Eur J Pharm Sci.* 2006;29: 306-14.
19. Shah VP, Konecny JJ, Everett RL, McCullough B, Noorizadeh AC, Skelly JP. *In vitro* dissolution profile of water-insoluble drug dosage forms in the presence of surfactants. *Pharm Res.* 1989; 6:612-8.
20. Balaxi M, Nikolakakis I, Kachrimanis K, Malamataris S. Combined effects of wetting, drying, and microcrystalline cellulose type on the mechanical strength and disintegration of pellets. *J Pharm Sci.* 2009;98:676-89.
21. Balogh E, Kállai N, Dredán J, Lengyel M, Klebovich I, Antal I. Application of computer image analysis for characterization of pellets. *Acta Pharm Hung.* 2007;77:123-31.
22. Jin Y, Wang YF, Wang CR, *et al.* Preparation of sustained-release and enteric coated pellets of pantoprazole. *Chinese Pharmaceutical Journal.* 2009;44:997-1001
23. Zhang SQ, Rahman Z, Thumma S, Repka MA, Chen GH, Li SM. Development and evaluation of a pH-dependent sustained release tablet for irritable bowel syndrome. *Drug Dev Ind Pharm.* 2009;35:57-64
24. Sinchaipanid N, Chitropas P, Mitrevej A. Influences of Layering on Theophylline Pellet Characteristics. *Pharm Dev Technol*. 2004;9:163-70.
25. Kleinebudde P, Schröder M, Schultz P, Müller BW, Waaler T, Nymo L. Importance of the Fraction of Microcrystalline Cellulose and Spheronization Speed on the Properties of Extruded Pellets Made from Binary Mixtures. *Pharm Dev Technol.* 1999;4:397-404.
26. Chatchawalsaisin J, Podczeck F, Newton JM. The preparation by extrusion/spheronization and the properties of pellets containing drugs, microcrystalline cellulose and glyceryl monostearate. *Eur J Pharm*. 2005;24:35-48.
27. Asghar LF, Chure CB, Chandran S. Colon specific delivery of indomethacin: Effect of incorporating pH sensitive polymers in xanthan gum matrix bases. *AAPS PharmSciTech*. 2009;10:335-45.