Original Research Article **Pharmaceutics**

International Journal of Pharma and Bio Sciences

ISSN 0975-6299

QUALITY EXCELLENCE IN PHARMACEUTICALS – A STUDY OF COMPARATIVE DISSOLUTION PROFILE FOR PANTOPRAZOLE SODIUM EC PELLETS 20% W/W (PFI)

VENKATESWARA REDDY BOYA[1*] AND DR. K. S. SEKHARA RAO[2]

*[*1]Research scholar of Koneru Lakshmaiah, Education foundation, (Department of management) Vaddeswaram, Guntur Dist., Andhra pradesh, India.*
[2]Associate professor & rpac chairman,koneru lakshmaiah education foundation, Vaddeswaram, Guntur Dist., Andhra pradesh, India

ABSTRACT

This study was carried out to prove the Quality Excellence of Pharmaceutical Formulation Intermediate (PFI) Pantoprazole Sodium EC Pellets 20% w/w by comparing it with the reputed market reference sample (Sun Pharmaceutical Industries Ltd.). This study was taken up on antiulcer drug to cure ulcers, as majority of people are suffering from gastric ulcer worldwide. One of the antiulcer drug known as Pantoprazole is, Proton Pump Inhibitor (PPI) which decreases acid secretion from parietal cells which are present in human stomach. Both Pantoprazole Sodium EC Pellets 20% w/w and PANTOCID® samples were analysed for dissolution studies in different dissolution media i.e. 0.1N Hydrochloric acid, pH 4.5 Acetate buffer, pH 6.8 Phosphate buffer for 12 units by taking testing method from USP-40. The Comparative Dissolution Profile (CDP) of Pantoprazole Sodium EC Pellets 20% w/w sample was found to be as good as the reference sample of PANTOCID®. The f2 values were found more than 50 (76 in 0.1 N HCl, 79 in pH 4.5 Acetate buffer & 77 in pH 6.8 Phosphate buffer) in all the dissolution media with reference to dissolution guidelines of Medicines Control Council (MCC), South Africa, and hence the CDP was considered acceptable and thus the quality excellence for Pantoprazole Sodium EC Pellets 20% w/w has been achieved.

KEYWORDS: *Ulcer, Pantoprazole, PPI, USP, MCC, CDP*

VENKATESWARA REDDY BOYA*

Research scholar of Koneru Lakshmaiah, Education foundation, (Department of management) Vaddeswaram, Guntur dist., Andhra pradesh, India.

Received on: 07-06-2018
Revised and Accepted on: 23-07-2018
DOI: http://dx.doi.org/10.22376/ijpbs.2018.9.4.p1-7

Creative commons version 4.0

INTRODUCTION

Several studies revealed that the overall occurrence of ulcers is about 12.5% in men and 10.5% in women worldwide. Normal causes of ulcer include the presence of microscopic organisms Helicobacter pylori and NSAIDs. About 33% of seasoned individuals have no symptoms.[1] Complication may include lesions in stomach. The first description of a perforated peptic ulcer was in 1670 in Princess Henrietta of England.[2] Other less regular causes include smoking tobacco, worry because of genuine sickness, Behcet illness, Zollinger-Ellison disorder, Crohn infection and liver cirrhosis, among others.[3] Barry Marshall and Robin Warren in the late 20th century, received the Nobel Prize in 2005 for discovery of *Helicobacter Pylori.*[4, 9] Older individuals are more delicate to the ulcer-causing impacts of NSAIDs. During 2015, about 87.4 million people worldwide have suffered from ulcer disease.[5] 267,500 deaths are reported in 2015 down from 327,000 deaths in 1990.[6,8] About 10% of people develop a peptic ulcer at some point in their life.[7 ,9] A antiulcer drug called as Pantoprazole, is Proton-pump inhibitor (PPI). it's core action is to perform a definite and long-lasting decrease of the creation of acid in stomach by blocking the hydrogen/potassium adenosine triphosphatase enzyme system (gastric proton pump) of the parietal cells in stomach.[10] Pellets can be manufactured by the compaction and drug-layering being which are most commonly used processing methods today. Pellets may have diverse applications in pharmaceutical industries. It just requires an innovative bend to use it to derive maximum cost-effectiveness. The proper formulation, processing conditions and processing equipment is very important in pellets manufacturing. To enable a controlled release rate of different drugs, coating can be done on pellets. The delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over a prolonged period of time, controlled release oral solid dosage forms are usually intended. The larger surface area of pellets enables it's for immediate release products for better dispersal. It is used to avoid powder dusting in the chemical industries. Pellets confirm improved flow properties and flexibility in formulation development and manufacturing. The coating material may be coloured with a dye material so that the beads of different coating thickness will be darker in colour and distinct from those having less coats. The pellets or granules are blended in the desired proportions of different thickness of coatings to give the desired effect. The aforesaid objective of the title can be accomplished through the comparative study of dissolution of the Pantoprazole Sodium EC Pellets 20% w/w with a reputed market sample PANTOCID® for *invitro* studies in different dissolution media.

MATERIALS AND METHODS

Materials used for the manufacturing

Table 1

(Ingredients used in the formulations with manufacturing formula)

S. o.	Ingredients	Quantity (in g)	Rationale	Vendor
Drug Coating:				
1.	Sugar Spheres ASTM (20#24)	195.0	Core	Credo Life Sciences Pvt. Ltd.
2.	Pantoprazole Sodium Sesquihydrate	136.0	API	Everest Organics Ltd.
3.	Hypromellose (HPMC-E5)	25.0	Film forming Polymer	C. Jivanlal& Company
4.	Sodium Carbonate	15.0	Alkalizer	Merck
5.	Sodium Lauryl Sulphate (SLS)	7.0	Surfactant	Godrej Industrial Ltd.
6.	Hydroxy Propyl Cellulose (HPC)	7.0	Disintegrate	Huzhou Zhan Wang Pharmaceutical
7.	Sodium Hydroxide (NaOH)	1.0	Alkalizer	Merck
8.	Disodium Ortho Phosphate	10.0	Stabilizer	Sky Chemie Pvt Ltd.
9.	Purified Water	650.0	Solvent	Credo Life Sciences Pvt. Ltd.
Barrier Coating:				
10.	Drug Coated Pellets	396.0	NA	NA
11.	Hypromellose (HPMC E5)	53.0	Film forming Polymer	Taianruitai cellulose Co. Ltd, china
12.	Purified Talc	2.0	Anti-tacking agent	Neelkanth Mine chem.
13.	Purified Water	900.0	Solvent	Credo Life Sciences Pvt. Ltd.
Enteric Coating:				
14.	Barrier Coated Pellets	451.0	NA	
15.	Methacrylic Acid Copolymer Dispersion (L-30D)	425.00 (127.5 g of Solid content)	Enteric Polymer	Dhara life sciences Pvt, Ltd, Gujarat.
16.	Diethyl Phthalate	10.5	Plasticizer	The Lakshmi Chemicals
17.	Purified Talc	5.0	Anti-tacking agent	Neelkanth Mine Chem
18.	Tween 80	1.0	Surfactant	Vasudha chemical Pvt. Ltd
19.	Titanium Dioxide	4.0	Opacifier	Huntsman P and A, Italy
20.	Sodium Hydroxide	1.0	Alkalizer	Merck
21.	Purified Water	380.0	Solvent	Credo Life Sciences Pvt. Ltd.

Table 2
Process parameters for the formulation

S. No.	Stage	Equipment	Process Parameters			
			Inlet Temperature	Product Temperature	Atomization air Pressure	Spray Pump Speed
1.	Drug Layering	Fluid Bed Equipment (GPCG 1.1 Wurster Coater)	55±2°C	42±2°C	0.8-1.2 bar	2-8 RPM
2.	Barrier Coating		55±3°C	42±2°C	0.8-1.2 bar	2-8 RPM
3.	Enteric Coating		48±2°C	40±2°C	0.8-1.2 bar	4-12 RPM

Procedure for preparation/formulation of pellets
Drug Coating Solution Preparation & Drug Coating
Purified water was collected into a clean SS container and to this Pantoprazole sodium sesquihydrate, Hypromellose (HPMC-E5), Sodium carbonate, Sodium Lauryl Sulphate, Hydroxy propyl cellulose and Sodium Hydroxide, Di Sodium Ortho phosphate were added one after the other as per the Table No. 1 under continuous stirring to obtain clear solution. The sugar spheres (20#24) were charged into FBE (GPCG 1.1) bowl as per Table No. 1 and the process parameters like Inlet temperature, product temperature, atomization air pressure and the spray pump were maintained as per the Table No. 2 during the drug coating stage and all the process parameters were within the acceptance limit and found satisfactory.

Barrier Coating Solution Preparation & Barrier Coating on Drug Coated Pellets
Purified water was collected into a clean SS container to which Hypromellose (HPMC E5) and Purified Talc were added one after another as per Table No. 1 and stirring was continued up to obtain uniform solution. Barrier coating was done on the Drug Coated pellets and the Process parameters like Inlet temperature, Product temperature, atomization air pressure and the Spray pump speed as per the Table No. 2 was maintained and found satisfactory.

Enteric Coating Solution Preparation & Enteric Coating on Barrier Coated Pellets
Step No.1
Purified water was collected in a clean SS container and toL-30 D, Diethyl phthalate, Purified Talc, Tween 80 and Titanium Dioxide were added one after the other as per Table No.1 under continuous stirring till uniform solution was obtained.

Step No.2
Sodium Hydroxide was dissolved in Purified water and the pH was adjusted to 5.3 ± 0.05 by adding the NaOH solution slowly in Step No.1. Finally, the solution was filtered through 100 mesh (SS) and collected into a separate SS container. Enteric coating was started on Barrier Coated Pellets and the process parameters like inlet Temperature, Product Temperature, atomization air pressure and the spray pump speed was maintained as per the Table No. 2 and stirring was continued till the completion of coating activity and found all the parameters were within the acceptance criteria and found satisfactory.

Drying
After completion of enteric coating the enteric coated pellets were dried in FBE (GPCG 1.1) for about 60 minutes by maintaining the atomization air pressure 1.2-1.5 bar and product temperature 40±2°C during the drying stage.

Sifting
After completion of drying the Enteric Coated Pellets were sifted through 16#20 sieves and collected the passing's and retains separately and good pellets separately into a duly labeled sample covers. The Materials which were used in the experiments were gifted by M/s Credo Life Sciences Private Limited, Hyderabad.

METHODS [13]

Table 3
(Instruments used for testing)

S. No.	Equipment Name	Make	Model
1.	Analytical balance	Mettler Toledo	ML204T
2.	pH Meter	Mettler Toledo	Five Easy Plus FP20
3.	UV/VIS Spectro photo meter	PerkinElmer	Lambda 365
4.	Dissolution Test Apparatus	Lab India	DS-8000
5.	Dissolution Test Apparatus	Electro Lab	EDT-14LX

Dissolution (By UV)
The dissolution test has been performed in 900 mL of 0.1 N HCl, pH 4.5 Acetate buffer and pH 6.8 phosphate buffer media with USP type II (Paddle), 50 rpm, temperature 37°C ± 0.5°C and checked the absorbance at 295 nm for all the media and calculated for f2 value. The acceptable value for f2 is more than 50.

RESULT AND DISCUSSION

Table 4
Details of Reference sample and Formulation F3

Reference Sample (Rt) Details		Test Sample (Tt) Details	
Product name	PANTOCID®	**Product name**	Pantoprazole EC Pellets 20% w/w
Strength	200mg	**Strength**	20%
Batch No.	EMS2063	**Batch No.**	RD/PS/001 (F3)
Mfg. Date	11/2017	**Mfg. Date**	Jan 2017
Exp. Date	10/2019	**Exp. Date**	Dec 2018
Manufactured by	Sun Pharmaceutical Industries Ltd.	**Manufactured by**	Credo Lifesciences Pvt. Ltd.

Comparative Dissolution Profile (CDP) of Reference Sample and Formulation F3

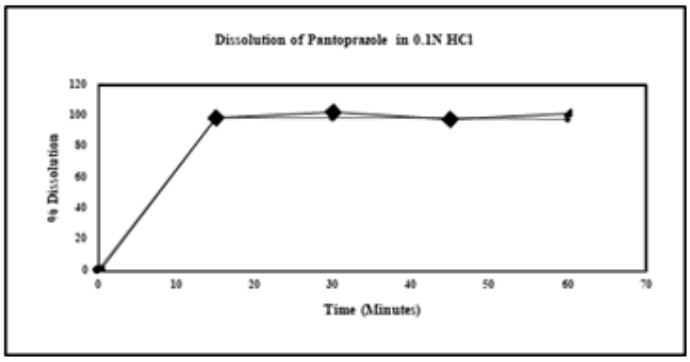
Time Points (minutes)	**Dissolution of Reference sample in 0.1N HCl**												Mean	SD
	B-1	B-2	B-3	B-4	B-5	B-6	B-7	B-8	B-9	B-10	B-11	B-12		
15	99	98	98	98	98	100	98	98	99	98	99	99	99	0.67
30	99	99	99	99	98	99	99	98	99	99	99	99	99	0.39
45	99	98	98	97	97	97	99	98	100	100	99	100	99	1.17
60	98	98	98	97	97	98	97	97	98	97	97	98	98	0.52
Time Points (minutes)	**Dissolution of Reference sample in pH 4.5 Acetate buffer**												Mean	SD
	B-1	B-2	B-3	B-4	B-5	B-6	B-7	B-8	B-9	B-10	B-11	B-12		
15	103	99	101	98	98	99	99	99	99	96	97	99	99	1.78
30	103	99	99	96	96	98	99	99	101	98	101	99	99	2.00
45	99	104	102	100	100	101	99	100	96	97	98	99	100	2.15
60	98	99	98	101	100	100	101	100	100	99	98	100	100	1.09
Time Points (minutes)	**Dissolution of Reference sample in pH 6.8 Phosphate buffer**												Mean	SD
	B-1	B-2	B-3	B-4	B-5	B-6	B-7	B-8	B-9	B-10	B-11	B-12		
15	101	100	101	101	101	102	101	101	102	101	101	101	101	0.51
30	102	101	100	101	102	101	101	101	101	102	102	102	101	0.65
45	102	100	101	100	102	102	101	101	102	102	101	102	101	0.78
60	100	103	103	101	102	103	102	102	102	104	103	103	102	1.07
Time Points (minutes)	**Dissolution of F3 sample in 0.1N HCl**												Mean	SD
	B-1	B-2	B-3	B-4	B-5	B-6	B-7	B-8	B-9	B-10	B-11	B-12		
15	97	101	100	100	99	100	96	100	100	100	99	101	99	1.51
30	99	104	103	105	104	104	98	102	102	104	103	103	103	2.11
45	100	100	100	100	98	98	94	97	97	98	99	98	98	1.76
60	101	102	102	103	102	103	100	101	103	102	102	102	102	0.90

Time Points (minutes)	Dissolution of F3 sample in pH 4.5 Acetate buffer												Mean	SD
	B-1	B-2	B-3	B-4	B-5	B-6	B-7	B-8	B-9	B-10	B-11	B-12		
15	96	97	96	96	97	97	97	96	96	97	96	96	96	0.51
30	94	95	95	96	99	97	97	97	97	97	97	97	97	1.31
45	97	97	96	97	97	98	98	98	95	98	98	98	97	0.97
60	97	97	**96**	98	98	98	97	98	98	97	98	97	97	0.67
Time Points (minutes)	Dissolution of F3 sample in pH 6.8 Phosphate buffer												Mean	SD
	B-1	B-2	B-3	B-4	B-5	B-6	B-7	B-8	B-9	B-10	B-11	B-12		
15	93	99	99	99	99	98	98	98	99	98	98	99	98	1.68
30	96	100	100	100	102	100	98	97	97	100	98	99	99	1.73
45	93	97	100	98	97	96	101	100	97	98	98	99	98	2.12
60	95	102	102	101	101	102	102	98	100	100	100	99	100	2.08

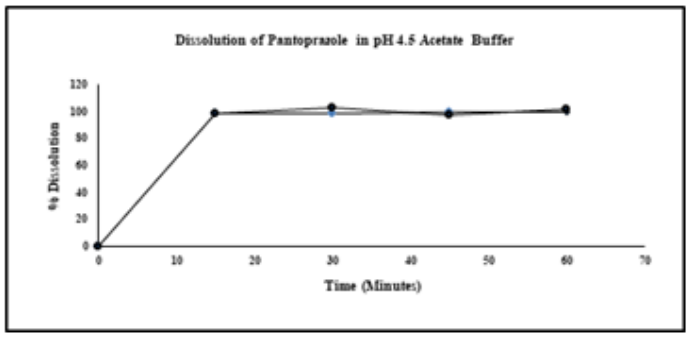
Table 5

f2 Calculation for CDP in 0.1 N HCl, pH 4.5 AcetateBuffer & pH 6.8 Phosphate Buffer

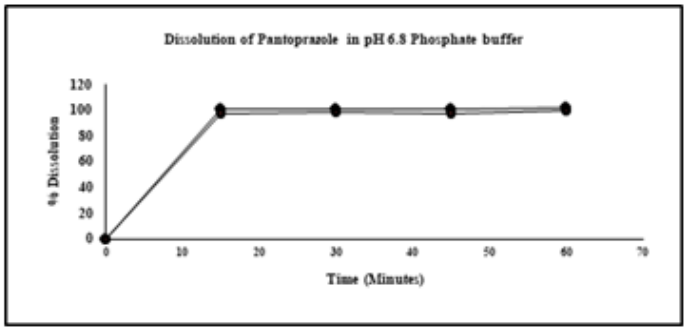
Dissolution Details		0.1N HCl, 900 mL, Paddle, 50 RPM		
Time (mins)	Reference (Rt) % Dissolution (Recovery)	Test (Tt) % Dissolution (Recovery)	(Rt-Tt)	(Rt-Tt)2
0	0	0	0	0
15	99	99	0	0
30	99	103	-4	16
45	99	98	1	0
60	98	102	-4	16
			n	**4**
			f2	**76**



Dissolution Details		pH 4.5 Acetate buffer, 900mL, Paddle, 50 RPM		
Time (mins)	Reference (Rt) % Dissolution	Test (Tt) % Dissolution	(Rt-Tt)	(Rt-Tt)2
0	0	0	0	0
15	99	99	0	0
30	99	103	-4	17
45	100	98	2	2
60	100	102	-2	4
			n	**4**
			f2	**79**



Dissolution Details		pH 6.8 Phosphate buffer, 900mL, Paddle, 50 RPM		
Time (mins)	Reference (Rt) % Dissolution	Test (Tt) % Dissolution	(Rt-Tt)	(Rt-Tt)2
0	0	0	0	0
15	101	98	3	9
30	101	99	2	5
45	101	98	3	10
60	102	100	2	6
			n	**4**
			f2	**77**



DISCUSSIONS

As mentioned in my previous study for the Operational excellence in pharmaceuticals – a process-based Approach in pantoprazole sodium EC pellets 20% w/w (PFI) By using managerial techniques, proceeded for quality excellence of the same formulation which was already published in IJPBS[12].We have compared F3 formulation of Pantoprazole Sodium EC Pellets 20% w/w with a reputed manufacturer (Sun Pharmaceutical Industries Ltd.) sample PANTOCID® for Comparative Dissolution Profile (CDP) as per the guidelines of Medicines Control Council (MCC), South Africa (SA) and USP-40. The acceptance criteria for f2 value must not be less than 50 as per USP-40[13] and MCC, SA.[14] The f2 value achieved is 76 in 900 mL of 0.1 N Hydrochloric Acid (HCl) with USP type II (Paddle), 50 rpm, temperature 37°C ± 0.5°C and absorbance at 295 nm. The f2 value achieved is 79 in 900 mL of pH 4.5 Acetate buffer with USP type II (Paddle), 50 rpm, temperature 37°C ± 0.5°C and absorbance at 295 nm. The f2 value achieved is 77 in 900 mL of pH 6.8 Phosphate buffer with USP type II (Paddle), 50 rpm, temperature 37°C ± 0.5°C and absorbance at 295 nm.The Equipment's and Instruments used in analysis were Pre-Qualified and Pre-calibrated. The Comparative Dissolution Profile of F3 formulation of Pantoprazole Sodium EC Pellets 20% w/w and PANTOCID® were reviewed and found the results were well within the acceptance criteria of f2 value.

ACKNOWLEDGEMENTS

I am very much grateful to my Managing Director (A. Siva Rama Prasad), Directors (A. Vamsi Krishna, K. Madhava Rao & E. Vineeth Rao) and Plant Head (N. Ramgopal Prasad) of M/s Credo Life Sciences Private Limited for their kind support. I would like to thank Dr. K. S. Sekhara Rao, Associate Professor & RPAC Chairman, Koneru Lakshmaiah Education Foundation, (K.L. University) Vaddeswaram, Guntur Dist., AP, India for his guidance and support. I would also like to thank Dr. K. Ch. Sri Kavya, Associate Dean, Academic Research, Koneru Lakshmaiah Education Foundation, (K.L. University) Vaddeswaram, Guntur Dist., AP, India for her kind support. I extend my very special gratitude to my wife, daughter and my son Master Praveen Kumar Reddy Boya, who entered eternity on 12th November 2011. He was the one who gave me immense inspiration and energy to continue my academics. And finally, I'm very much thankful, also to my colleagues of Credo Life Sciences Private Limited, Hyderabad.

CONCLUSION

Based on the findings of f2 values, it was concluded that the Comparative Dissolution Profile of Pantoprazole Sodium EC Pellets 20% w/w sample was as good as the reference sample of PANTOCID®. The f2 values were found more than 50 in all the dissolution media (0.1 N HCl, pH 4.5 Acetate buffer & pH 6.8 Phosphate buffer) with reference to dissolution guidelines of Medicines Control Council (MCC), South Africa, hence the CDP was considered acceptable and the quality excellence of Pantoprazole Sodium EC Pellets 20% w/w has been achieved.

AUTHOR CONTRIBUTION STATEMENT

It is my individual idea and the study was carried out on my own by taking guidance from my guide cum co-author Dr. K. S. Sekhara Rao, Koneru Lakshmaiah Education Foundation (KL University) Vaddeswaram, Guntur Dist., AP, India.

CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

1. Najm WI. Peptic ulcer disease. Primary care. 2011 Sept; 38(3): 383-94. DOI: https://doi.org/10.1016/j.pop.2011.05.001.
2. Milosavljevic T, Kostic-Milosavljevic M, Jovanovic I, Krstic M. Complications of peptic ulcer disease. Digestive diseases. 2011; 29(5): 491–3. DOI: 10.1159/000331517.
3. Steinberg KP. Stress-related mucosal disease in the critically ill patient: risk factors and strategies to prevent stress-related bleeding in the intensive care unit. Critical Care Medicine. 2002 Jun; 30(6Suppl): S362-4. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12072662.
4. Wang AY, Peura DA. The prevalence and incidence of Helicobacter pylori-associated peptic ulcer disease and upper gastrointestinal bleeding throughout the world. Gastrointestinal Endoscopy Clinics of North America. 2011 Oct; 21(4):613-35. DOI: 10.1016/j.giec.2011.07.011.
5. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016 Oct 8;388(10053):1545-1602. DOI:10.1016/S0140-6736(16)31678-6.
6. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016 Oct 8;388(10053):1459-1544. DOI: 10.1016/S0140-6736(16)31012-1.
7. Snowden FM. Emerging and reemerging diseases: a historical perspective. Immunol Rev. 2008 Oct; 225:9-26. DOI: 10.1111/j.1600-065X.2008.00677.x.
8. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality

for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015 Jan 10; 385 (9963): 117-71. DOI: 10.1016/S0140-6736(14)61682-2.

9. Nobelprize.org. The Nobel Prize in Physiology or Medicine 2005. Available from: https://www.nobelprize.org/nobel_prizes/medicine/laureates/2005/.
10. H Sakai, T Fujii, N Takeguchi. Chapter 13, Proton-Potassium (H+/K+) ATPases: Properties and Roles in Health and Diseases, In: A Sigel, H Sigel, R.K.O. Sigel (eds). The Alkali Metal Ions: Their Role in Life, Metal Ions in Life Sciences. 16. Switzerland: Springer; 2016. p. 459-83.
11. Protonix I.V. (pantoprazole sodium) Label, inventor; Pfizer. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020987s045lbl.pdf.
12. Venkateswara Reddy Boya, Dr. K.S. Sekhara Rao. Operational excellence in pharmaceuticals – a process-based Approach in pantoprazole sodium EC pellets 20% w/w (PFI) By using managerial techniques. Int J Pharm Bio Sci. Volume 9. Issue 3. 2018 (July-September): 89-98.Availablefrom:http://www.ijpbs.net/abstract.php?article=6470
13. United States Pharmacopeia, USP40-NF35. 2017. Volume 3. p 3157-60.
14. Medicines Control Council. July 2015. Available from:http://www.mccza.com/documents/0ca3cfe7 2.07_Dissolution_Jun15_v5.pdf