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Gastroprotective Delivery of Rabeprazole Sodium Along with Metoclopramide Hydrochloride Using Treated Agar

Raikar Prasiddhi Ratnakar*[1], Gajare Pankaj[2] and Naik Santoshi[3]
[1]Department of Pharmaceutics, KLE College of Pharmacy, KLE Academy of Higher Education and Research, JNMC Campus, Belagavi-590010, Karnataka, India
[2]Assistant Professor at P.E.S's Rajaram and Tarabai Bandekar College of Pharmacy, Goa
[3]Research Scholar - Manipal Academy of Higher Education, Karnataka, India

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*Corresponding Author Email: prasiddhiraikar07@gmail.com

Abstract
Particle engineering is a technique of physical modification of the excipient at sub-particle level without altering chemical properties to achieve desired functionality [5]. For development of immediate layer of Metoclopramide Hydrochloride Treated Agar was used as disintegrating agent and was compared with untreated agar.

Keywords
Gastroesophageal reflux disease, Particle engineering

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1. INTRODUCTION
Gastroesophageal reflux disease a pathological condition in which reflux of a gastric content into the oesophagus is exceeds the normal limit causing a variety of symptoms such as heartburn, difficulty in swallowing, sore throat, chest pain. Although proton pump inhibitors are the most effective and preferred agents for the treatment of Gastroesophageal reflux disease (GERD), the use of combination of proton pump inhibitors in combination with a prokinetic agent gives much effective compare to monotherapy with Proton Pump Inhibitors [1]. Rabeprazole Sodium is more effective a proton pump inhibitor than to other for treatment of GERD [2]. But on exposure to acidic environment of stomach Rabeprazole Sodium may get degraded to coloured product and results in reduced bioavailability [3]. Metoclopramide hydrochloride is a prokinetic agent which improve significantly gastric emptying and oesophageal sphincter pressure and diffuse upper gastrointestinal motor disturbances present in reflux esophagitis patients [4] .The present study the attempt was made to develop a drug delivery system containing a Delayed Release layer of Rabeprazole Sodium and Immediate Release Layer of Metoclopramide Hydrochloride.

Particle engineering is a technique of physical modification of the excipient at sub-particle level without altering chemical properties to achieve desired functionality [5]. For development of immediate layer of Metoclopramide Hydrochloride Treated Agar was used as disintegrating agent and was compared with untreated agar.

2. MATERIALS AND METHODS
Rabeprazole sodium and Metoclopramide Hydrochloride were supplied as a gift sample by Aristo Pharmaceuticals, Pvt. Ltd. Mumbai and Vaikunth Pvt Ltd. Panoli respectively. Agar, Ethyl Cellulose, HPMC, Micro Crystalline Cellulose, Magnesium Stearate and talc were procured from SD-Fine Chem Limited, Mumbai.

METHODS
2.1 Preformulation studies:
The received samples of drug and excipients were subjected to UV Spectral analysis, IR Spectral analysis and Melting point determination to confirm their

identity and purity. Drug-excipient compatibility study was carried out using FTIR spectroscopy [6, 7].

2.2 Formulation design and development

The development of the Bilayer tablets of Rabeprazole Sodium and Metoclopramide Hydrochloride consist of four Steps as

1. Preparation of Treated Agar Powder
2. Development of Blend for Immediate Release layer of Metoclopramide Hydrochloride
3. Development of Blend for Delayed release layer of Rabeprazole Sodium
4. Development of Bilayer Tablet of Rabeprazole Sodium and Metoclopramide Hydrochloride

Preparation of Treated Agar Powder

10% w/v aqueous solution of agar was prepared in 250 ml glass beaker with continuous stirring for 24 hours using mechanical stirrer. Prepared solution was kept aside in dark for 72 hours to swell the Agar. Swollen agar was separated from the solution and dried at 60^0C using hot air oven. Dried mass was grounded in a mortar using pestle and passed through sieve number 100. The powder passed through the sieve was used as one of the excipients (Treated Agar) for preparation of blend of immediate release layer as per Formulation Table No. 1 [8, 9].

Development of Blend for Immediate Release layer of Metoclopramide Hydrochloride

Various formulation blends for immediate release layer of Metoclopramide Hydrochloride were prepared as per Table I and evaluated for various precompression parameters such as bulk and tap density, compressibility, flow property. Prepared formulation blends were subjected for compressed on multi-station Karnavati Tablet Compression machine with 8 mm tooling using direct compression method. The prepared tablets were subjected for post compression parameters such as in vitro drug release studies, disintegration test, content uniformity and weight variation. The best fit formulation among the eight formulations was selected for development of bilayer tablet [10, 11, 12].

Formulation code	Agar (mg)	Treated agar (mg)	SSG (mg)	MCC (mg)	Magnesium stearate (mg)	Lactose (mg)	Talc (mg)	Sunset yellow (mg)	MTH (mg)
IR 1	6	-	6	30	8	28	8	4	10
IR 2	12	-	12	22	8	24	8	4	10
IR 3	18	-	18	15	8	19	8	4	10
IR 4	24	-	24	13	8	9	8	4	10
IR 5	-	6	6	30	8	28	8	4	10
IR 6	-	12	12	22	8	24	8	4	10
IR 7	-	18	18	15	8	19	8	4	10
IR 8	-	24	24	13	8	9	8	4	10

Table I: Formulation blends for immediate release layer of metoclopramide hydrochloride.

Development of Blend for Delayed release layer of Rabeprazole Sodium

Various formulation blends for immediate release layer of Rabeprazole Sodium were prepared as per Table II and evaluated for various precompression parameters such as bulk and tap density, compressibility, flow property. Prepared formulation blends were subjected for compressed on multi-station Karnavati Tablet Compression machine with 8 mm tooling using direct compression method. The prepared tablets were subjected for post compression parameters such as in vitro drug release, weight variation and uniformity of drug content. The best fit formulation among the eight formulations was selected for development of bilayer tablet. [13, 14, 15].

Table II: Formulation blends for delayed release layer of Rabeprazole sodium.

Formulation code	HPMC K100M (mg)	Ethyl cellulose (mg)	MCC (mg)	Magnesium Stearate (mg)	Talc (mg)	Rabeprazole sodium (mg)
DR 1	15	25	34	3	3	20
DR 2	25	25	24	3	3	20
DR 3	35	25	14	3	3	20
DR 4	25	30	19	3	3	20
DR 5	20	15	39	3	3	20
DR 6	30	10	34	3	3	20
DR 7	30	15	29	3	3	20
DR 8	15	25	24	3	3	20

Development of Bilayer Tablet of Rabeprazole Sodium and Metoclopramide Hydrochloride: A best fit formulation of Metoclopramide Hydrochloride and Rabeprazole Sodium was selected among the formulations mentioned in table No.1 and 2 respectively for development of bilayer tablet. As per procedure reported previously, the blend of best fit formulation for immediate release layer containing Metoclopramide Hydrochloride and of delayed Release Layer containing Rabeprazole Sodium were prepared separately. The formulation blend of delayed release layer was subjected for primary compression using Karnavati Rotary Tablet Machine and followed by compression of second layer of immediate release formulation blend using 8 mm round flat faced punch and die set. Prepared bilayer tablets were subjected for evaluation of post compression parameters. [16, 17, 18].

3. RESULTS AND DISCUSSION

3.1 Preformulation Studies:

Preformulation studies were carried out to confirm the identity and purity of the received samples of drug and excipients. The results of compatibility studies obtained confirms the compatibility of selected drugs and excipients.

3.2 Immediate Release layer of Metoclopramide Hydrochloride:

3.2.1 Evaluation of Precompression Parameters:

Pre-compression evaluation

All the formulation blends were subjected for evaluation of pre compression parameters such as bulk and tap density, flow property, compressibility. The results obtained revealed that use of optimum concentration of Talc and Magnesium stearate, improves the compressibility along with flow property. The results of precompression parameters were summarized in table III.

Table III: Evaluation of precompression parameters of immediate release layer formulation blend.

Formulation code	Bulk density(g/ml) (n=3)	Tapped density(g/ml) (n=3)	Carr's index (%) (n=3)	Hausner's ratio (n=3)	Angle of repose (n=3)
IR1	0.421 ±0.008	0.482 ±0.007	12.65±0.191	1.144±0.012	26.04±1.123
IR2	0.427 ±0.005	0.499 ±0.008	14.42±0.762	1.168 ±0.023	27.20 ±1.198
IR3	0.419 ±0.007	0.477 ±0.005	12.15±0.731	1.138 ±0.025	21.60 ±1.150
IR4	0.418 ±0.002	0.469 ±0.007	10.87±0.822	1.122 ±0.034	21.75 ±1.198
IR5	0.421 ±0.010	0.482 ±0.011	12.65 ±0.867	1.145 ±0.024	25.03 ±1.103
IR6	0.435 ±0.003	0.517 ±0.010	15.86 ±0.234	1.188 ±0.026	25.69 ±1.099
IR7	0.438 ±0.011	0.521 ±0.003	15.93 ±0.678	1.189 ±0.025	22.86 ±1.099
IR8	0.493 ±0.011	0.559 ±0.008	11.80 ±0.898	1.133 ±0.016	21.99 ±1.076

3.2.2 Evaluation of Post Compression Parameters:

The prepared formulations were evaluated for various pharmaceutical parameters as per Pharmacopoeial Specification. The results of disintegration studies showed that use of treated agar in combination with sodium starch glycolate has better disintegration time compare to untreated agar. Combination of treated agar with sodium starch glycolate in concentration of 24% of total formulation gives better in vitro drug release profile. Thus formulation No. IR 6 was considered as best fit formulation blend and selected as an immediate release layer for development of Bilayer Tablet. The results of evaluation of post compression parameters were summarized in table IV. The *in-vitro* release pattern of Metoclopramide Hydrochloride in acid buffer pH 1.2 was graphically presented as Fig. I.

Table IV: Evaluation of post compression parameters of immediate release layer of metoclopramide hydrochloride

Formulation code	Thickness (mm) (n=3)	Weight Variation (n=3)	Disintegration time (S) (n=3)	Drug Content (n=3)	% CDR at the end of 15 Minutes in acid buffer pH 1.2 (n=3)
IR1	1.663±0.009	99.72± 0.7	70 ± 2	93.37±0.07	73.80±0.12
IR2	1.698±0.011	99.94± 0.9	69 ± 2	97.54±0.06	73.80±0.55
IR3	1.715±0.006	100.2± 0.3	78 ± 3	92.65±0.09	76.20±0.12
IR4	1.723±0.004	99.93± 0.4	84 ± 2	97.33±0.06	70.80±0.78
IR5	1.722±0.002	99.80± 0.6	48 ± 4	98.34±0.02	73.56±0.11
IR6	1.688±0.010	99.85± 0.7	36 ± 2	98.65±0.06	91.8±0.43
IR7	1.676±0.013	99.98±0.66	60 ± 3	97.98±0.02	67.20±0.57

IR8	1.709±0.004	99.85 ± 0.6	71 ± 2	98.33±0.07	78.80±0.85

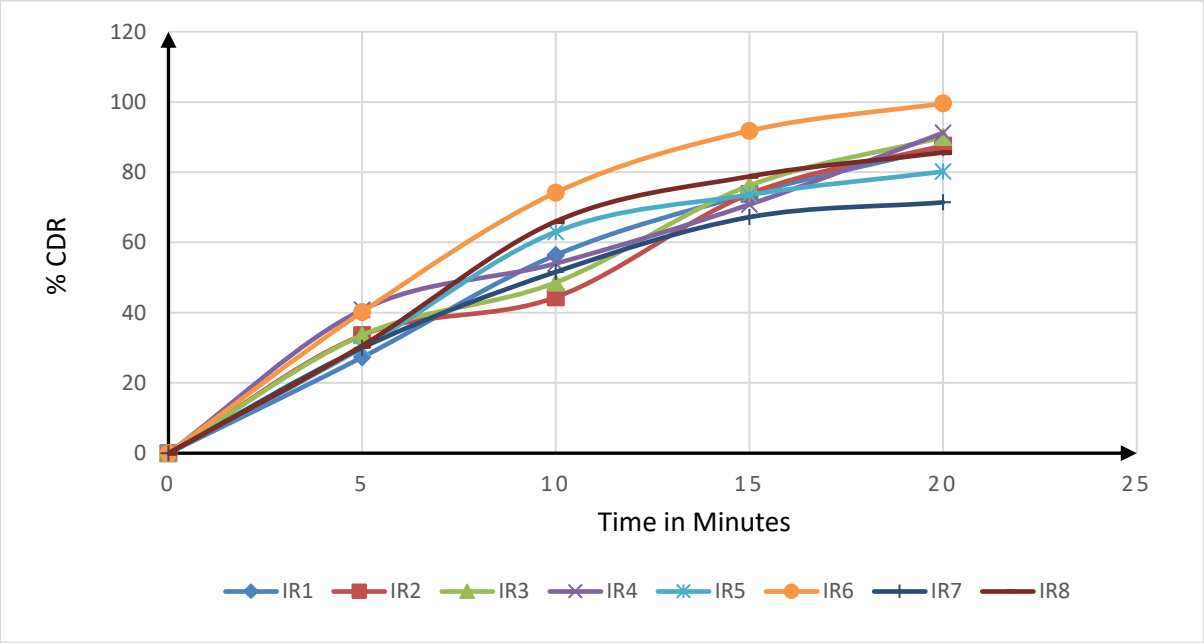

Fig I: Comparative *in vitro* release profile of metoclopramide hydrochloride

3.3 Delayed Release layer of Rabeprazole Sodium:

3.3.1 Evaluation of Precompression Parameters:

All the formulation blends were subjected for evaluation of pre compression parameters such as bulk and tap density, flow property, compressibility. The results obtained revealed that use of optimum concentration of Talc and Magnesium stearate, improves the compressibility along with flow property. The results of precompression parameters were summarized in table V.

Table V: Evaluation of precompression parameters of immediate release layer formulation blend.

Formulation code	Bulk density (g/ml) (n=3)	Tapped density. (g/ml) (n=3)	Carr's index (%) (n=3)	Hausner's ratio (n=3)	Angle of repose (n=3)
DR 1	0.290±0.013	0.333±0.008	12.91±0.67	1.148±0.021	24.64±1.150
DR 2	0.330±0.021	0.380±0.005	13.15±0.29	1.151±0.034	21.89±1,158
DR 3	0.308±0.034	0.366±0.019	20.05±0.84	1.188±0.015	33.56±1.141
DR 4	0.299±0.022	0.354±0.014	15.53±0.14	1.183±0.024	33.26±1.164
DR 5	0.293±0.037	0.355±0.007	17.46±0.91	1.211±0.055	30.23±1.103
DR 6	0.295±0.054	0.364±0.021	18.95±0.53	1.233±0.047	29.23±1.182
DR 7	0.321±0.049	0.362±0.023	12.77±0.48	1.127±0.035	25.54±1.171
DR 8	0.294±0.051	0.389±0.033	16.23±0.34	1.211±0.064	24.21±1.142

3.3.2 Post-compression evaluation

All the prepared formulations were complied with Pharmacopoeial specifications for weight variation test and Test for Drug Content. Results of in vitro drug release studies in acid buffer pH 1.2 for first 2 hours, followed by in phosphate buffer pH 6.8, showed that Ethyl cellulose alone can control the release in acidic medium. But its use in combination with HPMC K 100 M can extend the release for desired period of time due to its gel forming property. Optimum use of ethyl cellulose with HPMC K 100 M also helps to modify drug release pattern due to its hydrophobicity which acts as a weaker barrier than gel of HPMC. Use of HPMC K100 M and Ethyl Cellulose in a ratio of 1:1 can retard the release of Rabeprazole Sodium in acidic medium and extend the release for more than 8 hours in phosphate Buffer pH 6.8. The results of evaluation of post compression parameters were summarized in table VI. Based on the results obtained formulation No. 2 was considered as best fit formulation and was

selected as a delayed release layer for development of Bilayer tablet.

Table VI: evaluation of post compression parameters for delayed release layer

Formulation code	Thickness (mm) (n=3)	Weight Variation (n=3)	Drug Content (n=3)	% CDR in Acid Buffer pH 1.2 at end of 2 Hours (n= 6)	Time in hours required to Release Drug in Phosphate Buffer pH 6.8	
					$T_{50\%}$ (n=6)	$T_{80\%}$ (n=6)
DR 1	1.723±0.004	99.95 ± 0.6	91.56±0.007	8.5± 0.9	2.1	8.0
DR 2	1.689±0.004	99.95 ± 0.7	95.33±0.007	7.4± 0.87	1.8	7.4
DR 3	1.663±0.005	99.90 ± 0.6	95.67±0.007	8.4± 0.67	1.7	8.0
DR 4	1.703±0.006	99.95 ± 0.6	93±0.0066	6.1± 0.72	3.1	5.9
DR 5	1.673±0.005	99.75 ± 0.7	92.09±0.007	10.1± 0.81	1.7	4.0
DR 6	1.699±0.005	99.95 ± 0.7	98.99±0.007	12.5± 0.79	1.8	3.9
DR 7	1.712±0.005	100.3 ± 0.7	98.21±0.008	10.1± 0.57	1.7	7.5
DR 8	1.728±0.004	99.95 ± 0.7	96.50±0.007	8.8± 0.49	1.6	8.0

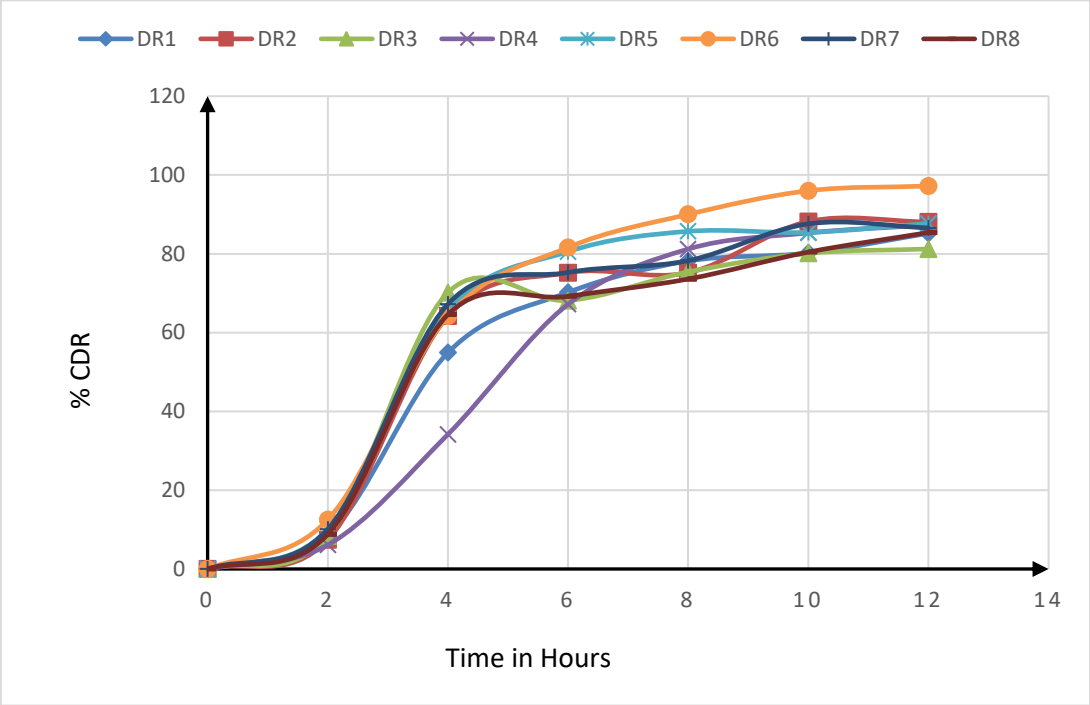

Fig II: Comparative in vitro drug release profile of Rabeprazole Sodium in acid buffer pH 1.2 for 2 hours followed by in Phosphate Buffer pH 6.8 for 10 hours.

3.4 Bilayer Tablet of Metoclopramide Hydrochloride and Rabeprazole Sodium:

Selected best fit formulations for immediate release layer of metoclopramide IR 6 and delayed release layer of Rabeprazole Sodium DR 2 were compressed and evaluated as a Bilayer Tablet as per procedure reported previously. The Results of the same were tabulated in table VII.

Table No. VII: Evaluation of Bilayer Tablet of Metoclopramide Hydrochloride and Rabeprazole Sodium

Hardness (n=3)	5.6±0.40
% Friability (n=3)	**0.056** ± 0.003
Drug Content (n=3)	
Metoclopramide Hydrochloride	98.65±0.06
Rabeprazole Sodium	95.33±0.007

In vitro Release of Metoclopramide Hydrochloride in acid Buffer pH 1.2	$T_{50\%}$	**7 minutes**			
	$T_{80\%}$	**13 Minutes**			
	Release at the end of 15 Minutes	**91.8** ± 0.11			
In vitro Release of Rabeprazole Sodium	In acid Buffer pH 1.2 at the end of 2 Hours	**7.4 %**			
	$T_{50\%\ of}$ Rabeprazole Sodium in Phosphate Buffer pH 6.8	**1.8 Hours**			
	$T_{80\%\ of}$ Rabeprazole Sodium in Phosphate Buffer pH 6.8	**7.4 Hours**			
Drug Release Kinetic of Delayed Release Layer	**Zero-order R^2**	**First order R^2**	**Higuchi Model R^2**	**Korsmeyer-Peppas R^2**	**Best fit**
	0.681	0.140	0.644	0.646	Zero order

4. CONCLUSION:

Bilayer Tablet for Gastroprotective delivery of Rabeprazole sodium along with metoclopramide Hydrochloride was formulated successfully using direct compression method. Stomach specific immediate delivery of Metoclopramide Hydrochloride was achieved by using Treated Agar as disintegrating agent along with Sodium Starch Glycolate. The results of evaluation studies showed that modification of agar at sub particulate level, improve functionality of agar. Rabeprazole Sodium is highly sensitive to gastric acid. Hence attempt was made to retard the release of Rabeprazole Sodium using various combinations Ethyl Cellulose and HPMC K 100 M. The results of *in vitro* drug release studies revealed that combination of Ethyl Cellulose with HPMC K 100 M in the ratio of 1:1 can retard the release of Rabeprazole Sodium in acidic medium and can extend the release for more than 8 hours in Phosphate Buffer pH 6.8. In conclusion, the bilayer tablet is a strategy of choice for delivery of containing immediate release layer of Metoclopramide Hydrochloride and delayed release layer of Rabeprazole Sodium.

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REFERENCES

1. Suzanna N. Combination of PPI with a Prokinetic Drug in Gastroesophageal Reflux Disease. Acta Med Indones-Indones J Intern Med 2011;43(4):233-236.
2. Fabio P, Stefano P, Stefania C, Gabriele BP. A review of rabeprazole in the treatment of acid-related diseases. Ther Clin Risk Manag. 2007 Jun; 3(3): 363–379.
3. Mukharya A et al. Stable and bioequivalent formulation development of highly acid labile proton pump inhibitor: rabeprazole. International Journal of Pharmaceutical Research & Innovation 2011 January; 2:1-8
4. McCallum RW, Fink SM, Winnan GR, Avella J, Callachan C. Metoclopramide in gastroesophageal reflux disease: rationale for its use and results of a double-blind trial. Am J Gastroenterol. 1984 Mar;79(3):165-72.
5. Somnache SN, Godbole AM, Gajare PS, Kashyap S· Significance of Pharmaceutical Excipients on Solid Dosage form Development: A Brief Review. Asian J Pharm Res. 2016; 6(3): 193-202.
6. Deodatt AW, Abu TM, Serajuddin, Harol DJ, Squibb ER. Preformulation Testing. In: Lieberman HA, Lachman L, Schwartz JB. editors. Pharmaceutical Dosage Forms Tablets. New York (NY): Marcel Dekker, Inc; 1989. p. 1-73. (Pharmaceutical Dosage Forms Tablets; Vol 1).
7. Karin L, Trine GL, Birgitte W, René H. Solid state compatibility studies with tablet excipients using non thermal methods. J Pharmaceut Biomed 2011; 55:424-8.
8. Prabhu KH, Shaista O, Sharada R, Pranesh KP. Formulation and evaluation of mouth disintegrating tablets of Famotidine by using Hibiscus Rosa - sinensis mucilage and Treated Agar. International Journal of Research in Ayurveda & Pharmacy. 1 (2); 2010: 497 – 505.
9. Akihiko I, Masayasu S. Development of Oral Dosage Form for Elderly Patient: Use of Agar as Base of Rapidly Disintegrating Oral Tablets. Chemical and Pharmaceutical Bulletin 1996; 44(11):2132-2136.
10. York P. Crystal Engineering and Particle Design for the Powder Compaction Process. Drug Dev. Ind. Pharm.1992;18(6): 677-721
11. Dandare M.S, Sarage R.D, Bhaskaran S. Bilayer Tablet: A Novel Approach for Immediate Release of Telmisartan and Hydrochlorthaizide Combination.International Journal of Pharmacy and Tech.2012; 4(1):3970-83

12. Godbole AM, Somnache SN, Thakker SP, Iliger SR, Joshi AS, Patel BV Formulation and In-vitro Evaluation of Sublingual Tablets of Ondansetron Hydrochloride using Coprocessed Excipients. Ind J Pharm Edu Res. Oct-Dec2014; 48(Suppl):7-17.
13. Patel SR, Patel PR, Vora CN. Formulation Process Parameters Optimization and Evaluation of Delayed Release Tablets of Rabeprazole Sodium. International Journal Of Pharmacy and Pharmaceutical Sciences 2010;2(3):144-56
14. Godbole AM, Patel BV, Somnache SN, Prajapati AR, Yadav P. Optimization of Various Grades of HPMC for Development of Sustained Release Matrix Tablets of Theophylline. Asian J Pharm Tech. 2017; 7(1): 19-26.
15. James L.F, Michael H.R, Fionan M.C, John E.H, Penny J.E.Importance of Drug type, Tablet Shape and added Diluents on Drug Release Kinetics from Hydroxypropylmethylcellulose Matrix Tablets. Int J Pharm. 1987; 40(3): 223-34
16. Shirse P. Formulation and Evaluation of Bilayer Tablets of Diclofenac Sodium and Ranitidine HCl for Sustained and Immediate Release. JAPS 2012;2(5):136-41
17. Aruna R, Padma R, Kinnera K, Venkateswara RT. Study of Formulation Variables on Bi-Layered Floating Tablets of Diltiazem Hydrochloride, Int J Pharm Chem Sci.2013; 2(1): 335-41
18. Nirmal J, Saisivam S Peddamma C, Muralidharan S Nagarajan M. Bilayer Tablets of Atorvastatin Calcium and Nicotinic Acid: Formulation and Evaluation. Chem. Pharm. Bull.2008;56:1455-8