ORIGINAL ARTICLE

Development of Controlled-Release Formulation to Improve Bioavailability of Esomeprazole

C. Soujanya, B. Lakshmi Satya, Chandrika Marepally, Bhavya Sri Vinjamuri, Rupika Reddy Ettadi

Department of Pharmaceutics, Vishnu Institute of Pharmaceutical Education and Research, Narsapur, Telangana, India

Abstract

Aim: The aim of this study was to release the active drug immediately after oral administration, to acquire quick, and enter systemic drug absorption. Such immediate-release products result in comparatively rapid drug absorption and onset of associated pharmacodynamic effects. **Materials and Methods:** The prepared esomeprazole CR tablets were evaluated for the dissolution studies in acid buffer (pH-1.2) for 2 h, 4.5 pH acetate buffers for 2 h, 6.8 pH phosphate buffers for 8 h, and 7.4 pH phosphate buffers for 12 h % drug release that was calculated at various time intervals. **Results and Discussion:** The present study was aimed to developing controlled-release tablets of esomeprazole using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies. **Conclusion:** The current research work envisaged was an attempt to development of controlled-release formulations of esomeprazole to improve bioavailability.

Key words: Bioavailability, esomeprazole, oral drug delivery system

INTRODUCTION

Oral drug delivery system

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to acquire quick, and entire systemic drug absorption. Such immediate-release products result in comparatively rapid drug absorption and onset of associated pharmacodynamic effects.[1-2] Although, after absorption of the drug from, the dosage form is whole, plasma drug concentrations refuse according to the drug's PK profile. Ultimately, plasma drug concentrations reduce below the minimum effective plasma concentration, ensuing in loss of therapeutic activity. Before this point is reached, another dose is frequently given if a sustained therapeutic effect is required.[3-5] A substitute to administer an additional dose is to use a dosage form that will afford sustained drug release and, hence, maintain plasma drug concentrations, ahead of what is typically seen using immediate-release dosage forms.[6]

The term modified-release drug products used to depict products that amend the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one, for which the drug release characteristics of time course and/or location are preferred to achieve therapeutic or convenience objectives not accessible by conventional dosage forms such as solutions, ointments, or punctually dissolving dosage forms as presently recognized."[7-9]

Several types of modified-release drug products are recognized

Extended-release drug products

Extended Release (ER) drugs are employed to improve patient compliance and therapeutic outcomes. They can

Address for correspondence:
C. Soujanya, Department of Pharmaceutics,
Vishnu Institute of Pharmaceutical Education and Research, Narsapur, Medak, Telangana, India.
E-mail: soujanya.c@viper.ac.in

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be utilized to reduce the number of times the patient has to administer medication over the course of the day. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.[10-12]

Delayed-release drug products

Delayed-release products are modified-release. They involve the release of discrete amount(s) of drug some time after drug administration. Enteric-coated dosage forms are the most common delayed-release products.[13-16]

Targeted-release drug products

Targeted drug delivery, sometimes called smart drug delivery, is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others.[17-19]

Modified-release drug products

These are considered for altered routes of administration based on the physicochemical, pharmacologic, and PK properties of the drug and on the properties of the materials used in the dosage form.[20] Numerous unlike terms are now defined to describe the available types of modified-release drug products based on the drug release characteristics of the products [Table 1].

MATERIALS AND METHODS

Materials

Esomeprazole is a gift sample from Astra Zeneca Pharma Ltd, Bangalore. Eudragit-S 100, Eudragit L 100 from Evonik Health Care, Germany and Eudragit RSPO from Yarrow Chem. Products, Mumbai, remaining ingredients were from SD Fine chemicals, Mumbai, India.

Drug excipient compatibility studies

The compatibility of drug excipients was tested using a Perkin-Fourier Transform Infrared Spectrophotometer to ensure a satisfactory blend of physical and chemical characteristics.[21]

Method of formulation of tablets

Direct compression method was used in the preparation of tablets; all powders were passed through 60 mesh. Required quantities of drug and polymers were mixed thoroughly, magnesium stearate was added as lubricant. Talc was used as glidant. Micro crystalline cellulose was used as diluent. Finally, the powder mix was subjected to compression after mixing uniformly in a polybag. Before compression, the blends were evaluated for several preformulation tests.[21-24] Various blends of formulations are shown in Table 2a and b.

After compression of the tablets, they were subjected to post formulation studies.[25-28]

RESULTS AND DISCUSSION

Drug excipient compatability studies

According to the FTIR spectra of drug [Figure 1] and the drug-excipients mixture, the drug and excipients proved to be compatible [Figure 2]. There was no peak interference or the existence of extra prominent peaks. Peaks in a pure drug's spectrum were compared to peaks in drug and excipients physical mixtures' spectra. In a physical blend with no change in position, the typical IR absorption peaks of esomeprazole were found to remain unaltered. The interaction of the drug with the polymer was ruled out, revealing that the drug was compatible and stable with in the dosage form. This was confirmed in [Figure 2].

Preformulation studies

Tablet powder blend was subjected to various preformulation parameters that results are shown in Table 3. The bulk density of all the formulations was found to be in the range of 0.48 ± 0.07–0.56 ± 0.02 (g/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.52 ± 0.05–0.63±0.04 showing that the powder has good flow properties. The Hausner's ratio ranging between 0.94 ± 0.06 and 1.14 ± 0.08 indicating the powder has good flow properties. The Carr's index of all the formulations was found to be in the range of 11.14 ± 0.05–16.98 ± 0.08. The angle of repose of all the formulations was found to be in the range of 23°.36' ± 0.36–27°.79' ± 0.79. All these value indicates that the powder blend has good flow properties.

Post compressional parameters: [Table 4]

Appearance

The tablets were observed visually and did not show any defect such as capping, chipping, and lamination.

Physical characteristics

The physical characteristic of esomeprazole controlled-release tablets (F1 to F19) such as weight variation, hardness, friability, thickness, and drug content was determined and results of the formulations (F1 to F19) found to be within the limits specified in official books.

Weight variation

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for

Table 1: Modified drug deliveries

Route of administration	Drug product	Examples	Comments
Oral drug products	Extended-release	Diltiazem HCl extended-release	Once-a-day dosing.
	Delayed-release	Mesalamine delayed-release	Coated for drug release in terminal ileum.
	Oral mucosal drug delivery	Oral transmucosal fentanyl citrate	Fentanyl citrate is in the form of a flavored sugar lozenge that dissolves slowly in the mouth.
Ophthalmic drug delivery	Insert	Controlled-release pilocarpine	Elliptically shaped insert designed for continuous release of pilocarpine following place mention the cul-de-sac of the eye.
Parenteral drug delivery	Intramuscular drug products	Depot injections	Lyophilized microspheres Containing leuprolide acetate for depot suspension.
		Water immiscible injections	Medroxy progesterone acetate (Depo-Provera®)
	Subcutaneous drug products	Controlled-release insulin	Basculin is a controlled-release, recombinant human insulin delivery.
Transdermal drug delivery systems	Transdermal therapeutic system (TTS)	Clonidine transdermal therapeutic system	Clonidine TTS is applied every 7 days to intact skin on the upper arm or chest.
	Iontophoretic drug delivery		Small electric current moves charged molecules across the skin.

Table 2a: Compositions of esomeprazole CR tablets

S. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Esomeprazole	20	20	20	20	20	20	20	20	20
2.	Eudragit S 100	20	40	-	-	-	--	20	20	-
3.	Eudragit L 100	-	-	20	40	-		20	--	20
4.	Eudragit RSPO	-	-	-	--	20	40	-	-	-
5.	Talc	3	3	3	3	3	3	3	3	3
6.	Magnesium Sterate	3	3	3	3	3	3	3	3	3
7.	Di Calcium Phosphate	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
8.	Total weight	100	100	100	100	100	100	100	100	100

Table 2b: Compositions of esomeprazole CR tablets

S. No.	Ingredients (mg)	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19
1.	Esomeprazole	20	20	20	20	20	20	20	20	20	20
2.	Eudragit RS 100	20	15	-	-	20	30	15	-	-	-
3.	Eudragit RL 100	-	15	20	40	-	-	20	30	15	20
4.	Eudragit RLPO	-	-	-	--	-	-	-	-	20	15
5.	Talc	3	3	3	3	3	3	3	3	3	3
6.	Magnesium stearate	3	3	3	3	3	3	3	3	3	3
7.	Di calcium phosphate	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
8.	Total weight	100	100	100	100	100	100	100	100	100	100

each tablet. Average weight of the tablet is approximately in range of 98.4 ± 0.53–101.6 ± 0.86, so the permissible limit is ±7.5% (more than 80 mg <250 mg). The tablet weights were within the pharmacopoeial specifications.

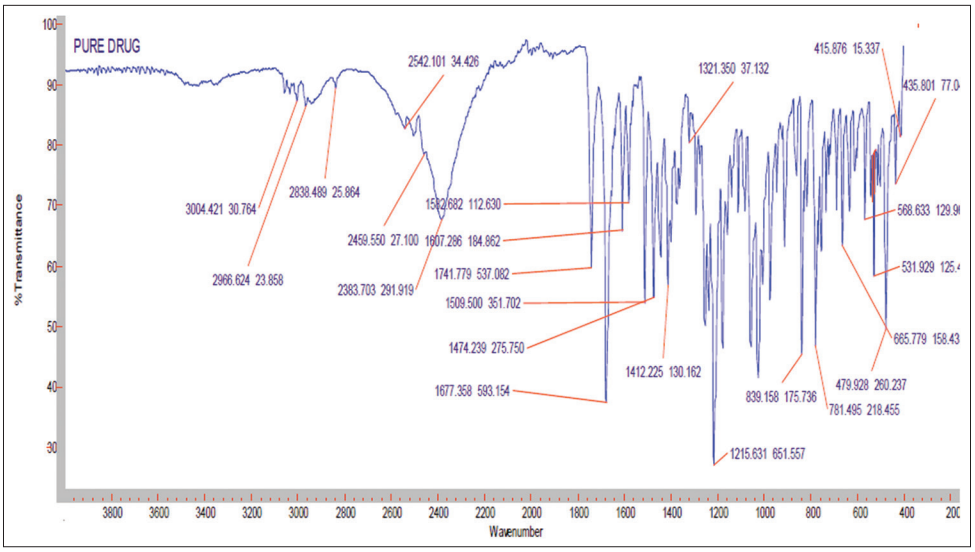

Figure 1: FTIR spectrum of esomeprazole pure drug

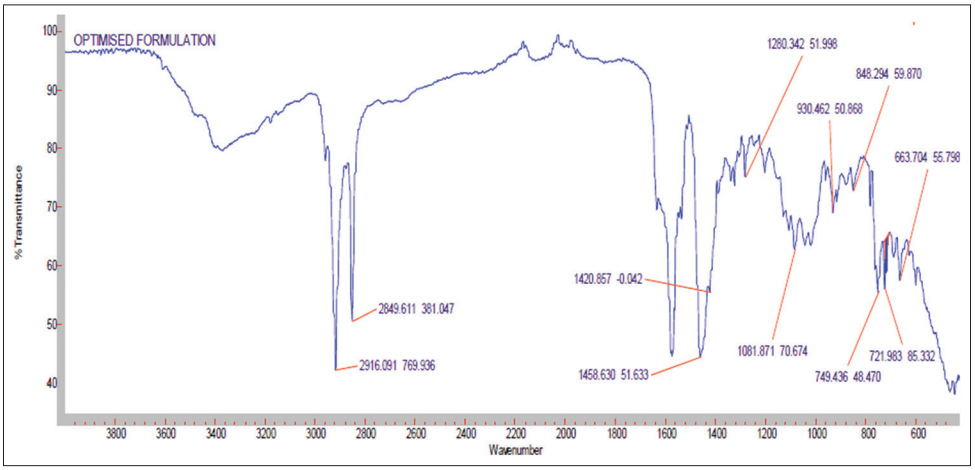

Figure 2: FTIR spectrum of esomeprazole optimized formulation

Tablet hardness

Hardness of the three tablets of each batch was checked using Monsanto hardness tester. The results showed that the hardness of tablets was found to be in the range of 3.3 ± 0.11–4.5 ± 0.41 kg/cm^2. This indicates good tablet strength.

Percent friability

Percentage friability of all the formulations was found to be in between 0.49 ± 0.33 and 0.75 ± 0.66%. This indicated good handling property of the prepared CR tablet.

Dimension (diameter and thickness)

Thickness and diameter specifications may be set on an individual product basis. Excessive variation in the tablet thickness and diameter can result in problems with packaging as well as consumer acceptance. The size (diameter) of the tablets of all formulations was found to be 6.0 ± 0.0 mm and thickness ranged between 3.3 ± 0.61 and 4.9 ± 0.57.

Drug content

The content of active ingredients in the formulation was found to be between 98.59 ± 0.25 and 99.74 ± 0.64 % w/w, which is within the specified limit as per IP (i.e., 90–110% w/w).

All the parameters such as weight variation, friability, hardness, thickness, and drug content were found to be within limits.

In vitro dissolution studies of esomeprazole controlled-release tablets: [Figures 3-6]

The prepared esomeprazole CR tablets were evaluated for the dissolution studies in acid buffer (pH-1.2) for 2 h, 4.5 pH acetate buffer for 2 h, 6.8 pH phosphate buffer for 8 h, and 7.4 pH phosphate buffer for 12 h % drug release that was calculated at various time intervals.

To prepare, the different controlled-release formulations of esomeprazole tablets with different polymers like

Table 3: Preformulation studies of esomeprazole powder blend

Formulation code	Bulk density (g/cm^3)*	Tapped density (g/cm^3)*	Hausner ratio (HR)*	Carr's index (CI)*	Angle of repose (θ)*
F1	0.51±0.02	0.53±0.03	0.98±0.05	15.96±0.08	24°.13'±0.64
F2	0.50±0.03	0.54±0.06	1.03±0.06	16.18±0.04	23°.36'±0.36
F3	0.49±0.09	0.57±0.04	1.08±0.09	14.68±0.07	24°.69'±0.62
F4	0.52±0.07	0.53±0.06	1.01±0.03	16.59±0.09	25°.26'±0.71
F5	0.53±0.07	0.58±0.05	1.1±0.07	15.84±0.06	24°.98'±0.58
F6	0.54±0.02	0.55±0.08	1.10±0.08	14.98±0.02	24°.12'±0.54
F7	0.55±0.08	0.58±0.03	0.94±0.06	15.98±0.04	23°.86'±0.87
F8	0.56±0.02	0.63±0.04	1.14±0.08	14.84±0.03	25°.02'±0.22
F9	0.54±0.03	0.53±0.04	1.09±0.03	16.98±0.08	24°.98'±0.35
F10	0.49±0.01	0.53±0.09	0.98±0.07	13.98±0.03	25°.64'±0.63
F11	0.48±0.07	0.52±0.05	1.11±0.04	14.54±0.06	27°.79'±0.79
F12	0.50±0.02	0.54±0.03	1.12±0.06	15.34±0.03	26°.98'±0.25
F13	0.49±0.03	0.61±0.07	1.1±0.05	13.52±0.02	24°.63'±0.11
F14	0.47±0.08	0.57±0.02	0.99±0.03	12.34±0.05	26°.35'±0.73
F15	0.51±0.07	0.59±0.04	1.12±0.07	14.63±0.02	27°.19'±0.59
F16	0.50±0.05	0.56±0.06	1.14±0.06	11.14±0.05	25°.23'±0.34
F17	0.49±0.01	0.59±0.09	1.12±0.08	12.34±0.03	26°.55'±0.27
F18	0.50±0.06	0.58±0.04	1.11±0.06	13.43±0.06	24°.99'±0.13
F19	0.49±0.03	0.55±0.07	0.99±0.02	12.39±0.01	25°.45'±0.45

Table 4: Post compressional parameters of esomeprazole tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm2)	Friability (%)	Thickness (mm)	Drug content (%)
F1	100±0.48	4.5±0.41	0.50±0.13	3.8±0.29	99.17±0.73
F2	101.4±0.86	4.1±0.23	0.59±0.48	4.1±0.24	98.96±0.36
F3	99.1±0.86	3.9±0.16	0.61±0.29	3.4±0.14	99.74±0.64
F4	101.6±0.86	3.5±0.39	0.75±0.66	4.9±0.57	98.96±0.11
F5	98.9±0.11	4.2±0.22	0.56±0.25	3.9±0.35	99.59±0.35
F6	99.8±0.32	4.4±0.56	0.65±0.18	4.1±0.23	99.87±0.13
F7	98.4±0.53	3.8±0.12	0.59±0.74	3.4±0.24	98.85±0.37
F8	101.3±0.42	3.3±0.11	0.49±0.33	3.3±0.61	99.36±0.31
F9	99.1±0.44	3.8±0.37	0.57±0.37	3.5±0.27	99.61±0.44
F10	101±0.52	3.7±0.25	0.64±0.42	3.9±0.65	98.67±0.76
F11	99.2±0.43	4.2±0.62	0.59±0.52	4.2±0.45	99.56±0.52
F12	99.5±0.72	3.9±0.53	0.67±0.76	3.8±0.17	98.59±0.25
F13	101.2±0.21	3.7±0.18	0.64±0.17	4.7±0.89	99.62±0.29
F14	98.8±0.82	4.1±0.52	0.59±0.44	3.6±0.42	99.42±0.27
F15	101.2±0.23	3.9±0.47	0.66±0.52	4.2±0.59	98.95±0.26
F16	99.1±0.71	4.2±0.24	0.65±0.46	3.7±0.62	99.46±0.52
F17	101.5±0.65	3.8±0.43	0.56±0.52	3.8±0.55	99.59±0.56
F18	99.5±0.65	3.9±0.53	0.59±0.19	3.7±0.74	99.68±0.96
F19	100.3±0.89	4.1±0.71	0.57±0.34	3.9±0.28	98.97±0.35

polymethacrylates such as Eudragit-S100, L-100, RSPO, RS-100, RL-100, RLPO, and Talc is glidant, magnesium stearate is lubricant and Di. Calcium phosphate was used as diluents by direct compression method.

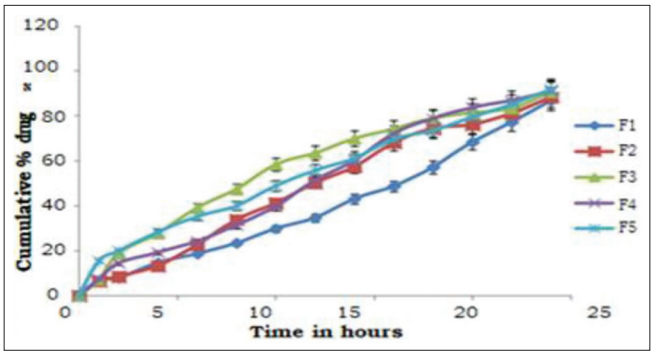

Figure 3: Dissolution graphs for the formulations F1 to F5

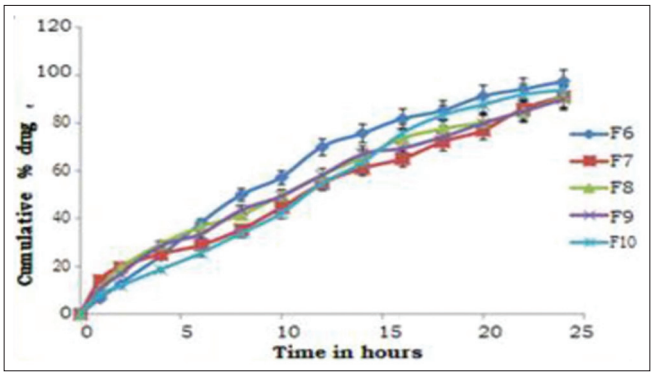

Figure 4: Dissolution graphs for the formulations F6 to F10

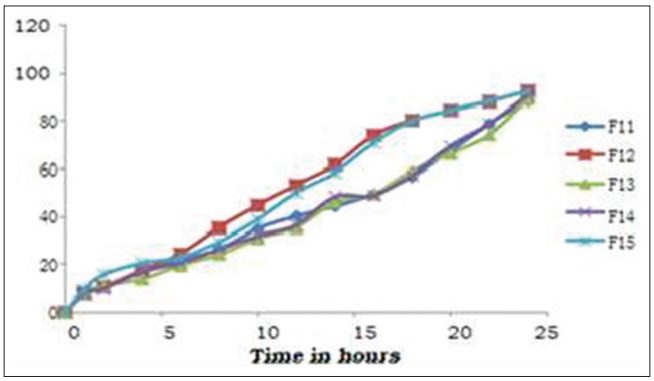

Figure 5: Dissolution graphs for the formulations F11 to F15

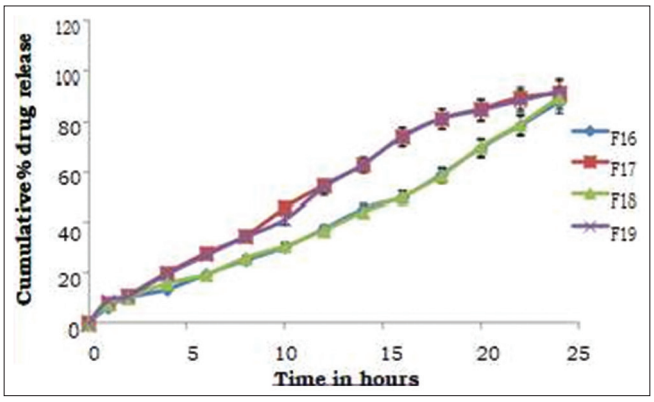

Figure 6: Dissolution graphs for the formulations F16 to F19

Formulation F1 and F2 containing Eudragit-S100. The Formulation F1 and F2 have shown cumulative % drug release of 86.77 ± 0.28% and 88.27 ± 0.45%, respectively, at the end of 24th h. Formulation F3 and F4 containing Eudragit-L100. The Formulation F3 and F4 have shown drug release of 90.67 ± 0.96% and 91.03 ± 0.25%, respectively, at the end of 24th h.

Formulation F5 and F6 containing Eudragit-RSPO. The Formulation F5 and F6 have shown drug release of 91.93 ± 0.54% and 97.47 ± 0.97 %, respectively, at the end of 24th h. Formulation F7 containing combination of Eudragit-S100 and Eudragit-L100.

The Formulation F7 has shown drug release of 91.12 ± 0.78 % at the end of 24th h. Formulation F8 containing Eudragit-S100. The Formulation F8 has shown drug release of 90.87 ± 0.84 % at the end of 24th h. Formulation F9 containing combination of Eudragit-L100 and Eudragit-RSPO. The Formulation F9 has shown drug release of 89.98 ± 0.97 % at the end of 24th h.

Formulation F10 containing Eudragit-RS100. The Formulation F10 has shown drug release of 93.82 ± 0.24 % at the end of 24th h. Formulation F11 containing combination of Eudragit-RS100 and Eudragit-RL100. The Formulation F11 has shown drug release of 88.29 ± 0.34% at the end of 24th h. Formulation F12 and F13 containing Eudragit-RL100. The Formulation F12, F13 has shown drug release of 92.61 ± 0.65% and 89.13 ± 0.43%, respectively, at the end of 24th h.

Formulation F14 and F15 containing Eudragit-RS100. The Formulation F14 and F15 has shown drug release of 90.77 ± 0.98% and 92.47 ± 0.33%, respectively, at the end of 24th h. Formulation F16 containing combination of Eudragit-RS100 and Eudragit-RL100. The Formulation F16 has shown drug release of 87.93 ± 0.45% at the end of 24th h. Formulation F17 containing Eudragit-RL100.The Formulation F17 has shown drug release of 91.43 ± 0.28% at the end of 24th h.

Formulation F18 and F19 containing combination of Eudragit-RL100 and Eudragit-RLPO. The Formulation F18 and F19 have shown drug release of 89.79 ± 0.74% and 92.12 ± 0.25%, respectively, at the end of 24th h.

The results of drug release shown that the esomeprazole was released in a controlled behavior from all the formulations, where formulation F-6 showed maximum cumulative % drug release, that is, 97.47 ± 0.97 at the end of 24th h which was the intent of the finalized formulation while others being not reached to the time point of maximum release still extending the release.

CONCLUSION

Esomeprazole is a proton pump inhibitor used to treat gastroesophageal reflux disease. It has a short biological half-life (1–1.5 h), poor bioavailability (50–68%), and narrow

therapeutic index. Based on all the parameters Esomeprazole was chosen as a good candidate for controlled drug delivery systems. The current research work envisaged was an attempt to development of controlled-release formulations of esomeprazole to improve bioavailability. Developed formulations are deliberate for *in vitro* dissolution and release kinetic studies. Based on the results, F-6 formulation was chosen as a superlative among all the formulations in the point of drug release and mechanism.

REFERENCES

1. Jain NK. Controlled and Novel Drug Delivery. 1st ed. New Delhi: CBS; 1997. p. 1-26.
2. Loyd V. Allen and Howard Delivery Systems. 10th ed. Netherlands: Wolters Kluwer; 2014. p. 263-98.
3. Chien YW. Novel Drug Delivery Systems. New York: Marcel Dekker Inc.; 2007. p. 139-96.
4. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. New Delhi: CBS Publications; 2009. p. 430-56.
5. Mansuri NS, Parejiya PB, Soniwala MM. Glimpse of drug delivery systems for proton pump inhibitors. Int J Pharm Sci Rev Res 2016;36:81-8.
6. Kumar PR, Doddayya H, Reddy SR. Enteric coated tablets of novel proton pump inhibitor with super disintegrants design, *in-vitro* evaluation and stability studies. J Appl Pharm Sci 2011;1:106-11.
7. Varma MM, Kumar MS. Formulation and evaluation of matrix tablets of ropinirole hydrochloride for oral controlled release. Indian J Pharm Pharmacol 2015;2:27-42.
8. Dewan I, Jahan SA, Gazi M, Nath J, Asaduzzaman M, Al-Hasan M. Design, preparation, evaluation, compatibility and *in-vitro* studies of naproxen and esomeprazole multilayer tablets: Layer by layer tablet technology. World J Pharm Res 2015;4:472-92.
9. Asija R, Sharma D, Kumawat J. Formulation and evaluation of mucoadhesive microsphere of esomeprazole. Int J Pharm Res Bio Sci 2014;3:89-116.
10. Majeed SM, Khalil YI. Formulation and evaluation of bilayer matrix tablets of amoxicillin and esomeprazole as an oral modified release dosage form for treatment of peptic ulcer. Int J Pharm Pharm Sci 2014;6:134-42.
11. Singh P, Bajaj A, Apsegaonkar P. Design development and evaluation of matrix tablets of ambroxol hydrochloride: *In vitro in vivo* study. Int J Pharm Pharm Sci 2014;6:445-9.
12. Naik RN, Potti LR, Mogali RK, Rao MP, Sivasankar R, Valli B. Formulation and evaluation of esomeprazole magnesium dihydrate multiple unit particulate system (pellets) as a delayed release dosage forms. Int J Res Dev Pharm Life Sci 2014;3:935-42.
13. Vivekananda A, Babu CH, Krishna TV. Formulation and evaluation of esomeprazole magnesium micropellets. Int J Res Pharm Nano Sci 2014;3:491-500.
14. Rukari TG, Ahire GV. Formulation and evaluation of esomeprazole delayed release tablets. Asian J Pharm Clin Res 2013;6:121-5.
15. Banerjee ND, Singh SR. Formulation and evaluation of compression coated tablets of Cefpodoxime proxetil. Int J Pharma Sci Res 2013;4:104-12.
16. Srinivasulu M, Ahad HA, Venupriya R. Formulation and evaluation of natural gum based esomeprazole sustained released tablets. Int J Adv Pharm 2013;3:78-83.
17. Kishanrao CG, Harsha SN, Kumar DY, Neelima KS, Sambamoorthy U. Formulation and evaluation of colon specific matrix tablets of Esomeprazole. Int J Curr Trends Pharm Res 2013;1:217-24.
18. Nalluri BN, Jyotheermayi D, Anusha D, Maheswari KM. Controlled release tablet formulations of carvedilol. J Chem Pharm Res 2012;4:4266-74.
19. Reddy DS, Rao BP. Development and *in vitro-in vivo* evaluation of controlled release matrix tablets of desvenlafaxine. Pharmacol Pharm 2012;3:15-9.
20. Yehia SA, Elshafeey AH, ElMeshad A, Al-Bialey HA. A pharmaceutical study on different approaches for itopride hydrochloride sustainment: *In-vitro* and *in-vivo* evaluation. J Chem Pharm Res 2012;4:1398-412.
21. Halder S, Shuma ML, Kabir AK, Rouf AS. *In vitro* release kinetics study of esomeprazole magnesium Trihydrate tablet available in Bangladesh and comparison with the originator brand (Nexium®). Stamford J Pharm Sci 2011;4:79-83.
22. Purohit A, Jain A, Patel SS, Sharma A. Formulation and evaluation of cephalexin extended release tablets. Int J Pharm Life Sci 2011;2:606-9.
23. Kumar DV, Kumar O, Premalatha A, Ramesh KV, Kumar MR. Formulation and evaluation of Deflazacort controlled release tablets. Der Pharm Sin 2011;2:78-86.
24. Syed IA, Narsu ML, Rao YM. *In-vitro* release kinetics and bio availability of oral controlled release layered matrix tablets of diltiazem hydrochloride. Int J Drug Dev Res 2011;3:234-41.
25. Kibria G, Roni MA, Jalil RU. *In-vitro* studies of controlled release alfuzosin matrix tablets prepared with ethyl cellulose and hydroxy propyl methyl cellulose. Iran J Pharm Sci 2009;5:59-68.
26. Keny RV, Mankame SA, Lourenco CF. Formulation-and-evaluation-of-once-daily-minocycline-hydrochloride-extended-release-matrix-tablets. Indian J Pharm Sci 2009;71:295-302.
27. Paudel A, Shrestha ST, Pandey YR, Shrestha SC. Formulation and *in-vitro* evaluation of bupropion hydrochloride controlled release tablet. Int J Pharm Sci Res 2014;5:2783-90.
28. Gowda DV, Ram AS, Venkatesh MP, Khan S. Development and evaluation of Clozapine pellets for controlled release. Int J Res Ayurveda Pharm 2012;3:611-8.

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