RESEARCH ARTICLE

INTERNATIONAL JOURNAL OF PHARMACEUTICAL TECHNOLOGY LETTERS

13(1) (2023) 9-16

OPEN ACCESS

Design and evaluation of gastroretentive mucoadhesive tablets of furosemide

Ganesh Kumar Gudas[1*], Kola Venu[2], Santhosh Kumar Chinnaiyan[3]

Abstract

The present investigation concerns the development of mucoadhesive tablets of Furosemide which were designed to prolong the gastric residence time after oral administration. Matrix tablets of Furosemide were formulated using different mucoadhesive polymers such as Carbopol 934 P, Hydroxyl Propyl Methyl Cellulose (HPMC) K100M Sodium Carboxy methyl cellulose (SCMC) in various ratios for treatment of hypertension. Currently hypertension has become a common problem in all over the world, due to effectiveness and intensive use of Furosemide as a drug of choice in the treatment of hypertension and congestive heart failure, development of oral sustained release dosage form of Furosemide has been an interested topic of research for a long period of time. The tablets were evaluated for various parameters such as compatibility studies, drug content, weight variation, hardness, thickness, friability, swelling studies, in vitro drug release studies, in vitro mucoadhesion strength ,Ex vivo residence time test and release rate kinetics. The in vitro release kinetics studies reveal that all formulations fits well with Zero order, followed by Korsmeyer-Peppas, Higuchi and the mechanism of drug release is erosion. After analysis of different evaluation parameters and drug release kinetics, formulation code F12 was selected as a promising formulation for delivery of Furosemide as a mucoadhesive Gastroretentive tablet with best mucoadhesive strength and 98.93% drug release at 12th hour. Stability studies of the selected formulation was carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 40°C/75% RH for 90days. There was no significant change in the physical property and weight variation, hardness, thickness, friability, in vitro drug release studies, in vitro mucoadhesion strength drug content during the study period.

Keywords: Furosemide, Gastro-retentive tablet, Mucoadhesive tablets, Swelling Index.

Author Affiliation: [1] Department of Pharmaceutics, Srikrupa Institute of Pharmaceutical Sciences, Siddipet - 502277, India.
[2] Department of pharmacy, Dr. N J Paulbudhe college of pharmacy -641021, Tamil nadu, India.
[3] Faculty of pharmacy, Karpagam academy of higher education, Eachaanari, Coimbatore-641021, Tamil nadu, India
Corresponding Author: Ganesh Kumar Gudas. Department of Pharmaceutics, Srikrupa Institute of Pharmaceutical Sciences, Siddipet - 502277, India.
Email: gkganeshpharmaco@gmail.com
How to cite this article: Ganesh Kumar Gudas, Kola Venu, Santhosh Kumar Chinnaiyan, (2023). Design and Evaluation of Gastroretentive Mucoadhesive Tablets of Furosemide, 13(1) 9-16.Retrieved from https://ijptl.com/index.php/journal
Received: 19 February 2023 **Revised:** 27 March 2023 **Accepted:** 28 March 2023

1. Introduction

One of the novel approaches for drug delivery system is Gastro-retentive delivery system (GRDS). Prolonging the gastric retention of a delivery system are desirable for achieving therapeutic benefit of drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT) or that are less soluble in GIT or are degraded by the alkaline. GRDS are thus beneficial for such drugs by improving their bioavailability, therapeutic efficacy and by possible reduction of dose. had first introduce the term "Bioadhesion". Bioadhesive polymers are platforms for oral controlled drug delivery method to study bioadhesion has been studied extensively in the last decade and applied to improve the performance of these drug delivery systems [1].

Mucoadhesive controlled release dosage formulations have gained considerable attention due to their ability to adhere to the mucus layer and release the drug in a sustained manner. The relevant routes of mucoadhesive formulations have involved nasal, gastrointestinal, buccal, ocular, vaginal and rectal ways. By using these dosage forms, the intimate contact time with the mucus surface would increase, thus resulting in an increased drug retention time and drug concentration in the local sites. This would lead to an improved therapeutic effect for the local diseases. [5,6] Mucoadhesive delivery systems offer several advantages over other oral controlled release (CR) systems by virtue of prolongation of residence time of drug in GIT, and targeting and localization of the dosage form at a specific site. Mucoadhesive polymers are able to interact with mucus which is secreted by

the underlying tissue. More specifically, it is predicted that such polymers interact with mucus glycoprotein, called mucins, which are responsible for gel-type characteristics of the mucus. Mucoadhesive polymers can increase the contact time with the mucosal tissue and moreover, also increase directly drug permeability across epithelial barriers [2].

Furosemide, an antihypertensive agent, has been widely used for the treatment of hypertension and congestive heart failure. Furosemide, like other loop diuretics, acts by inhibiting the luminal Na-K-Cl cotransporter in the thick ascending limb of the loop of Henle, by binding to the chloride transport channel, thus causing sodium, chloride, and potassium loss in urine. The action on the distal tubules is independent of any inhibitory effect on carbonic anhydrase or aldosterone; it also abolishes the corticomedullary osmotic gradient and blocks negative, as well as positive, free water clearance. Because of the large NaCl absorptive capacity of the loop of Henle, diuresis is not limited by development of acidosis, as it is with the carbonic anhydrase inhibitors. Furosemide is acid stable and completely absorbed in gastric pH. It has been reported, that the duration of antihypertensive action after a single oral dose of Furosemide is only 6–8 h, biological half life is 2-3 h and bioavailability in the stomach is 43- 46%. The pKa value is 4.5. Hence, as the pH increases, it becomes unstable and undergoes a degradation reaction and thus reducing its bioavailability 10-12%. Water-soluble drugs are considered difficult to deliver in the form of sustained or controlled release preparation due to their susceptibility to ''dose dumping phenomenon.'' Attempts have been made to regulate their release process by use of mucoadhesive polymers in order to achieve a once-a-day dose treatment [3]. The current study aims at developing and evaluating oral mucoadhesive drug delivery system of Furosemide, as it may prove to be more productive than the conventional CR systems by virtue of prolongation of drug residence time in GI tract. Furosemide exhibits pH dependent degradations and is more stable in acidic pH compared to neutral or alkaline pH conditions. Hence, an attempt was made to develop mucoadhesive tablets of Furosemide which would increase the bioavailability of Furosemide. The prepared tablets were evaluated for physical properties (thickness, weight variation, friability and hardness), swelling index, bio adhesion test, in vitro drug release and accelerated stability studies.

2. MATERIALS AND METHODS:

Materials:

The Furosemide was obtained as a gift sample from Aurbindo Pharma Ltd., Aurangabad. Sodium Carboxy Methyl Cellulose, Hydroxyl propyl methyl cellulose (HPMC) and Carbopol-934P were obtained from S.D. fine, Hyderabad.

Method of preparation of Mucoadhesive oral tablets:

Mucoadhesive gastrointestinal tablets were formulated by direct compression method. All the ingredients of the formulation were passed through sieve no 60 and were blended in a mortar with a pestle to obtain uniform mixing. The blended powder was then evaluated for precompression parameters. The blended powder of the core was compressed on 8mm punch in a single stroke multi station tablet punching machine was removed. It was shown in Table 1. The formulations are made by using design of experiment method (factorial designs) Study type: Response surface; Design type: central composite; Design mode: quadratic

Evaluation of Mucoadhesive Tablets

Physical parameters & In vitro Swelling studies

Tablets were tested for hardness, friability, weight variation and drug content. Hardness of the tablets was tested using a Monsanto hardness tester and Friability of the tablets was determined in a Roche friabilator, In vitro Swelling studies, In vitro Mucoadhesion study.

The degree of swelling of mucoadhesive polymer is an important factor affecting adhesion. For conducting the study, a tablet was weighed and placed in a petri dish containing 5 ml of 0.1 N Hcl buffer pH 1.2 in 6 hrs at regular intervals of time (1, 2,4 and 6hrs) the tablet was taken carefully by using filter paper. The swelling index was calculated using the following formula

Swelling Index (S.I) = (Wt-Wo)/Wo×100

Where S.I = swelling index, Wt = weight of tablet after swollen at time t Wo= weight of the initial tablet.

In vitro Mucoadhesion study:

Mucoadhesion strength of the tablets was measured on a modified two-arm physical balance. The sheep gastric mucosa was used as biological membrane for the studies. The sheep gastric mucosa was obtained from the local slaughter house and was used within 3hours of procurement. The membrane was washed with distilled water and then with 0.1N HCl buffer pH 1.2 at 37 ºC. The sheep gastric mucosa was cut into pieces and washed with 0.1N HCl buffer pH 1.2 The left pan of physical balance was removed. To the left arm of balance, a thick thread of suitable length was hung. To the free end of thread attach a glass stopper of circular base (diameter 2.5 cm). A clean 250 ml beaker was placed below the glass stopper. A piece of gastric mucosa was tied to the glass vial, which was filled with 0.1N HCl buffer. The glass beaker was tightly fitted into a glass beaker filled with 0.1 N HCl buffer pH 1.2 at 37±0.5 0C, so that it just touches the mucosal surface. The tablet was suck to the lower side of a rubber stopper. The two sides of the balance were made equal before the study. By keeping a 5gm weight on the right hand pan. A weight of 5gm was removed from the right hand pan which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 1 min contact time.

Table 1: Formulations F1 – F14 of Mucoadhesive Tablets of Furosemide

Formulation code	Furosemide	Na CMC	HPMC K100M	Carbopol 934P	Di calcium phosphate	Aerosil	Total weight
F1	40	0	50	0	102	8	200
F2	40	20	25	15	92	8	200
F3	40	0	50	30	72	8	200
F4	40	40	0	0	112	8	200
F5	40	0	0	0	152	8	200
F6	40	0	25	25	92	8	200
F7	40	40	50	50	12	8	200
F8	40	20	0	0	132	8	200
F9	40	20	50	50	32	8	200
F10	40	0	25	25	102	8	200
F11	40	40	0	50	62	8	200
F12	40	40	25	25	62	8	200
F13	40	20	50	50	38	8	200
F14	40	0	0	0	152	8	200
F15	40	20	25	25	82	8	200
F16	40	0	50	50	52	8	200
F17	40	0	25	25	102	8	200
F18	40	20	0	0	132	8	200
F19	40	20	0	0	132	8	200
F20	40	40	25	25	62	8	200
F21	40	0	50	50	52	8	200
F22	40	40	25	0	87	8	200
F23	40	20	50	50	32	8	200
F24	40	40	0	0	112	8	200
F25	40	0	0	0	152	8	200
F26	40	40	0	0	112	8	200
F27	40	20	25	25	82	8	200

Mucoadhesive strength was assessed in terms of weight (gm) required to detach the tablet from the membrane. The mean value of three trials was taken for each tablet. Mucoadhesive strength which was measured as force of adhesion in Newton's. The following formula was used and the results are shown in table

Force of adhesion (N) =Mucoadhesive strength / 100×9.81

In-vitro Dissolution study

The USP dissolution test apparatus (apparatus II paddle type) was used to study the drug release from the tablets. The dissolution medium was 900 ml of 0.1N HCl pH 1.2. The release was performed at 37 ± 0.5°C, with a rotation speed of 50 rpm. 5 ml samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through whatmann filter paper and analyzed after appropriate dilution by UV spectrophotometer at 275 nm and drug release was determined from standard curve.

Ex-vivo residence time test:

The disintegration test apparatus is used for the study of Ex-vivo residence time of tablets. The gastric mucosa is collected and is cut in to 2×2 size pieces. These pieces are placed on the glass sides and tied with rubber bands. The formulations are placed on the tissue and kept aside for few minutes. Then all glass slides are fitted to the disintegration test apparatus and the apparatus is allowed to start this process is continued for 12 hours. The residence time of of each formulation is noted as Ex-vivo residence time.

3. RESULT AND DISCUSSION:

It was desirable to deliver such drug in a gastro retentive dosage form or mucoadhesive drug delivery systems which would prolong the gastric residence time of drug delivery thereby giving sufficient time for drug delivery system to release the drug and efficient absorption of active moiety.

Table 2: Post Compression Evaluation Test

Formulation code	Hardness (Kg/cm^2)	% Friability	Weight Variation	Thickness (mm)	Content Uniformity
F1	5.8±0.5|	0.526±	201±0.2	3.37±0.13	98.24±0.8
F2	6.1±0.3	0.748	198±0.7	3.14±0.29	99.12±0.2
F3	5.9±0.1	0.913	200±0.5	3.20±0.34	99.28±0.9
F4	5.7±0.4	0.658	1999±0.3	3.08±0.45	100.66±0.1
F5	5.8±0.6	0.884	200±0.4	3.33±0.76	98.25±0.5
F6	5.9±0.2	0.756	201±0.6	3.24±0.82	99.86±0.9
F7	5.9±0.3	0.562	199±0.2	3.32±0.12	99.78±0.8
F8	5.8±0.5	0.986	198±0.8	3.38±0.14	98.27±0.4
F9	5.7±0.4	0.639	200±0.5	3.00±0.17	99.96±0.9
F10	6.2±0.7	0.914	201±0.8	2.98±0.76	99.03±0.5
F11	5.8±0.3	0.786	199±0.3	3.11±0.31	98.27±0.4
F12	6.3±0.2	0.549	200±0.1	3.06±0.48	100.28±0.8
F13	5.6±0.4	0.613	198±0.4	3.03±0.55	99.33±0.7
F14	5.8±0.2	0.862	199±0.7	3.09±0.17	99.13±0.5
F15	5.4±0.5	0.842	201±0.9	3.18±0.29	99.35±0.8
F16	5.9±0.7	0.654	200±0.4	3.13±0.11	98.29±0.5
F17	6.0±0.2	0.756	198±0.9	3.15±0.17	98.65±0.3
F18	6.2±0.3	0.613	199±0.5	3.46±0.32	99.31±0.8
F19	5.7±0.4	0.426	200±0.3	3.76±0.57	99.53±0.9
F20	5.5±0.9	0.289	201±0.7	3.19±0.73	98.26±0.2
F21	5.4±0.5	0.864	200±0.8	3.32±0.54	99.11±0.4
F22	5.9±0.7	0.569	199±0.2	3.12±0.96	98.04±0.5
F23	6.0±0.5	0.556	199±0.7	3.24±0.17	99.71±0.7
F24	5.4±0.3	0.625	200±0.6	3.19±0.82	99.38±0.2
F25	5.9±0.4	0.846	201±0.4	3.12±0.39	97.56±0.9
F26	5.6±0.7	0.904	200±0.3	3.38±0.45	99.04±0.1
F27	5.8±0.4	0.665	199±0.8	3.17±0.81	98.22±0.8

It was suggested that mucoadhesive drug delivery system are easiest approach for technical and logical point of view among gastro retentive drug delivery system, so for present study mucoadhesive drug delivery system was chosen.Mucoadhesive tablets were evaluated for its physical characteristics; the results are shown in Table 2.

FTIR Studies:

FTIR studies were carried out on drug, excipients and drug-excipient samples. No new peaks were found and hence compatibility between the drug and the excipients was found. It was shown in Fig 1 & 2.

Design of Experiments

This method is mainly used to explain the effect of one factor on other factor. Whether this effect is significant or not. If significant how it influence the response. In this present work the effect of one factor (Carbopol 934 P) on other factors (SCMC, HPMCK100M) is explained. It was shown in Fig 6.

In the above graph the effect of carbopol on % cumulative drug release is examined and it clearly indicates that there is a very significant effect of Carbopol 934P on % cumulative drug release. The formulations with all 3 factors shown % drug release in between 54.62-98.93 %. but when carbopol is removed from the formulations the maximum % CDR is near 62. This is the effect of factor (carbopol) on response.

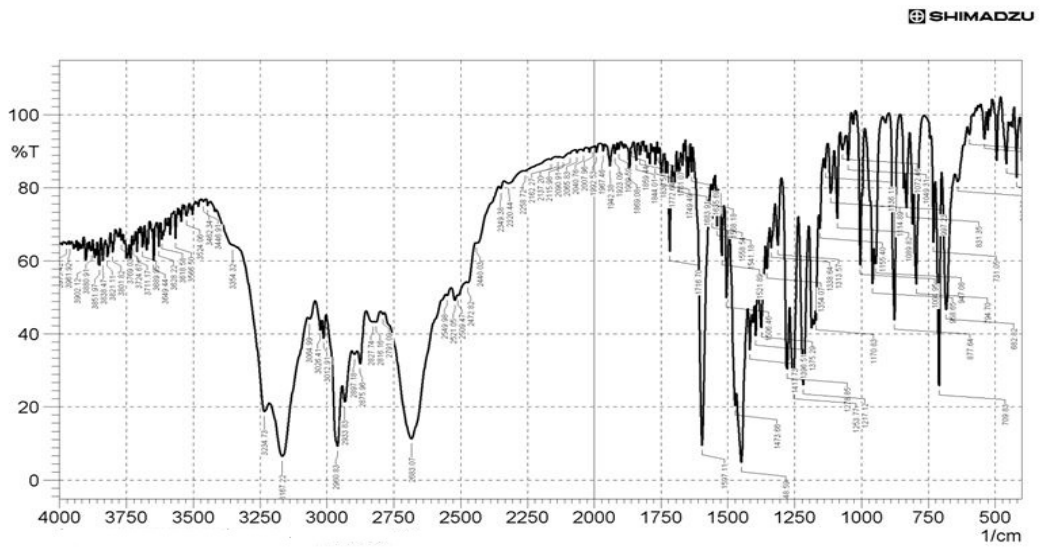

Fig 1: FTIR spectra of Furosemid

There is a small effect of carbopol on Ex vivo residence time of formulations. The formulations without carbopol have shown maximum Ex vivo residence time is nearly 10 hours. It was shown in Fig 7.

There is a negligible effect on mucodhesive strength of formulations because all formulations have excellent mucoadhesive property and there is no influence on mucoadhesive strength by carbopol. It was shown in Fig 8.

Kinetic Data / Model fitting

The in vitro drug release data were fit to different equations and kinetic models to explain the drug release profiles. The coefficient of correlation of each of the kinetics was calculated and compared. The in vitro drug release profile of the optimized formulation of Mucoadhesive buccal tablets i.e. F12 fit to Zero order model. The data was further treated as per Korsmeyer's equation. The slope (n) values obtained by this equation indicated that the drug released by Super case-II Transport dissolution (erosion) mechanism.

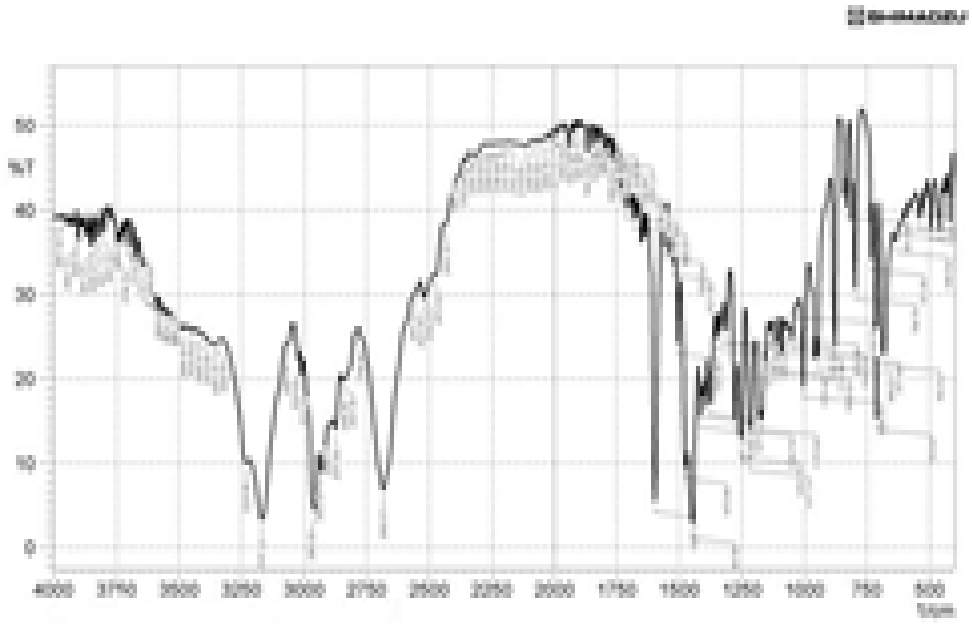

Fig 2: FTIR spectra of optimized formulatione

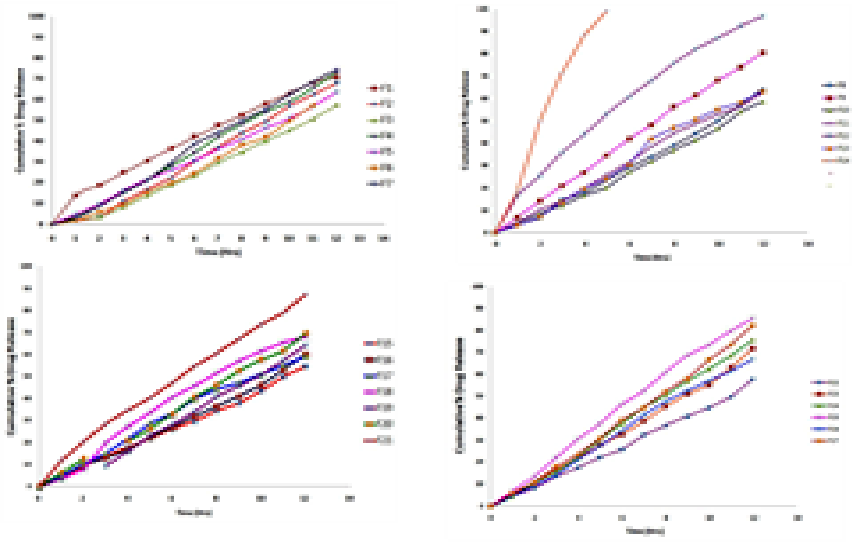

Fig 3: Comparison of in vitro drug release profile of F1 – F27 formulations

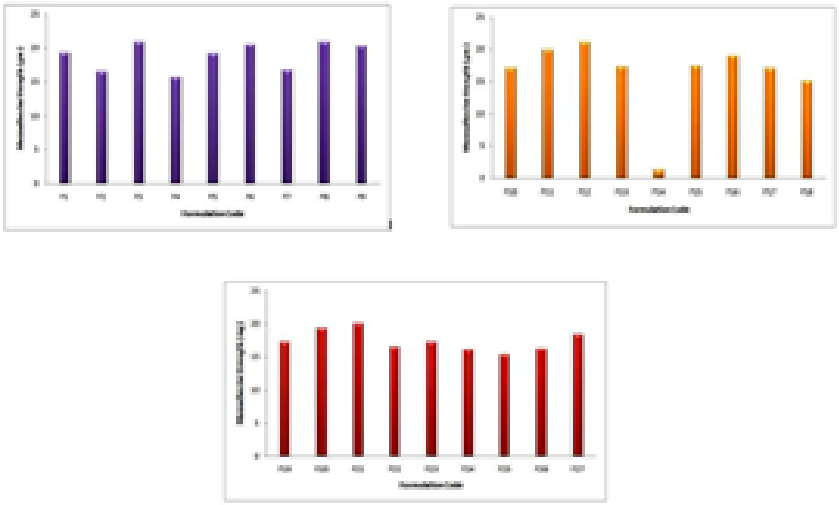

Fig 4: Mucoadhesive Strength Test for F1 – F27 Formulations

Fig 5: Ex-vivo residence time test

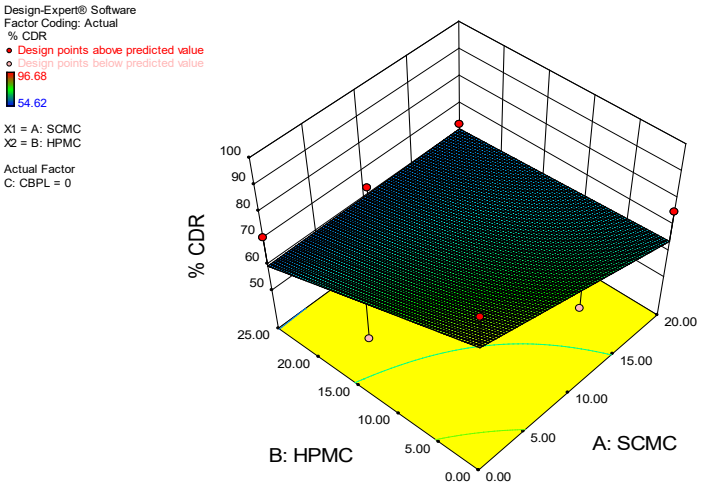

Fig 6: Response surface plot for %CDR

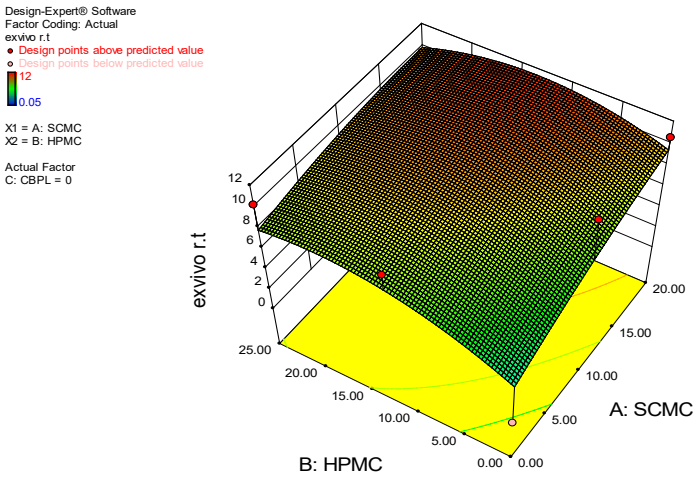

Fig 7: Response surface plot for Ex vivo residence time

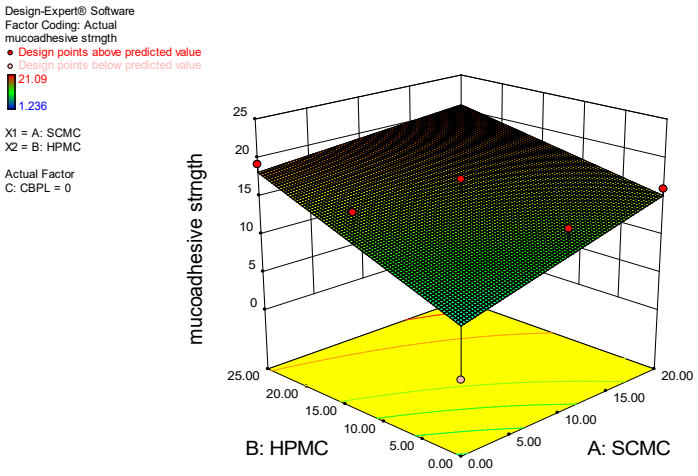

Fig 8: Response surface plot for mucoadhesive strength

CONCLUSION

Furosemide mucoadhesive oral tablets could be formulated using the drug, Carbopol 934P and HPMC K100M, Na CMC with different proportions. It can be seen that there is a synergistic effect when polymers are used in combinations. There is a significant effect of Carbopol 934P in formulations on drug release rate from the tablets and mucoadhesive strength was also increased. The in vitro release kinetics studies reveal that all formulations fits well with Zero order, followed by Korsmeyer-Peppas, Higuchi and the mechanism of drug release is erosion.

From the formulations F1-F27 the formulation F12 was selected as optimized formulation because it showed maximum release and the other properties such as swelling index was also low, mucoadhesion force shown good and the Post and pre compression parameters were found to be within the Pharmacopeial limits.

Acknowledgement

Nill

Funding

No funding was received to carry out this study.

References

1. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlledrelease drug delivery systems for prolonged gastric residence: an overview. Drug Dev Ind Pharm. 1996; 22 (6): 531-539.
2. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Rel. 2000; 63(3): 235–259.
3. Chavanpatil MD, Jain P, Chaudhari S, Shear R, Vavi PR. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. Int J Pharm. 2006; 316(1): 86–92.
4. Park, K. Robinson, J.R. Bioadhesive polymers as platforms for oral-controlled drug delivery: method to study bioadhesion. Int J Pharm. 1984; 19(2): 107–127.
5. Shinde A J. Gastro retentive Drug Delivery System: AnOverview.Pharmainfo.net.2008:6(1):182.
6. Hwang S J. Park H. and Park K.Gastric Retentive Drug-Delivery Systems Critical Reviews in Therapeutic Drug Carrier Systems.1998:15(3):243–284.
7. Whitehead L. Fell J T and Collett J H. Development of a Gastroretentive Dosage Form. Eur. J. Pharm .Sci.1996:4 (1):182.
8. Xiaoling L. and Bhaskara R J. Design of controlled release drug delivery systems. Mc Graw Hill,New York. 2006: 173-176.
9. Deshpande A. A.Rhodes C T. Shah N H and Malick A W. Controlled-release drug delivery systems for prolonged gastric residence: An overview. Drug Dev Ind. Pharm.1996:22 (6):531- 539.
10. Bardonnet P L. Faivre V. Punj W J. Piffaretti J C.and Falson F.Gastroretentive dosage forms: overview and special case of Helicobact pylori. Journal Control Release. 2006:111,1-18.
11. Bernkop A. Mucoadhesive polymers strategies, achievements and future challenges. Adv Drug Deliv Rev.2005: 57, 1553– 1555.
12. Thripathi KD, Essentials of medical pharmacology, 6th edition: 489- 90.
13. Sweetman SC. Ed Martindale: The complete drug reference. 35th Edition Pharmaceutical Press: London 2007; 1250-1253.
14. Raymond J, Rowe C, Paul J Sheskey, sian c owen, editors. Handbook of pharmaceutical excipients 5th ed. London: Pharmaceutical Press; 2009: 118-121, 110-114, 185-188, 94-98.