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FORMULATION AND DEVELOPMENT OF MUCOADHESIVE TABLETS OF CAPTOPRIL

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ABSTRACT

The development of mucoadhesive tablets of captopril which were designed to prolong the gastric residence time after oral administration. Matrix tablets of captopril were formulated using different mucoadhesive polymers such as carbopol 940 p, hydroxyl propyl methyl cellulose (HPMC) K45M, SCMC, RH (Relative Humidity) 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 captopril as a drug of choice in the treatment of hypertension and congestive heart failure, development of oral controlled release dosage form of captopril 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 captopril as a mucoadhesive gastroretentive tablet with best mucoadhesive strength and 96.68% 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: Captopril, gastro-retentive tablet, mucoadhesive tablets, swelling index.

INTRODUCTIÓN

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] Captopril, an antihypertensive agent, has been widely used for the treatment of hypertension and congestive heart failure. Captopril 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 captopril is only 6–8 h, biological half life is 2-3 h and bioavailability in the stomach is 60- 75%. 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 captopril, as it may prove to be more productive than the conventional cr systems by virtue of prolongation of drug residence time in gi tract. Captopril exhibits pH dependant 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 captopril which would increase the bioavailability of captopril. The prepared tablets were evaluated for physical properties (thickness, weight variation, friability and hardness), swelling index, bioadhesion test, *in vitro* drug release and accelerated stability studies.

MATERIALS AND METHODS

MATERIALS

The captopril was obtained as a gift sample from wockhardt ltd., aurangabad. Sodium carboxy methyl cellulose, hydroxyl propyl methyl cellulose (HPMC) and carbopol-940 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.

THE FORMULATIONS ARE MADE BY USING DESIGN OF EXPERIMENT METHOD (FACTORIAL DESIGNS)

- study type: **esponse surface**
- Design type: **central composite**
- Design mode: **quadratic**

Table 1: formulations f1 – f 14 of mucoadhesive tablets of captopril

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**
Captopril	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
Na cmc	**0**	**20**	**0**	**40**	**0**	**0**	**40**	**20**	**20**	**0**	**40**	**40**	**20**	**0**
HPMC k45	**50**	**25**	**50**	**0**	**0**	**25**	**50**	**0**	**50**	**25**	**50**	**25**	**50**	**0**
Carbopol 940p	**0**	**15**	**30**	**30**	**15**	**30**	**15**	**15**	**30**	**0**	**0**	**30**	**0**	**0**
Di calcium Phosphate	**92**	**82**	**62**	**72**	**127**	**87**	**37**	**107**	**42**	**107**	**52**	**37**	**72**	**142**
Aerosil	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**
Total weight	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Ingredients (mg)	**F15**	**F16**	**F17**	**F18**	**F19**	**F20**	**F21**	**F22**	**F23**	**F24**	**F25**	**F26**	**F27**
Captopril	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
Na cmc	20	0	0	20	20	40	40	40	20	40	0	40	20
HPMC k45	25	50	25	0	0	25	50	25	50	0	0	0	25
Carbopol940p	0	15	15	0	30	15	22	0	15	0	30	15	30
DicalciumPhosphate	97	77	102	122	92	62	30	77	57	102	112	87	67
Aerosil	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**
Total weight	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

EVALUATION OF MUCOADHESIVE TABLETS

PHYSICAL PARAMETERS

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

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
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 ^{0}c. 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 ^{0}c, 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. 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 227 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.

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. 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 3.

Table 3: post compression evaluation tests

Formulation code	Hardness (kg/cm^{2})	% friability	Weight variation	Thickness (mm)	Content uniformity
F1	5.8±0.5|	0.526±	249±0.2	3.37±0.13	98.24±0.8
F2	6.1±0.3	0.748	248±0.7	3.14±0.29	99.12±0.2
F3	5.9±0.1	0.913	250±0.5	3.20±0.34	99.28±0.9
F4	5.7±0.4	0.658	249±0.3	3.08±0.45	100.66±0.1
F5	5.8±0.6	0.884	250±0.4	3.33±0.76	98.25±0.5
F6	5.9±0.2	0.756	251±0.6	3.24±0.82	99.86±0.9
F7	5.9±0.3	0.562	249±0.2	3.32±0.12	99.78±0.8
F8	5.8±0.5	0.986	248±0.8	3.38±0.14	98.27±0.4
F9	5.7±0.4	0.639	250±0.5	3.00±0.17	99.96±0.9
F10	6.2±0.7	0.914	251±0.8	2.98±0.76	99.03±0.5
F11	5.8±0.3	0.786	249±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	248±0.4	3.03±0.55	99.33±0.7
F14	5.8±0.2	0.862	249±0.7	3.09±0.17	99.13±0.5
F15	5.4±0.5	0.842	251±0.9	3.18±0.29	99.35±0.8
F16	5.9±0.7	0.654	250±0.4	3.13±0.11	98.29±0.5
F17	6.0±0.2	0.756	248±0.9	3.15±0.17	98.65±0.3
F18	6.2±0.3	0.613	249±0.5	3.46±0.32	99.31±0.8
F19	5.7±0.4	0.426	250±0.3	3.76±0.57	99.53±0.9

Formulation code	Hardness (kg/cm^2)	% friability	Weight variation	Thickness (mm)	Content uniformity
F20	5.5±0.9	0.289	251±0.7	3.19±0.73	98.26±0.2
F21	5.4±0.5	0.864	250±0.8	3.32±0.54	99.11±0.4
F22	5.9±0.7	0.569	249±0.2	3.12±0.96	98.04±0.5
F23	6.0±0.5	0.556	249±0.7	3.24±0.17	99.71±0.7
F24	5.4±0.3	0.625	250±0.6	3.19±0.82	99.38±0.2
F25	5.9±0.4	0.846	251±0.4	3.12±0.39	97.56±0.9
F26	5.6±0.7	0.904	250±0.3	3.38±0.45	99.04±0.1
F27	5.8±0.4	0.665	249±0.8	3.17±0.81	98.22±0.8

All the values are represented as mean ± sd (n=3)

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.

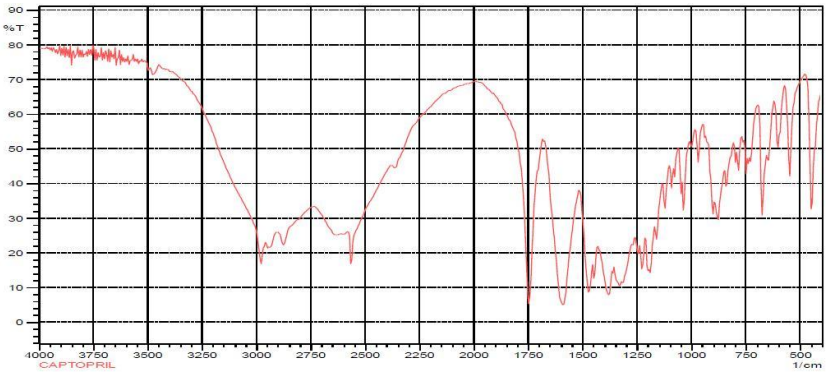

Fig 1: FTIR spectra of captopril

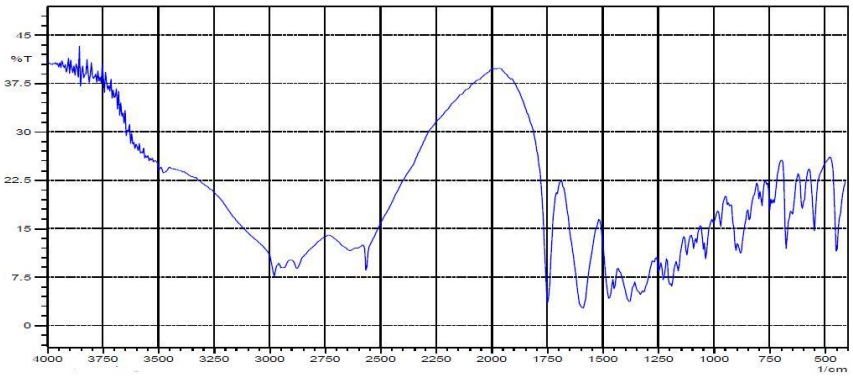

Fig 2: FTIR spectra of optimized formulation

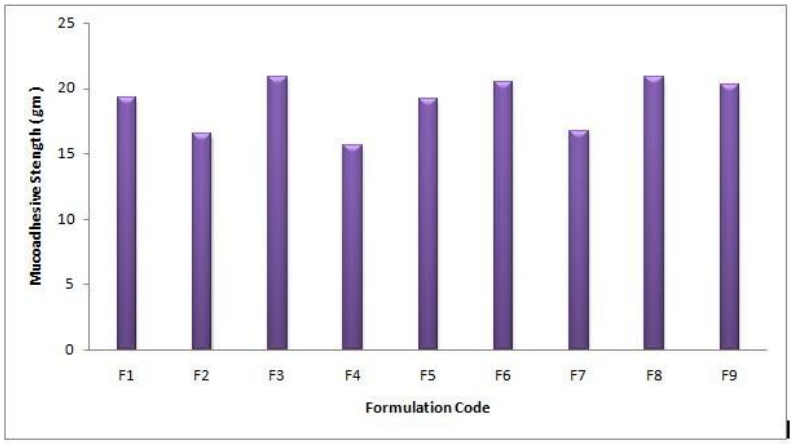

Fig 3: Mucoadhesive strength test for f1 – f9 formulations

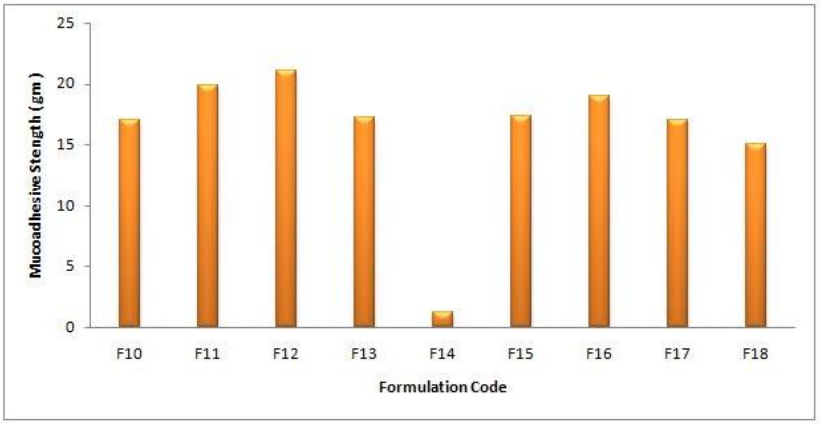

Fig 4: Mucoadhesive strength test for f10 – f18 formulations

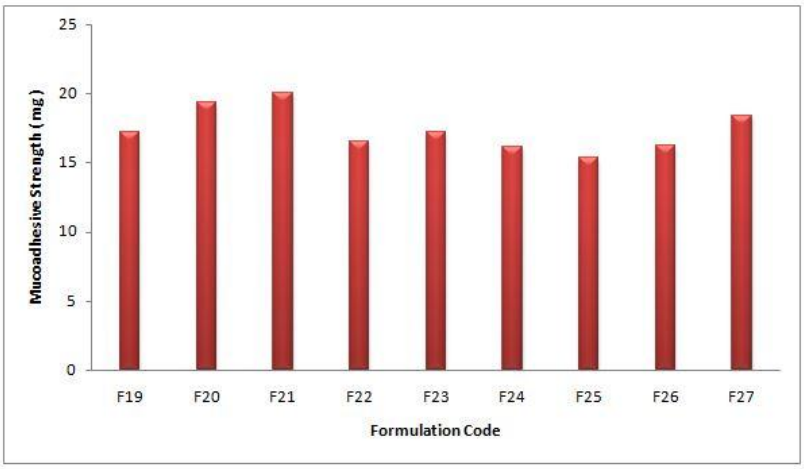

Fig 5: Mucoadhesive strength test for f19 – f27 formulations

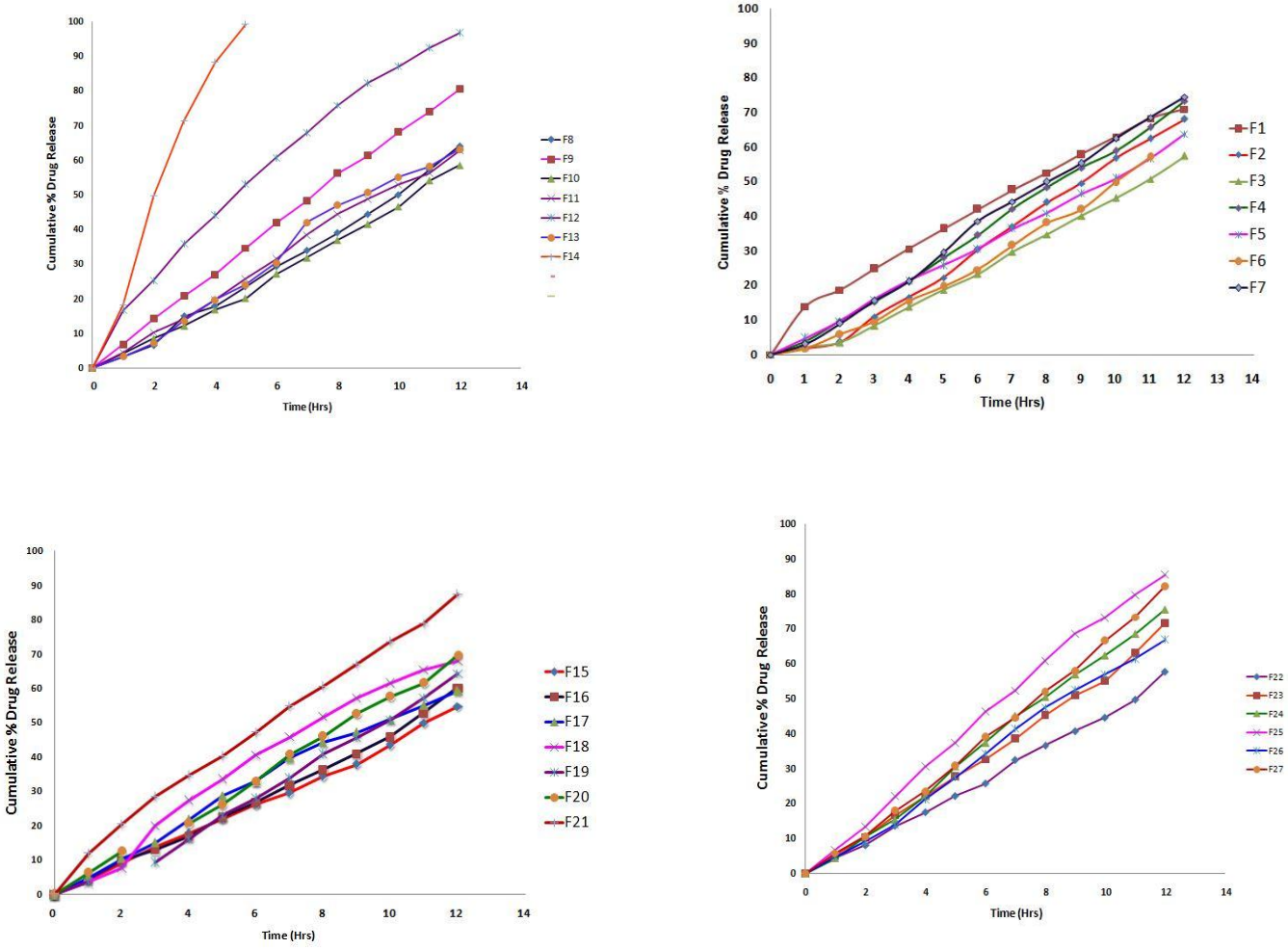

Fig 6: comparison of *in vitro* drug release profile of f1 – f27 formulations

Fig 7: *Ex-vivo* residence time test

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 940 p) on other factors (scmc, HPMCk15 [cr]) is explained.

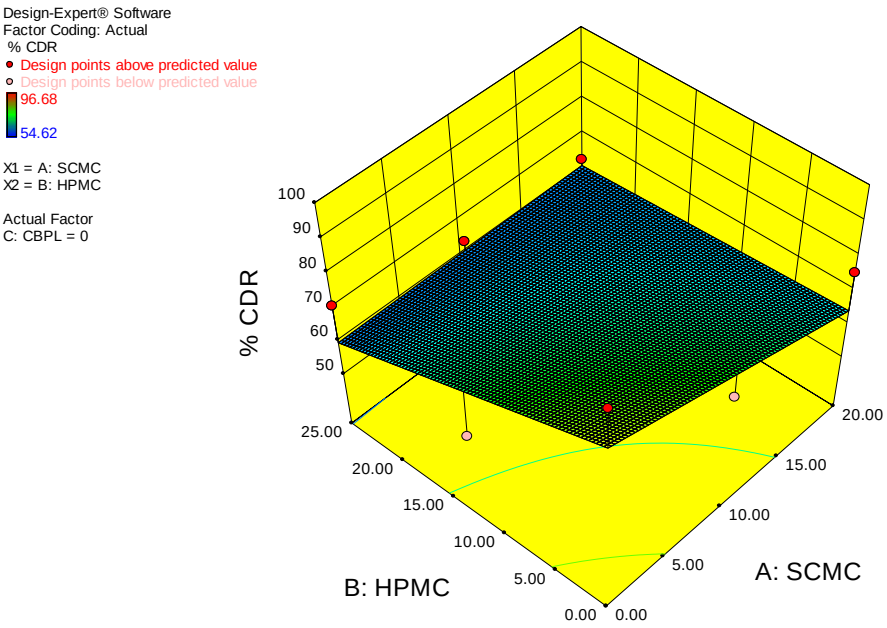

Fig 8: Response surface plot for % cdr

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 940 p on % cumulative drug release. The formulations with all 3 factors shown % drug release in between 54.62-96.68. But when carbopol is removed from the formulations the maximum % cdr is near 62. This is the effect of factor (carbopol**)** on response

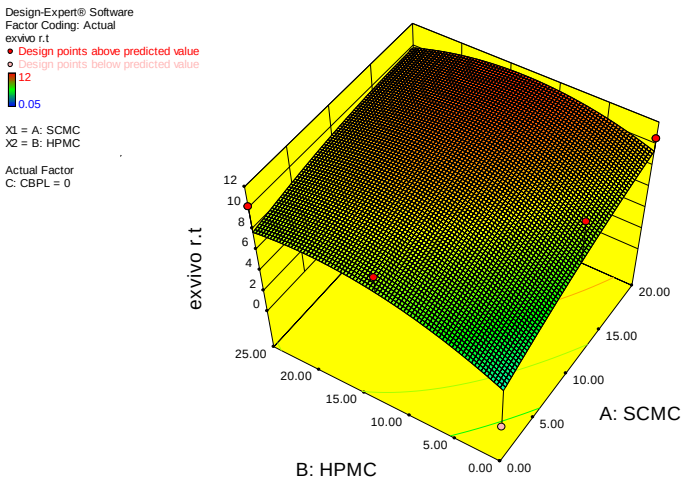

Fig 9: Response surface plot for *ex vivo* residence time

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.

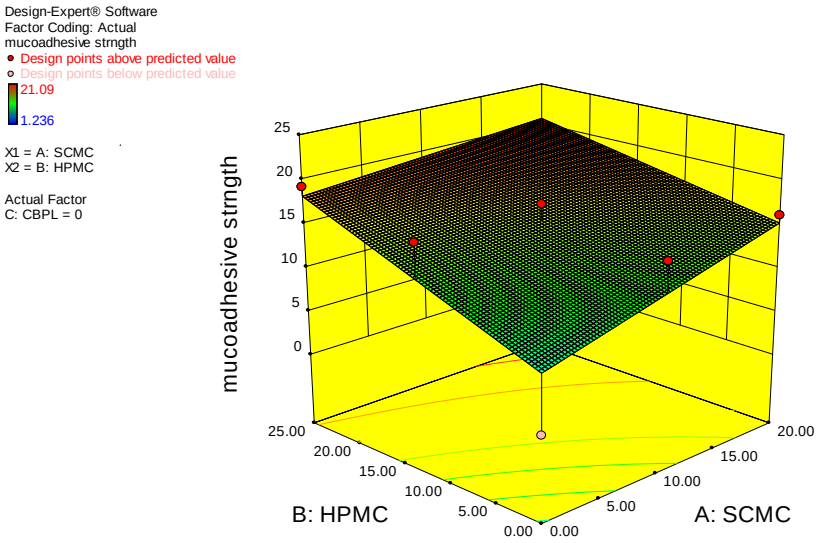

Fig 10: Response surface plot for mucoadhesive strength

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.

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.

CONCLUSION

Captopril mucoadhesive oral tablets could be formulated using the drug, carbopol 940p and HPMC K45 M (cr), 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 940p 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.

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