Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2014, 6 (6):257-265
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Formulation and evaluation of mucoadhesive matrix tablets of Carvedilol

Ramana B. V., Sabiya Sultana S., Neelofar S., Spandana D. S., Parmeswari C. S. and Nagarajan G.

Department of Pharmaceutics, Dr. K. V. Subba Reddy Institute of Pharmacy, Kurnool, A.P, India

---

ABSTRACT

Mucoadhesive polymer owing to its binding capacity with gastric mucin prolongs the gastricresidence time and thereby increases bioavailability. In the present research work an attempt was made to formulate and evaluate mucoadhesive matrix tablets of carvedilol. Matrix tablets were prepared by direct compression technology using different types and levels of polymers viz. HPMC 100M,HPMC E5, etc alone and in combinations. Compressed tablets were evaluated for thickness, friability, hardness, uniformity of weight, and in vitro dissolution studies. These studies indicates that the drug release can be modulated by varying the concentrations of polymers. It was observed that combination of both the polymers in equal concentrations exhibits the best release profile and able to sustain the drug release for 10hrs. Formulataion F11 shows the optimum mucoadhesive strength with drug release when compared to all other formulations in the test. Stability studies revealed that all the formulations was found to be stable under accelerated stability studies.

Keywords: carvedilol mucoadhesive matrix tablets, HPMC E5, HPMC K100M, gastric residence time.

INTRODUCTION

Oral route of drug administration is the ideal, convenient and preferred route[1]. Conventional oral drug administration does not generally offer target specificity or rate-controlled release. In controlled release drug delivery systems (CRDDSs), an active therapeutic is incorporated in the network structure of the polymer in such a way that the drug is released in a predefined controlled manner. Prolonging gastric residence time (GRT) is the most important objective of CRDDSs as short GRT is the major hindrance in the development of CRDDSs [2]. The prolonged residence time of the drug in the body is believed to prolong its duration of action.Mucoadhesive controlled drug delivery systems offer several advantages over other CR systems since they provide a controlled drug release over time and target and localize the dosage form to a specific site. Mucoadhesive drug delivery devices can be applied to any mucosal tissue in the body, including the gastrointestinal, ocular, respiratory, buccal, nasal, rectal, urethral and vaginal path [3].Carvedilol is a nonselective beta blocker/alpha-1 blocker indicated in the treatment of mild to severe congestive heart failure (CHF) and high blood pressure. Carvedilol was discovered by Fritz Wiedemann at Boehringer Ingelheim.[2] It has had a significant role in the treatment of congestive heart failure. Carvedilol (Carvil) is available at the following doses 3.125 mg (smallest), followed by 6.25 mg,12.5 mg, and 25 mg white tablets.

MATERIALS AND METHODS

Materials:
Carvedilol (MSN Laboratories,India), Hydroxypropyl Methylcellulose E5 (Colorcon Asia, Goa), Hydroxypropyl Methylcellulose K100M (Colorcon Asia, Goa), Hydroxypropyl Methylcellulose K100M (FMC Bio polymer,India), Polyvinylpyrrolidone K- 30 (FMC Bio polymer,India), Sodium starch glycolate (Ameshi drugs, India), Directly compressible lactose DCL-22 (FMC Bio polymer, India), Magnesium stearate (NitikaPharma, India), Hydrochloric acid (Rankem, India), Sodium hydroxide (Rankem, India), Potassium dihydrogen phosphate (Rankem, India).

Compatibility Studies
The drug-excipient compatibility studies were carried out using Fourier Transform Infrared Spectrophotometer (FTIR).Infrared spectra of pure drug and mixture of drug and mixture of drug and excipients were recorded. A base line correction was made using dried potassium bromide and then the spectra of the dried mixture of drug, formulation mixture and potassium bromide were recorded on FTIR.The FTIR spectra of carvedilol alone and carvedilol with different excipients were measured using ATR FTIR spectrophotometer (8400S, Shimadzu, Japan).ATR spectra were recorded over the wave number range of 4000-500 cm-1 at a resolution 1.0 cm-1. The powder is simply placed onto the ATR crystal and the sample spectrum is collected.

Method of preparation of mucoadhesive matrix tablets of carvedilol:
The granules were prepared by wet granulation method as per formula given in the Table (twenty tablets for each formulation). The drug carvedilol, hydrophilic polymer (HPMC K100M, HPMC E5), and mucoadhesive polymer sodium carboxy methyl cellulose were passed through sieve 40# separately and blended thoroughly. After proper mixing slowly add the binding solution containing PVP K-30 in IPA (Iso propyl alcohol) till fine uniform granules were obtained. The wet mass is now passed through sieve 16# and dried at 50 °C for 30 minutes to get the moisture content less than one. Then lubricate the dried granules with magnesium sterate which were already passed through sieve 40#. Then lubricated granules were compressed on cadmach tablet punch machine for all formulations with 8 mm diameter. The formulations containing various percentages of polymers were shown in Table 1 and 2.

Table 1: Composition of mucoadhesive matrix tablets (all quantities in mg) (F1-F8)

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Carvedilol	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
HPMC E5	75	50	25	-	-	-	25	25
HPMC K100M	-	-	-	75	50	25	25	50
Carboxy methyl cellulose	30	30	30	30	30	30	30	30
PVP K30	20	20	20	2S0	20	20	20	20
Magnesium stearate	10	10	10	10	10	10	10	10
Lactose	52.5	77.5	102.5	52.5	17.5	102.5	77.5	52.5
Total weight	200	200	200	200	140	200	200	200

Table2: Composition of mucoadhesive matrix tablets (all quantities in mg) (F9-F16)

Formulation code	F9	F10	F11	F12	F13	F14	F15	F16
Carvedilol	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
HPMC E5	50	50	25	25	25	25	50	50
HPMC K100M	25	50	25	25	25	50	25	50
Carboxy methyl cellulose	30	30	40	45	60	60	60	60
PVP K30	20	20	20	20	20	20	20	20
Magnesium stearate	10	10	10	10	10	10	10	10
Lactose	52.5	27.5	67.5	62.5	47.5	22.5	22.5	-
Total weight	200	200	200	200	200	200	200	200

Evaluation of mucoadhesive matrix tablets of carvedilol :
The physical evaluation tests for the mucoadhesive tablets of all the formulations were performed and mean values were calculated. Weight variation analysis was done by weighing 20 tablets individually, the average weight was calculated and % variation of each tablet from the average weight of tablets was calculated. Hardness and friability of the mucoadhesive tablet formulations were evaluated using Monsanto hardness tester and Roche friabilator respectively

Drug content[6]:

a) Standard Stock solution:

Accurately weighed 100 mg of carvedilol it was dissolved in 100 ml of different buffers (1.2pH 0.1N HCl) separately. The resultant solutions were having concentration of 1000 µg/ml (1 mg/ml). 10 ml of these solutions were further diluted up to 100.0 ml with buffer and to give a solution of Concentrations 100 µg/ml. This resultant solution is used as working stock solution for further study. Further dilutions were prepared from the same solution.

b) Preparation of caliberation curve for carvedilol:

Pipette out appropriate aliquots from the standard stock solution into a series of 10 ml volumetric flasks. And the volume was made up to the mark with the buffer to get a set of solutions having the concentration range of 4,8,12,16,20,24,28,32 and36 µg/ml for carvedilol. Absorbances of the above solutions were measured at 241nm and a calibration curve of absorbance against concentration was plotted and the drug follows the Beer's and Lambert's law in the concentration range of 2-10 µg/ml. The regression equation and correlation coefficient was determined.

For determining drug content, weigh and powder 5 tablets, from this accurately a quantity of powder equivalent to 100mg of carvedilol and transfer it in to 100ml volumetric flask and dissolve it in 100ml of methanol. The resultant solution was analyzed spectrophotometrically at 241nm.

***In vitro* mucoadhesive strength determination[4]:**

The *in vitro* mucoadhesive strength of tablet was measured with goat stomach mucosa, using a modified physical balance. On one side of the balance, a rubber closure tied with thread was attached and on other side empty polythene bag was attached. Goat stomach mucosa was obtained from a local slaughter house and stored in a phosphate buffer pH 6.8 upon collection. The experiments were performed within 3 h of collection of stomach mucosa which has been separated from sheep stomach. The goat stomach mucosa was fixed to the opening of the glass vial with thread and then placed in a beaker, well packed. Phosphate buffer pH 6.8 was added into the beaker up to the upper surface of the buccal mucosa to maintained stomach mucosal viability during the experiment. The tablet was sticked to the rubber closure with cyanoacrylate glue, then the beaker was raised slowly until contact between goat stomach mucosa and tablet was established. A preload of 5 gm was placed on the clamp for 5 min (preload time) to establish adhesion bonding between tablet and goat stomach mucosa. The preload time were kept constant for all the formulations. After completion of the preload time, preload was removed from the clamp and water was then added in the polythene bag by pipette in drop-wise manner, at a constant rate. The weight of water required to detach tablet from stomach mucosa was noted as in vitro mucoadhesive strength, and these experiments were repeated with fresh mucosa in an identical manner. The modified physical balance for *in vitro* mucoadhesive strength determination consisting of polythene bag (on one side) and rubber closure for attachment of tablet (on other side).

The mucoadhesive force, expressed as the detachment stress in dyne/cm2 was determined using following equation:

Detachment stress (dyne/cm2) = mg/A

Where, m = Weight of water added to polythene bag in grams;
G = Acceleration due to gravity taken as 980 cm/sec^2;
A = Area of the tissue exposed and is equal to πr^2

Dimensional stability[5]:

The dimensional stability of all formulations were studied by using USP dissolution Apparatus II. The dissolution medium was 0.1N HCL and the volume being 900ml, the temperature was maintained at 37^{0}C. The rotation speed was 100rpm. The dimensional stability of mucoadhesive matrix tablet was observed visually.

Drug release study:

Three tablets of each formulation were used in the release experiment. The release rates of carvedilol were determined using USP apparatus I (basket apparatus) at 37^{0}C in 900ml of 0.1N HCL solution (pH, 1.2) with the rotaion speed of 100 rpm. At appropriate time intervals 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12h, 5ml of sample was withdrawn and an equal volume of medium was added to keep the volume constant. Sample were analyzed spectrophotometrically at 241nm.

Accelerated stability study of optimized formulations[6,7]:
Accelerated stability study was carried out for optimized formulations, to assess its stability as per ICH guidelines. The optimized formulation were wrapped in the laminated aluminium foils and was placed in the accelerated stability chamber (6CHM-GMP, Remy iInstrument Lit, mumbai) at elevated temperature and humidity condition of 40^0C/ 75%RH and a control sample was placed at an amblient condition for a period of months. Sampling was done at a predetermined time of initial 0, 1, 2 and 3 months interval respectively. At the end of study, samples were analyzed for the drug content, in vitro drug release profile and other physicochemical parameters.

RESULTS AND DISCUSSION

Construction of Standard Graph:

Table 3: Carvedilol Standard graph in 0.1 N HCl

S.No	Concentration (mcg/ml)	Absorbance(nm)
1	4	0.129
2	8	0.205
3	12	0.307
4	16	0.412
5	20	0.518
6	24	0.650
7	28	0.753
8	32	0.894
9	36	0.995

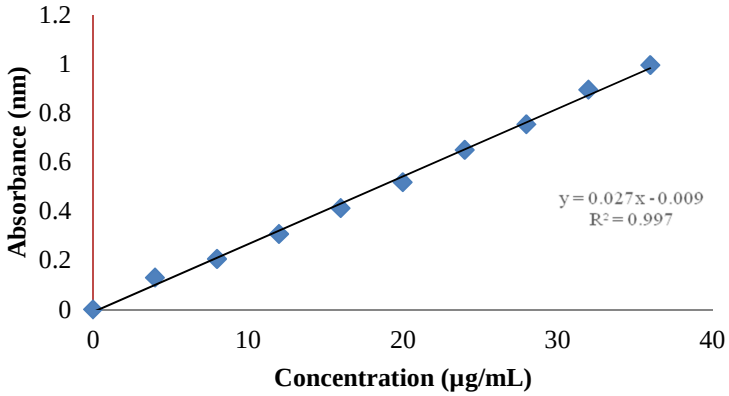


Figure 1: The standard calibration curve of carvedilol in 0.1 N HCl

Calibration curve of carvedilol was constructed by taking 0.1HCL as medium.Graph is plotted by taking concentration on x-axis and absorbance on y-axis.

Fig.4,5 shows the IR spectra of pure carvedilol and carvedilol excipient mixtures in 1:1M. The carvedilol showed IR absorption bands at 3338 cm-1 for N-H stretching. The absorption band at 2920 cm-1 was denoted for C-H (acids) stretching.

The band at 1338 cm-1 was denoted for OH sharp stretching. The band at 1589 cm-1 was denoted for N-H stretching in chain. Band at 1212 cm-1 was denoted for O-C stretching and the band at 1095 cm-1 was for C-N stretching.

All these characteristic peaks of carvedilol were observed in IR spectra of drug-excipient mixtures also. These characteristic IR absorption bands of carvedilol were all retained in the presence of the selected excipients indicates that there is no in situ interaction between the carvedilol and excipients.

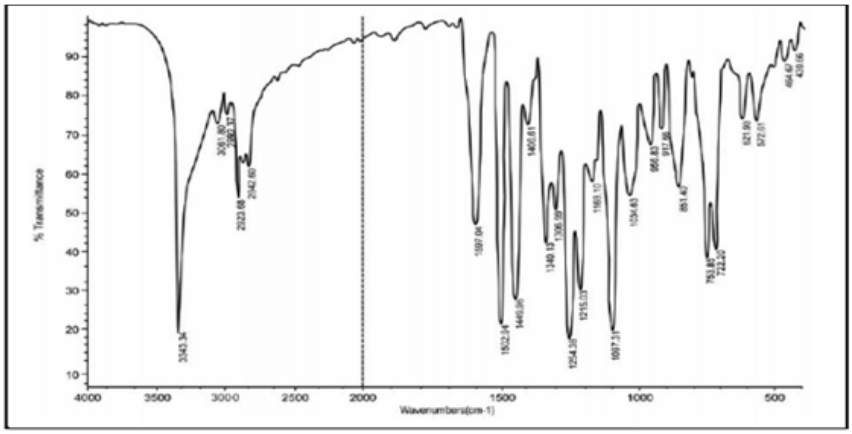


Figure 2: IR Spectra for Carvedilol

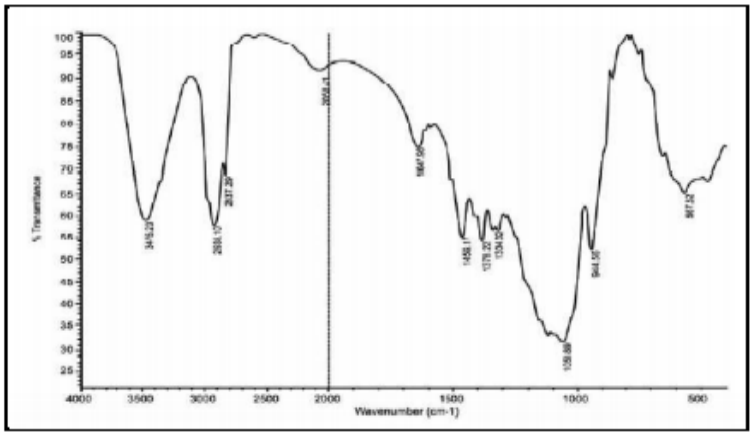


Figure 3: IR Spectra of Carvedilol with polymeric mixture

Table 4: Evaluation of Carvedilol Mucoadhesive Matrix tablet

Formulation	Weight Variation (mg) n=20	Thickness (mm) n=10	Hardness (N) n=10	Friability (%)
F1	201.10±1.24	3.20±0.1	80 N ± 10N	0.21
F2	202.15±1.11	3.20±0.1	80N ± 12N	0.11
F3	201.24±1.27	3.20±0.1	80N ± 9 N	0.25
F4	200.24±1.19	3.20±0.1	80 N ± 11N	0.15
F5	201.10±1.24	3.21±0.2	80 N ± 10N	0.21
F6	202.15±1.11	3.20±0.3	80N ± 12N	0.11
F7	201.24±1.27	3.22±0.5	80N ± 9 N	0.25
F8	203.24±1.19	3.20±0.4	80 N ± 11N	0.15
F9	202.10±1.24	3.22±0.5	80 N ± 10N	0.26
F10	202.15±1.11	3.21±0.2	80N ± 11N	0.24
F11	201.24±1.27	3.20±0.4	80N ± 9 N	0.11
F12	210.24±1.19	3.21±0.5	80 N ± 12N	0.28
F13	200.10±1.24	3.20±0.4	80 N ± 10N	0.24
F14	202.20±1.11	3.20±0.1	80N ± 10N	0.13
F15	201.24±1.53	3.20±0.1	80N ± 9 N	0.24
F16	203.24±1.21	3.21±0.2	80 N ± 8N	0.18

x= mean; ±SD; n= 3

The thickness of the tablets range from 4.46-5.65 mm respectively, The diameter of the tablet is in the range 12.98-13.03mm. There is no variation in tablet thickness and diameter between the formulations. Results are given in table 3. Hardness of tablet was within the range and optimum for controlled release, and ranges from 7.8-8.2 kg/cm^2 for all F1-F16 formulations. The friability of all formulation ranges from 0.089-0.198%w/w and passes as per IP limit

should not be more when 10%w/w. All formulation were complying with the official test the values were given in table 3.

Table 5: Evaluation parameters for Carvedilol mucoadhesive matrix tablet

Formulation	Detachment force (Dyne/Cm2)	Adhesion retention period (Hr)	Drug Content (%)	Dimensional stability
F1	1398.29	10	99.63±0.06	Excellent
F2	1255.79	9.5	99.79±0.03	Excellent
F3	1131.01	9	99.44±0.05	Very good
F4	1480.52	10.5	99.37±0.10	Excellent
F5	1420.68	10	99.19±0.11	Excellent
F6	1377.25	10	99.63±0.13	Excellent
F7	1325.78	10.5	99.47±0.09	Very good
F8	1443.58	11	99.34±0.10	Excellent
F9	1368.96	11.25	99.52±0.09	Excellent
F10	1584.99	11.5	99.29±0.06	Excellent
F11	1510.85	>12	99.46±0.13	Excellent
F12	1625.4	>12	99.39±0.09	Excellent
F13	1831.47	>12	99.28±0.06	Excellent
F14	1613.48	>12	99.45±0.16	Excellent
F15	1583.73	>12	99.67±0.15	Excellent
F16	1673.49	>12	99.49±0.11	Excellent

x= mean; ±SD; n= 3

The assays of all formulations from F1-F16 were between 99.19-99.79%. the result shows that all formulations contains drug within the limit of 99-101%. The results were given in table 4.

***In vitro* mucoadhesive strength determination:**

From the results it was found that as the concentration of sodium carboxy methyl cellulose increases the mucoadhesive strength increases and decreases the drug release. But formulation F11 shows the optimum mucoadhesive strength with good drug release when compared to all other formulations subjected in this test. Hence the mucoadhesive property of the formulation F11 could assist the tablet to stay in the upper part of gastro intestinal tract and enhance the gastro retention. The values were mentioned in Table 5.

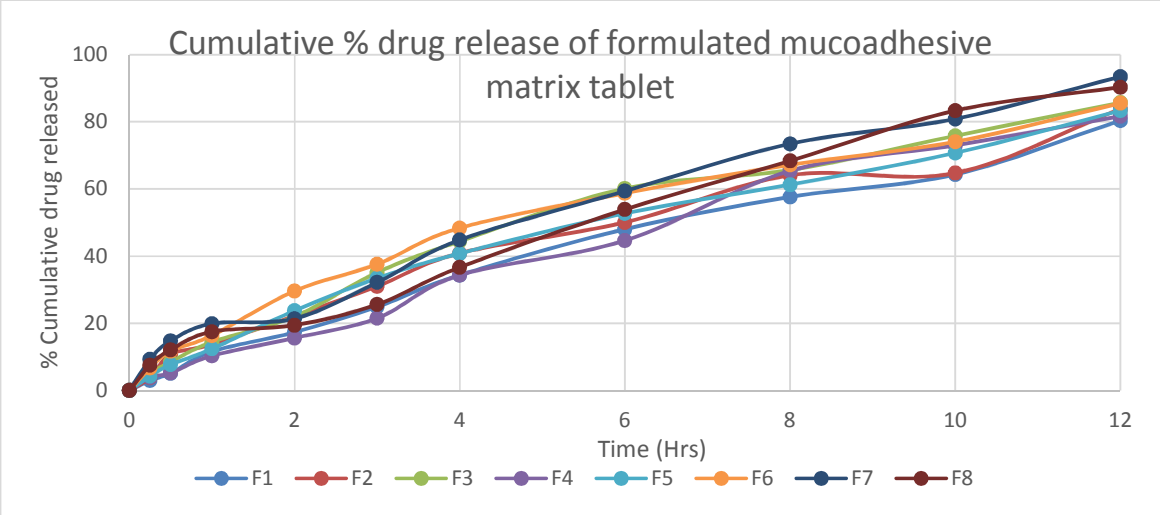


Figure 4: Cumulative % drug release of formulated mucoadhesive matrix tablet

Table 6: Cumulative % drug release of formulated mucoadhesive matrix tablet

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0.25	3.01	3.84	5.11	3.91	4.3	6.72	9.31	7.57
0.5	5.18	10.74	8.52	5.24	7.73	11.76	14.82	12.14
1	11.62	13.76	14.46	10.32	12.43	16.4	19.93	17.52
2	17.35	22.21	22.04	15.65	23.78	29.63	21.4	19.47
3	24.9	31.02	35.13	21.53	33.44	37.61	32.18	25.62
4	34.37	40.88	44.43	34.35	40.79	48.38	44.82	36.67
6	48.02	506.06	60.13	44.66	52.72	58.73	59.36	53.89
8	57.63	64.08	65.62	65.39	61.29	67.19	73.44	68.38
10	64.32	64.76	75.82	72.98	70.73	74.06	80.86	83.31
12	80.36	83.82	85.71	81.63	83.31	85.51	93.45	90.31

Table 7:Cumulative % drug release of formulated mucoadhesive matrix tablet

Time (hr)	F9	F10	F11	F12	F13	F14	F15	F16
0.25	6.24	2.98	5.31	4.83	5.62	4.16	3.43	2.93
0.5	9.15	6.02	8.67	9.46	10.03	8.32	7.15	5.02
1	14.81	11.78	14.56	13.78	14.63	19.92	11.93	8.95
2	21.23	18.38	19.94	16.43	20.75	22.17	20.42	16.84
3	31.42	26.32	28.18	23.1	29.53	30.21	29.47	25.53
4	38.71	31.63	39.36	34.52	35.68	34.4	34.97	31.01
6	50.92	43.78	54.61	52.34	53.61	47.36	52.88	43.83
8	63.47	55.83	71.85	68.96	63.43	57.43	64.63	57.87
10	79.64	73.29	86.27	80.25	67.58	72.08	75.46	71.3
12	90.57	80.25	92.88	89.94	80.32	88.36	89.03	83.98

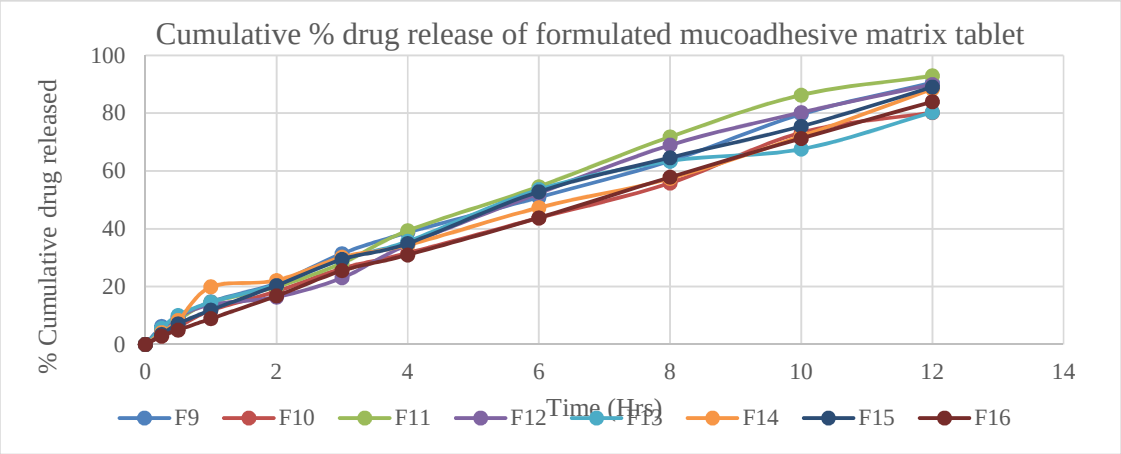


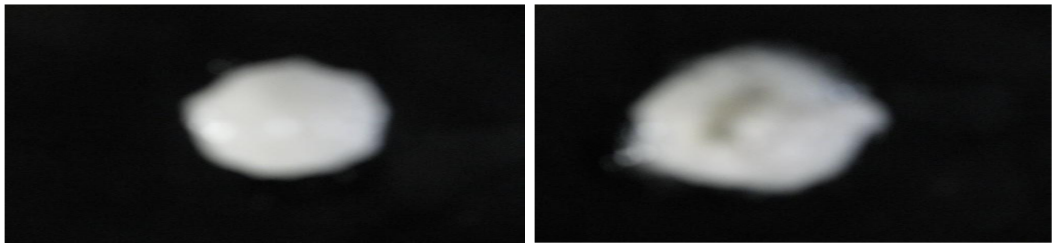
Figure 5: Cumulative % drug release of formulated mucoadhesive matrix tablet

5:Cumulative % drug release of formulated mucoadhesive matrix tablet

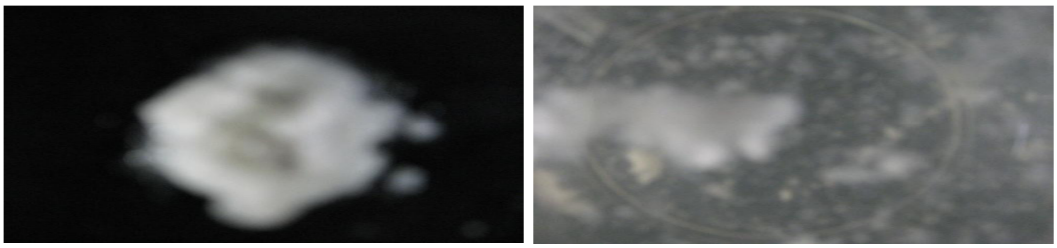
In the above studies we have shown the effect of polymers on invitro drug release of carvedilol. Formulation batch F1-F6 releases drug up to 80-85% only. Formulation F11 shows maximum drug release up to 92.88% with controlled manner which also exhibits excellent mucoadhesive strength. Cumulative % drug release of formulation F1-F16 showed in Table 5 and 6.

Dimensional Stability

It is important to maintain physical integrity of the tablet up to 12 hrs in case of once daily formulations. So increasing concentrations the dimensional integrity of tablet also increases. The dimensional integrity of formulation were represented with their code along with picture representation in table 4 and figure 7. The formulation F1-F16 shows excellent dimensional stability, except formulation F3 and F6 shows very good dimensional stability.



Excellent **Very good**



Good **poor**

Figure 7: Picture representation for dimensional stability

Accelerated stability study

Table 8: Results of accelerated stability studies of optimized formulations

	Optimized formulation (F11)		
	Drug content (%)	% Drug release	Detachment force (Dyne/cm^2)
Initial	99.46	92.88	1510.85
One Month			
Ambient	99.45	92.79	1504.47
40°C/75% RH	99.36	92.28	1501.31
Two month			
Ambient	99.35	92.47	1490.89
40°C/75% RH	99.32	91.98	1485.93
Three month			
Ambient	99.29	92.38	1488.62
40°C/75% RH	99.27	91.82	1482.64

In carvedilol optimized formulation F11 was to be stable during accelerated stability studies for drug content 99.46%, 99.36%, 99.32% and 99.27% at 0,1,2 and 3 months at 40^{0}C/ 75% RH. Results obtained were shown in table 7. Finally it was observed that there was no change in physic chemical and properties as well as in drug release profile even after storage at 45^{0}C and 75% for 3 months.

CONCLUSION

The present study concludes that the mucoadhesive matrix tablet of Carvedilol could be successful option for Adjunctive treatment of moderate to severe stable chronic heart failure.

Acknowledgement
We acknowledge to the management and the head of the institute for making the facilities to carry out the research work in a successful manner.

REFERENCES

[1] Press Release, FDA Approves First Generic Versions of Coreg, U.S. Food and Drug Administration, Sep. 5, **2007**.
[2] Fritz Wiedemann, Wolfgang Kampe, Max Thiel, Gisbert Sponer, Egon Roesch, Karl Dietmann, US Patents 4503067 A,**1985**

[3] PR Veerareddy, M Nama, CR Gonugunta, *AAPS Pharm Sci Tech*, **2008**, 9(1), 231-237.
[4] SS Vaghani, SG Patel, RR Jivani, NP Jivani, MM Patel, R Borda, *Pharm Dev Tech*, **2012**, 17(1), 55-65.
[5] ZA Senyigit, A Vetter, T Guneri, AB Schnurch, *Drug Del*, **2011**, 18(6), 405-414.
[6] DV Gowda, AS Ram, VK Gupta, A Ahmad, *Inventi Impact: NDDS*, **2012**, 2, 124-129.
[7] M Chavanpatil, P Jain, S Chaudhari, R Shear, P Vavia, *Int J Pharm*, **2005**, 304, 178-184.