

Formulation and Characterization Sustained Release Mucoadhesive Microcapsule of Baclofen

Kunal V Bhambar¹, Rajendra S Bhambar^{2,*}, Pravin P Gadakh¹

¹Department of Pharmaceutical Quality Assurance, MGV's Pharmacy College, Panchavati, Nashik, Maharashtra, INDIA.

²Department of Pharmacognosy, MGV's Pharmacy College, Panchavati, Nashik, Maharashtra, INDIA.

ABSTRACT

Background: Baclofen is used as skeletal muscle relaxant. Baclofen inhibit Polysynaptic and monosynaptic reflexes a hyperpolarisation. Baclofen drug absorbed rapidly and excreted in feces urine in unchanged form. **Objectives:** Aim of the current study was to formulate sustained release mucoadhesive microcapsules of Baclofen using different polymers like Chitosan, Carbopol934P, HPMC K4M. **Materials and Methods:** Ionotropic gelation method was used for preparation of microcapsules of baclofen. Dispersion of polymers and baclofen was dropwise added sodium tripolyphosphate solution to form microcapsule. The prepared microcapsules were evaluated for FTIR studies, micromeritic properties, drug entrapment efficiency, particle size and shape, SEM, swelling index, mucoadhesive strength, *in vitro* release studies. **Results:** Angle of repose of prepared microcapsules was in range 24.48 ± 1.39 to 38.08 ± 1.67 showed good flowability. Prepared microcapsules showed bulk density in the range of 0.49 ± 0.04 to 1.22 ± 0.06 . All formulations showed Carr's index and Hausner's ratio in the range of 14.68 ± 1.20 to 29.56 ± 1.97 and 1.16 ± 0.012 to 1.25 ± 0.016 respectively. Formulation F1 to F3 prepared with HPMC (K4M) showed drug release 77.78%, 74.94%, 77.99% and formulation F4 to F6 prepared with Carbopol 934P showed drug release 78.20%, 79.05%, 87.48% respectively in 12hr. **Conclusion:** Sustained release profile F6 formulation was obtained due to significant mucoadhesive efficiency of the Carbopol 934P. Hence the mucoadhesive microcapsules of Baclofen would be an effective strategy for the management of Muscle Pain.

Keywords: Baclofen, Microcapsule, Carbopol 934P, HPMC K4M, Sustained Release.

Correspondence:

Dr. Bhambar Kunal

Department of Pharmacognosy, MGV's Pharmacy College, Panchavati, Nashik, Maharashtra, INDIA.
Email id: kunalbhambar@gmail.com

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INTRODUCTION

Sustained drug release drug delivery devices used to improve therapeutic benefits, minimizing its side effects while improving the diseased condition.¹ Mucoadhesive drug delivery devices used to increase retention at the application site and also provide a sustained drug release for improved therapeutic efficacy. Mucoadhesion is phenomenon involve contact between mucous membrane and mucoadhesive. It also cause spreading with swelling of the dosage form, results in deep contact with the mucous layer.^{2,3} Baclofen drug widely used as an antispastic agent which relieve the muscle pain. Baclofen is GABA receptors direct agonist. Baclofen inhibit Polysynaptic and monosynaptic reflexes a hyperpolarisation. Baclofen drug absorbed rapidly and excreted in feces urine in unchanged form.^{1,2} Mucoadhesive microcapsules are tiny spherical particles have ability to form bio adhesion to the

gastric mucosa which improve the gastric residence time. Various theories have proposed to explain mucoadhesion like adsorption theory, fracture theory, diffusion theory, electronic theory.⁴ Sustained release microcapsules provide many advantages when compared with conventional therapy like modulated drug release, enhanced drug stability and reduced gastrointestinal irritation.⁵ It has been reported that the duration of action after a single dose of baclofen is only 4 hr so it requires dose of 5-20 mg to be taken three to four times a day. Hence to minimise frequency of dosing and to enhance bioavailability encapsulation of drug can be performed.^{6,7}

MATERIALS AND METHODS

Materials

The pure Baclofen was purchased from Yarrow Chem, Mumbai. HPMC K4M was obtained from Unichem Laboratories, Mumbai. Carbopol 934P was obtained from Corel Pharma, Ahmedabad. Chitosan and Sodium tripolyphosphate was obtained from Modern Science Laboratories, Nashik. Analytical grades materials were used for experimental study.



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Table 1: Formulation of Mucoadhesive microcapsule of Baclofen.

Ingredients	Formulation Code					
	F1	F2	F3	F4	F5	F6
Baclofen(mg)	100	100	100	100	100	100
Chitosan(gm)	1	1.2	1.4	1	1.2	1.4
Carbopol 934P(gm)	-	-	-	0.5	1	1.5
HPMC K4M	0.5	1	1.5	-	-	-
2% Acetic acid(ml)	10	10	10	10	10	10
Sodium tripolyphosphate (%w/v)	8	8	8	8	8	8

Formulation of chitosan microcapsules of Baclofen by ionotropic gelation method^{9,13}

Chitosan was dissolved in 2% acetic acid solution with continuous agitation. Then different concentration of carbopol 934P, HPMC K4M added in chitosan solution with agitation to prepare uniform dispersion. The prepared dispersions were allowed to stand overnight for removal of air bubbles and proper soaking. Drug Baclofen was added to the chitosan solution with continuous agitation.⁸ The solution of 8% w/v of sodium tripolyphosphate were prepared separately in distilled water. The dispersion of drug and chitosan were added in 8% w/v of sodium tripolyphosphate solution dropwise using syringe and needle with small diameter. The microcapsules formed were allowed to stand for sufficient time into the 8% w/v of sodium tripolyphosphate solution for proper hardening. The microcapsules formed were separated, washed using distilled water later dried at ambient temperature for 24 hr.^{9,10,11,12} Formula for Mucoadhesive microcapsule formulation is given in Table 1.

Characterization and Evaluation mucoadhesive microcapsules^{14,15}

Bulk Density, Tapped Density

Microcapsules were added using a glass funnel in cylinder up to 10 ml mark. Cylinder weight along with granules to fill cylinder was determined. Cylinder was later tapped from 2.0 cm height in bulk density apparatus up to the time when no decline in volume observed. Bulk and Tapped densities were calculated.^{13,14,15}

Bulk Density(g./ml) = Wt. of sample (gm.) / Volume of sample

Tapped Density(g./ml) = Wt. of sample (gm.) / Volume of sample

Carr's index

The Carr's index of microcapsules was calculated by the Carr's index formula

$$\text{Carr's index (\%)} = \frac{(\text{Tapped Density} - \text{Bulk Density}) \times 100}{\text{Tapped Density}}$$

Angle of Repose

Funnel method was used to determined Angle of Repose. The microcapsules allowed to flow from funnel onto surface microcapsules cone diameter was calculated. Following equation used to determine flow property

$$\tan \theta = H/R$$

Where H is the height and R is radius.

Mean particle size

Optical microscope was used to determine mean particle size. Following equation used to measure particle size.

$$D = \sum Nd / N$$

Where, N= number of microcapsules,

d= mean of the size range,

D= average size (μm).

Practical yield

The percent practical yield was calculated by the following formula

$$\% \text{ Practical Yield} = \frac{\text{Total wt. of the microcapsule}}{\text{Total wt. of the Polymer and Drug}} \times 100$$

Drug Loading

Accurately weighed 25 mg of microcapsules were triturated and added in 100 ml 0.1N HCl solution. Resulting solution was stirred for 2 hr. on magnetic stirrer. After stirring solution filtered through Whatman filter paper. Appropriate dilution was made from filtrate and absorbance was taken at 219.5 nm by utilising Shimadzu 2450 UV spectrophotometer.

$$\% \text{ Drug loading} = \frac{\text{Amount of drug actually present}}{\text{Theoretical weight of the drug}} \times 100$$

Entrapment efficiency of Drug

Weighed 25 mg of microcapsules triturated using mortar and pestle later added in 0.1N HCl solution (100 ml). Resulting solution stirred for 2 hr. on magnetic stirrer. After stirring

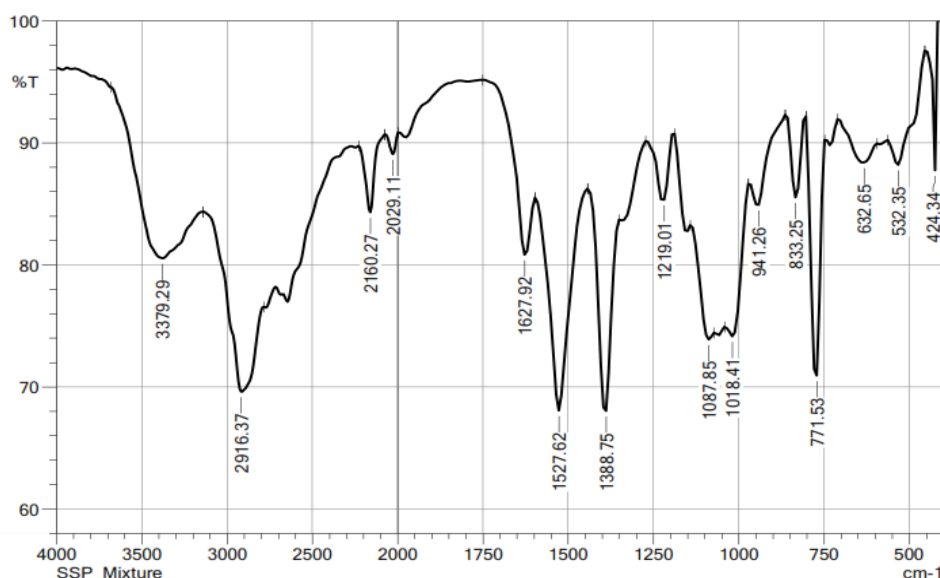


Figure 1: FTIR spectra of Baclofen Macrocapsules.

Whatman filter paper was used to filter solution. Appropriate dilution was made from filtrate and absorbance taken at 219.5 nm by Shimadzu 2450 UV spectrophotometer.

Entrapment

$$\text{Efficiency (\%)} = \frac{\text{Theoretical content of drug} - \text{Practical content of drug}}{\text{Theoretical content of drug}} \times 100$$

Swelling Index

Study was performed in 0.1N HCl. At specified time intervals (i.e., 1, 2, 3, 4, 5, 6, 7hr) the microcapsules were weighed.

$$\% \text{Swelling} = \frac{\text{Weight of microbeads after swelling} - \text{Initial weight of microbeads}}{\text{Initial weight of the microbeads}} \times 100$$

Mucoadhesive Strength

Detachment force method was used to determine mucoadhesive strength. Baclofen Microcapsules were placed between section of goat intestinal membrane and slides. Detachment force was calculated by minimum weight that detached two slides.

$$\text{Mucoadhesive force} = \frac{\text{Mucoadhesive strength (gm)} \times 9.81}{1000}$$

FT-IR of Baclofen microcapsules

KBr pellet technique was used to record FTIR spectrum of F6 formulation.

DSC of Baclofen microcapsules

Shimadzu-Thermal Analyzer DSC 60 was used to analyse F6 sample. Initially samples of formulations were heated using open aluminum pan (10°C/min) over a temperature range of 30 to 300°C. Nitrogen flow was maintained at 2 bar pressure.

Scanning Electron Microscopy

Samples were observed using scanning electron microscope at 47X resolution to determine the surface properties of microcapsules. For this study, chitosan microcapsules of optimized batch F6 were taken.

In vitro dissolution study

Dissolution study for baclofen was carried out by USP type I apparatus at 50 RPM, 37±0.5°C and 900 ml of 0.1N HCl was used as medium. Samples were taken at specified intervals and estimated by using Spectrophotometer (2450 Shimadzu – double beam UV-vis Spectrophotometer) at respective wavelength.

In vitro drug release Kinetics

Zero order, first order, Higuchi, Hixson Crowell and Korsmeyer-Pappas kinetic model were used to study baclofen release study.¹⁷

Stability Study

Mucoadhesive microcapsules of optimized batch F6 in aluminum strips were packed and stored for 3 months. All samples analysed for physical appearance, drug entrapment efficiency, drug loading, *in vitro* drug release and swelling index after 90 days.

RESULTS

The developed Microcapsules of Baclofen were evaluated for Bulk density, Tapped density, Angle of repose, Hausner's ratio and Carr's index. Bulk density of F1 to F6 batches was in range from 0.49 to 1.22 g/ml. Tapped density of F1 to F6 batches was in range from 0.59 to 1.43 g/ml. Hausner's ratio for F1 to F6 batches observed more than 1.25 and Carr's index of F1 to F6 batches was observed in range from 14.68 to 29.56. The Angle of

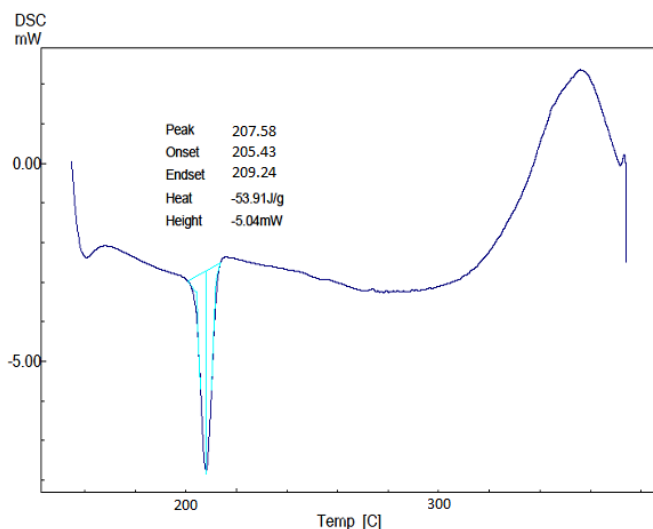


Figure 2: DSC of sustained release microcapsules of baclofen.

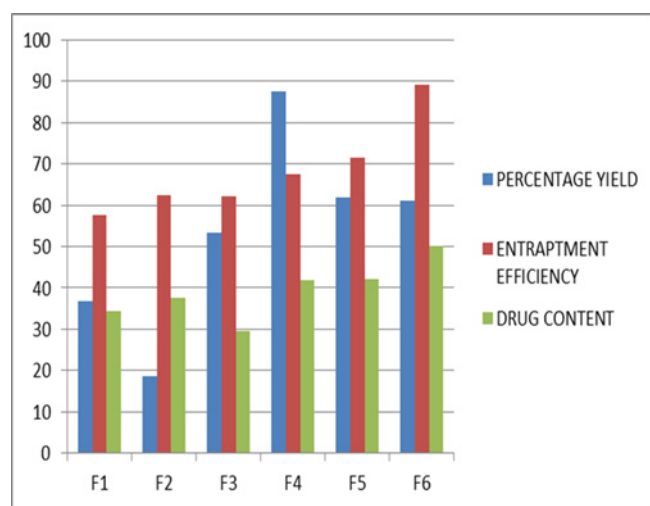


Figure 3: Percentage yield, Entrapment efficiency and drug content of sustained

release of F1 to F6 batches was observed in range from 28.48 to 38.08 that indicate flow property of microcapsules was found to be good results given in Table 2. The mean size of particles was calculated with the help of optical microscope using calibrated ocular micro meter. Characteristic peaks of functional group in FTIR study indicate purity shown in Table 6. Mean particle size of F1 to F6 batches was in the range of 383-630 μm . The percent yield of F1 to F6 batches was observed in wide range from 36.87% to 60.05%. Percent Entrapment efficiency of batches F1 to F6 was in range from 57.5% to 89% shown in Table 3. The drug loading of batches F1 to F6 was in range 34.5% to 50.09%. Highest % drug loading was obtained for F4-41.85%, F5-42.25% and F6-50.07% shown in Table 3. The mucoadhesive strength of batches F1 to F6 was in range from 0.019 to 0.098. Swelling studies for sustained release mucoadhesive microcapsules was performed in 0.1N HCl shows maximum swelling for all batches of microcapsules as the time increases. DSC of Baclofen microcapsule indicate

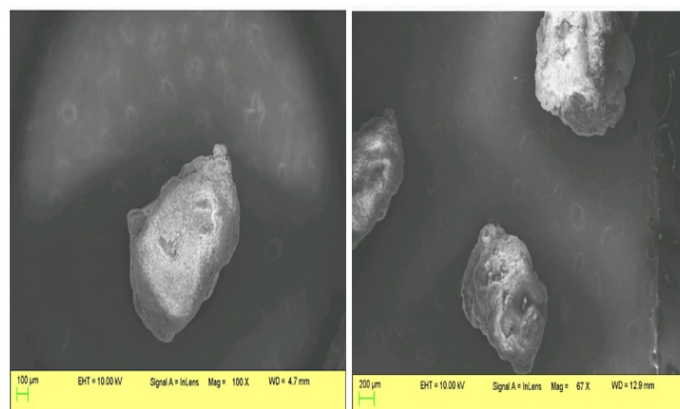


Figure 4: SEM analysis of sustained release microcapsules of baclofen.

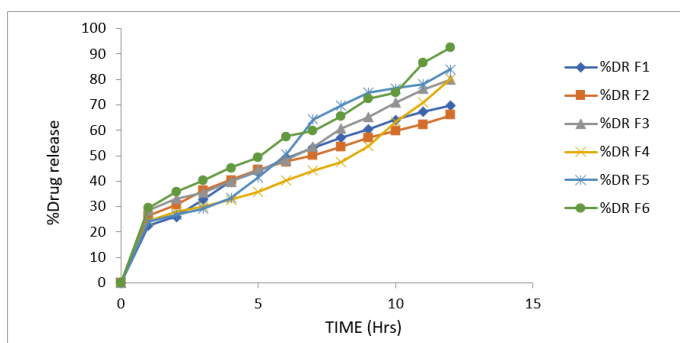


Figure 5: Cumulative % drug release of formulations F1 to F6.

endothermic peak at 206.65°C indicate sample melting shown in Figure 2. Absorption bands for baclofen shown in Figure 1. SEM of optimized batch F6 shows microcapsules were spherical in shape. The size of the microcapsule was observed in between 600 μm -800 μm shown in Figure 4. The dissolution studies conducted to evaluate dissolution character of baclofen from microcapsules. Formulation F6 shows highest drug release 92.48% whereas formulation F2 shows lowest 65.94% at the end of 12hr. Highest R^2 values were obtained for Korsmeyer Peppas Model shown in Table 4. Release exponent n value was more than 0.5 which indicate non-Fickian transport (Anomalous). Mechanism of Baclofen release from microcapsules was chain relaxation or swelling with diffusion and erosion. Short term stability testing was performed for formulation F6. It shows that no significant change was observed.

DISCUSSION

Ionotropic gelation technique was used for formulation of baclofen containing microcapsules. Average microcapsule size was calculated using optical microscope for F1 to F6 batches. The microcapsules form compact mass due to crosslinking. Percent Entrapment efficiency of batches F1 to F6 was in range from 57.5% to 89% shown in Figure 3. It was observed that sodium tripolyphosphate concentration did not affect percent Entrapment efficiency, but if chitosan concentration increases then percent entrapment efficiency was also increased. The mucoadhesive strength of batches F1 to F6 was in range from

Table 2: Flow propeties of sustained release microcapsule of baclofen.

Formulation Code	Bulk density	Tapped density	Hausner's ratio	Carr's index	Angle of repose
F1	0.49±0.04	0.59±0.028	1.20±0.024	16.94±1.61	38.08±0.78
F2	0.30±0.02	0.35±0.020	1.16±0.012	14.28±1.30	34.63±2.17
F3	0.81±0.02	1.15±0.021	1.41±0.020	29.56±1.97	39.27±1.67
F4	0.25±0.03	1.0.34±0.016	1.36±0.016	26.47±1.28	36.63±2.17
F5	0.86±0.07	1.08±0.018	1.25±0.016	20.37±1.68	39.90±0.99
F6	1.22±0.06	1.43±0.029	1.17±0.012	14.68±1.20	28.48±1.39

Table 3: Percentage yield, Entrapment yield, Drug loading of Baclofen Microcapsules.

Formulation Code	Percentage yield (%)	Entrapment efficiency (%)	Drug loading (%)
F1	36.87±1.54	57.5±2.37	34.5±2.37
F2	16.95±0.94	62.5±1.21	37.5±1.21
F3	46.33±1.59	62.25±2.67	29.5±2.67
F4	25.62±2.87	67.5±3.67	41.85±3.67
F5	61.9±1.88	71.5±1.72	42.25±2.11
F6	61.15±1.84	89.00±2.10	50.07±3.16

Table 4: Kinetic models of various formulations of Baclofen microcapsules.

Formulation Code	Zero order plot	First order plot	Hixson-Crowell plot	Higuchi plot	Korsemeyer -Peppas plot	
	Regression Coefficient (R ²)					n value
F1	0.7051	0.856	0.8895	0.8160	0.9026	0.7211
F2	0.8213	0.9081	0.9151	0.8606	0.9377	0.7449
F3	0.9144	0.9543	0.9642	0.9531	0.9670	0.8444
F4	0.9205	0.9581	0.9703	0.9581	0.9720	0.8258
F5	0.8083	0.8546	0.9013	0.8216	0.9118	0.7229
F6	0.8485	0.9214	0.9238	0.9066	0.9669	0.5197

Table 5: Stability studies of optimized preparation at different storage conditions according to ICH guidelines.

Sl. No.	Parameters	After one months	After two months	After three months
1	Physical appearance	No change	No change	No change
2	Drug loading	50.07±3.16	50.10±3.14	50.12±3.17
3	Entrapment efficiency	89.00±2.10	89.06±2.15	89.04±2.12
4	Swelling index	61.50±0.31	63.52±0.33	65.51±0.30
5	<i>In vitro</i> drug release study	91.48%	95.55%	93.53%

Table 6: Functional group present in the sustained release microcapsules of baclofen.

Functional group	Observed peaks (cm ⁻¹)	Standard peaks (cm ⁻¹)
NH ₂ stretching	3379.29	3300-3400
C-H stretching	2929.97	2850-3000
Amide I (C=O)	1666	1640-1690
Benzene	771.53	700-800
O-H Stretching	2916.37	2800-3300

0.019 to 0.098. It was observed that the mucoadhesive strength was more with Carbopol 934P than with HPMC K4M. In pH 0.1 HCl buffer medium all formulation shows maximum swelling of microcapsules as the time increases. The dissolution study shows that drug release was found to be in between 77.78% to 87.48% shown in Figure 5. Batch F1 shows the lowest drug release whereas F6 shows highest. All Formulations stable as there was no significant change in different parameter indicated in Table 5.

CONCLUSION

The microcapsules of baclofen were developed using polymers like Chitosan, HPMC K4M and Carbopol 934P. Formulation F6 indicate drug release 89% after 12 hr which indicate sustain drug release from the formulation. Highest R^2 Values were obtained for Korsmeyer Peppas Model and release exponent n was more than 0.5 indicate non-fickian transport.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

FTIR: Fourier Transforms Infrared; **HPMC:** Hydroxy Propyl Methyl Cellulose.

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