Formulation & Evaluation of Mucoadhesive Drug Delivery System of Nifedipine

Vipul*, Ashish Singh

Research and Development Department, Phyto Ingredients Biopharma Pvt. Ltd.,
Yamunanagar, Haryana, India

Corresponding author: Vipul
Address: Research and Development, Phyto Ingredients Biopharma Pvt. Ltd., Yamunanagar, Haryana, India
Email : phytoingredients@gmail.com, info@phytoingredients.com

ABSTRACT:

Mucoadhesive tablet of Nifedipine was fabricated with objective of avoiding first pass metabolism and to improve its bioavailability with reduction in dosing frequency. The Mucoadhesive polymers used in the formulations were Carbopol 934P, Chitosan, HPMC, and Sodium CMC. Tablets were prepared by direct compression method using polymer in different ratios. The formulations were characterized for Mucoadhesive time studies, in-vitro bioadhesion strength and in-vitro release studies. The best mucoadhesive performance and in- vitro drug release profile were exhibited by the tablet containing Carbopol 934P, Chitosan, HPMC, and Sodium CMC.

KEY WORDS: Gastro retentive Drug delivery, Carbopol -934, Nifedipine, Mucoadhesive

INTRODUCTION:

Gastro retentive approaches have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. Gastro retentive drug delivery of drugs provides long duration of action so the release of drug become sustained & so improves bioavailability The development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner.[1,2,4,5] This drug is not to be taken Sublingual Nifedipine has previously been used in hypertensive emergencies. This was found to be dangerous, and has been abandoned. Sublingual Nifedipine causes blood-pressure lowering through peripheral vasodilatation. It can cause an uncontrollable decrease in blood pressure, reflex tachycardia, and a steal phenomenon in certain vascular beds. There have been multiple reports in the medical literature of serious adverse effects with sublingual Nifedipine[8], including cerebral ischemia/infarction, myocardial

infarction, complete heart block, and death. So we prepared Mucoadhesive gastric tablet which gives release in sustained manner, and reduces adverse effect, and improve patient compliances, Nifedipine are the long-term treatment of hypertension (high blood pressure) and angina pectoris.

MATERIAL AND METHODS:

Nifedipine was obtained from Akums Drug Laboratories, Haridwar, Carbopol 934P, Chitosan, HPMC, and Sodium CMC, Lactose (Central Drug house, Delhi) were used. All the other reagents were of the analytical grade.

Preparation of Mucoadhesive tablets:

Mucoadhesive tablets of Nifedipine were prepared by direct compression techniques using different grades of polymer with varying concentration (Table1). The dummy Formulation batches from S1-S8 were showing very less Bio-adhesion time so they were discarded, and the bio-adhesion test results were showing that batches S21-S36 which were prepared using different polymer concentrations, the bio-adhesion time was the same, Therefore, these batches were discarded and no further Studies were performed on these batches. The tablets were prepared using Carbopol 934P, Chitosan, HPMC, and Sodium CMC as primary polymers and lactose as a secondary polymer. the effect of secondary polymer on drug release and mucoadhesion was studied. The tablets were compressed using 8 mm flat faced punch on a single stroke punching machine.

Table 1: Optimization of Mucoadhesive tablet batches:

Batch	S9	S10	S11	S12	S17	S18	S19	S20	S37	S38	S39	S40
Nifedipine	90	90	90	90	90	90	90	90	90	90	90	90
Chitosan	30	-	-	-	50	-	-	-	100	-	-	-
H P M C 15cps	-	30	-	-	-	50	-	-	-	100	-	-
Carbopol 934	-	-	30	-	-	-	50	-	-	-	100	-
Sodium C M C	-	-	-	30	-	-	-	50	-	-	-	100
Aerosil	4	4	4	4	4	4	4	4	4	4	4	4
Magnesiumsterate	2	2	2	2	2	2	2	2	2	2	2	2
Lactose	10	10	10	10	20	20	20	20	20	20	20	20

Determination of physicochemical parameters:

Twenty tablets were weighed individually and the Percentage weight was determined. Percentage deviation was calculated and checked for weight variation. Hardness of the tablet checked by the Pfizer tester, the resulting average hardness to be checked about 4-5 kg/cm$^{2.}$ Bioadhesive strength of the tablets were measured on a modified physical balance using method described by Gupta et al.[9] Sheep buccal mucosa was used as model Stomach membrane and simulated 1.2 pH buffer solution as moistening fluid. (Table 2, Fig 1)

Table 2: Physical parameters of Mucoadhesive tablets:

Batch code	Hardness(kg/cm^2) Mean± SD	Friability %	% Weight variation Mean± SD	Thickness Mean± SD	% drug content Mean± SD
S9	5.5 ± 0.23	0.65	2.5 ±0.44	4.92 ± 1.01	94.81 ± 0.68
S10	5.8 ± 0.52	0.85	3.0 ±0.23	4.02 ± 0.56	96.72 ± 0.54
S11	5.0 ± 0.48	0.66	0.03 ±0.85	4.90 ± 0.62	97.98 ± 0.84
S12	7.0 ± 0.41	0.97	0.5 ±1.00	4.34 ± 0.48	92.18 ± 0.47
S17	5.5 ± 0.36	0.85	3.56 ±0.64	4.49 ± 0.79	94.25 ± 0.72
S18	5.8 ± 0.57	0.66	2.5 ±0.96	4.08 ± 1.00	96.80 ± 0.69
S19	5.0 ± 0.53	0.78	0.045 ±0.95	4.37 ± 0.68	98.12 ± 0.83
S20	6.0 ± 0.71	0.65	4.25 ±0.56	4.12 ± 0.29	94.43 ± 0.74
S37	5.5 ± 0.31	0.66	0.5 ±0.63	4.29 ± 0.43	97.63 ± 0.68
S38	5.8 ± 0.42	0.85	1.0 ±0.58	4.68 ± 0.56	98.92 ± 0.74
S39	5.0 ± 0.86	0.97	0.5 ±0.47	4.45 ± 0.83	95.13 ± 0.68
S40	4.2 ± 0.77	0.66	0.2 ±0.43	4.28 ± 0.72	92.68 ± 0.46

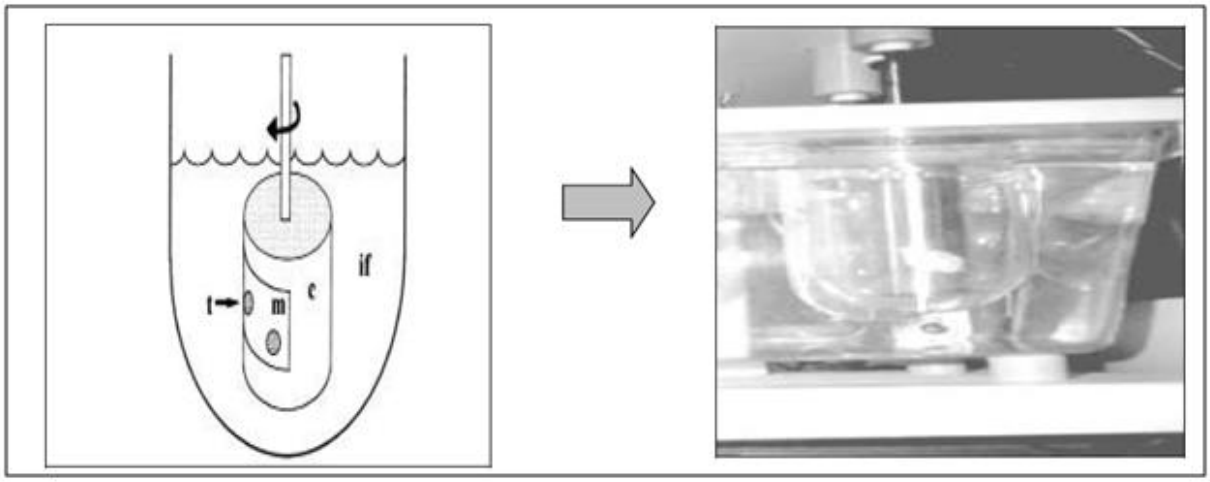

Figure 1- Schematic presentation of the test system used to evaluate the mucoadhesive properties of tablets based on various polymers. C- Cylinder; if- intestinal fluid; m-rat mucosa; t-tablet

In-vitro release studies:

In-vitro release studies of Nifedipine bioadhesive tablets were determined using USP Dissolution Testing Apparatus II (basket type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C at 50 rpm. Aliquot (5 ml) of the solution was collected from the dissolution apparatus hourly for 12 hours and were replaced with fresh dissolution medium. Aliquots were withdrawn at one hour interval from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall .The aliquots were filtered and the absorbance was measured at 238 nm spectrophotometrically.(fig -2,3)

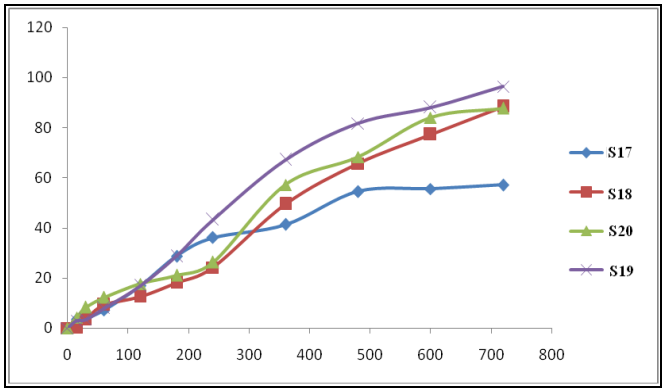

Figure 2 – Comparative study of optimized batches (S17-Chitosan, S18-HPMC 15 cps, S19- Carbobol -934. S20-Sod CMC)

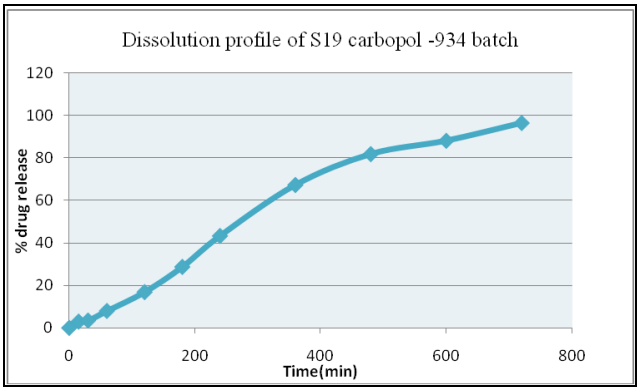

Figure 3- Dissolution profile of S19 carbopol -934 batch

Invitro mocoadhesive study:

The mucoadhesive strength of the tablets was measured on a modified physical balance. The apparatus consist of a modified double beam physical balance in which the right and the left pan have been replaced by lighter pans. The left side of the balance was made 5 g heavier than the right side by placing a 5 g weight on left side pan. Take the tablet & adhere the lower side of the pan ,A preload of 50 g was placed on the clamp for 5 minutes (preload time) to establish adhesion bonding between tablet and porcine or stomach mucosa. The preload and preload time were kept constant for all the formulations. After completion of the preload time, preload was removed from the clamp, and weight was then added into pan the addition of weight was stopped when tablet was detached from either porcine or stomach mucosa. The excess weight on the right pan ie., total minus 5 gm was taken as a measure of mucoadhesive strength from the mucoadhesive strength; the force of adhesion was calculated using the fallowing formula (Table 3 & fig.4,5)

$$\text{Force of adhesion} = \frac{\text{Mucoadhesive strength}}{100} * 9.81$$

Table 3 : in-vitro mucoadhesive strength study of the prepared mucoadhesive tablets

Batch no	Mucoadhesive strength	Mucoadhesion	Mucoadhesion time (hr)
S9	13.35	2.27	5.0 hr
S10	24.15	2.35	10.3hr
S11	21.41	2.25	8.2 hr
S12	15.68	1.86	5.8 hr
S17	19.52	2.52	7.0 hr
S18	18.73	2.83	6.3 hr
S19	27.18	1.19	15.0hr
S20	21.77	2.06	8.0 hr
S37	16.04	1.56	6.3 hr
S38	22.14	2.15	10.0 hr
S39	18.92	1.89	7.0 hr
S40	12.72	2.64	4.0 hr

Figure 4- Assembly for Determination of Bioadhesive Strength

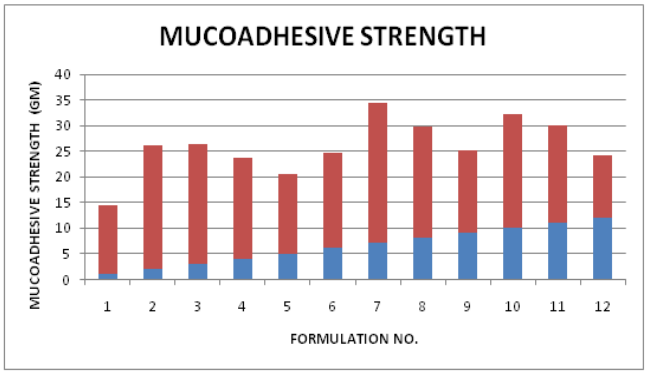

Figure.5 - Mucoadhesion of tablets in gm

DATA ANALYSIS:

To analyze the in- vitro release data various kinetic models were used to describe the release kinetics. The zero order rate equation (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from the system where release rate is concentration dependent. Higuchi describes the release of drugs from insoluble matrix as a square root of

time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in the surface area and diameter.

$$\mathbf{C = k_0 t} \qquad (1)$$

Where k is the zero order rate constant expressed in units if concentration / time and t is the time.

$$\mathbf{Log\ C = Log\ Co - kt/2.303} \qquad (2)$$

Where C is the initial concentration of drug and k is the first order constant.

$$\mathbf{Q = K\ t^{½}} \qquad (3)$$

Where, K is the constant reflecting the design variables of the system.

$$\mathbf{Q_o^{1/3} = Q_t^{1/3} = K_{HC}\ t} \qquad (4)$$

Where Q_t is the amount of drug released in time t, Q_o is the initial amount of the drug in the mucoadhesive tablet and K_{HC} is the rate of Hixson- Croswell rate equation.

The following plots were made: *cumulative % drug release vs. time* (zero order kinetic models); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative percent drug release vs. square root of time (higuchi model); cube root of drug % remaining vs. time (Hixson-Croswell cube root law); and log cumulative % drug release vs. log time (korsmeyer model)

MECHANISM OF DRUG RELEASE:

Korsemeyer et al (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60 % drug release data was fitted in Korsmeyer- Peppas model:

$$\mathbf{M_t / M_\infty = K\ t^n} \qquad (5)$$

Where, M_t / M_∞ is fraction of drug released at time t, K is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in table for cylindrical shape formulations. (Fig 6,7,8 and 9)

Zero order		First order		Higuchi		Korsmeyer – Peppas	
r2	Ko(h^{-1})	r2	K_1 ($h^{-1/2}$)	r2	K_H($h^{-1/2}$)	r2	K_{KP}(h^{-n})
0.968	0.146	0.955	-0.001	0.973	4.534	0.852	0.652

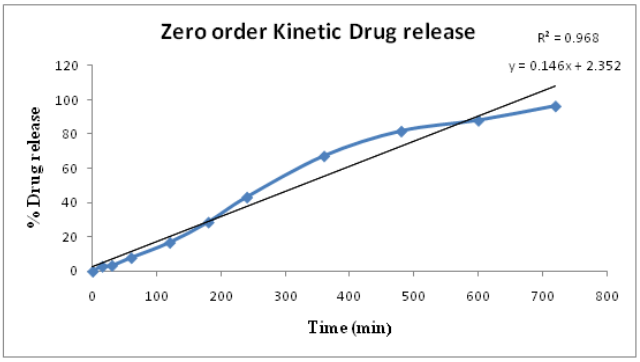

Figure 6 – Time vs Cumulative % drug Release (zero order kinetics)

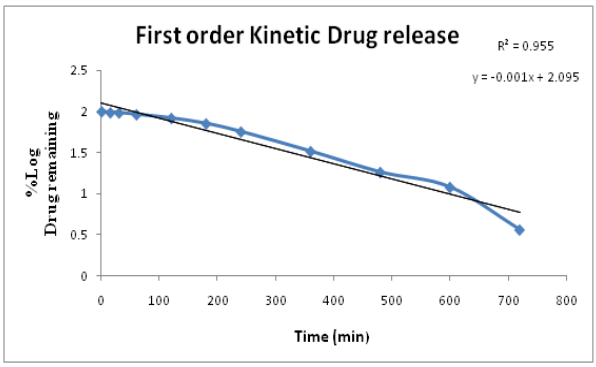

Figure 7 – Time vs Log cumulative % drug remaining (first order kinetics)

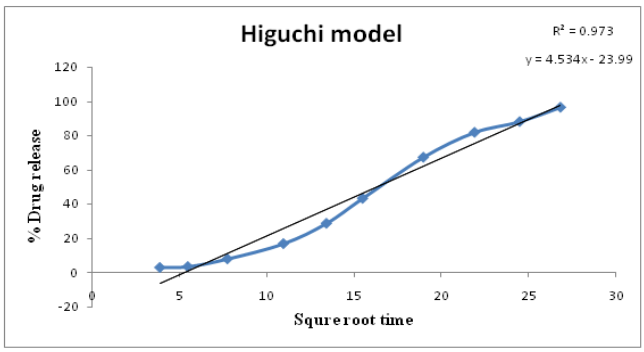

Figure 8 – Square root of Time vs Cumulative % drug release (Higuchi model)

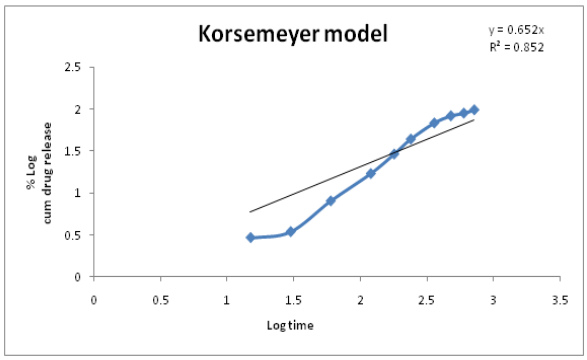

Figure 9- Log Time vs. % Log cum drug release (Korsemeyer model)

RESULTS AND DISCUSSION:

In-vitro mucoadhesive study

In-vitro mucoadhesive study of formulation S17, S18, S19, and S20 was determined on the basis of their adhesion and retention time in stomach; it was found that formulation S19 is optimized formulation of

mucoadhesive tablet because of good adhesion & retention time.S19 formulation releases 43.24 % drug in 4 hr in a sustained manner and releases almost 96.37 % drug in 12 hr.

Formulation S19 is the optimized formulation because of their mucoadhesion time and shows better release profile than that of other formulation . S19 formulation releases 43.24 % drug in 4 hr in a sustain manner and releases almost 96.37 % drug in 12 hr.

Ex-vivo Bioadhesive Strength Determination

Figure.3 shows the bar chart depicting significant variation in the values of bioadhesive strength, obtained using different ratios of polymers. The figure depicts an increasing trend in bioadhesive strength, as observed with porcine mucosa, with an increase in the amount of either polymer. Maximum bioadhesive strength.

CONCLUSION:

The present work was aimed to develop the mucoadhesive drug delivery system for Nifedipine with prolonged effect and to avoid first pass metabolism. It was observed that formulation S19 was best in terms of drug release, bioadhesive performance and physicochemical properties. Therefore it can be concluded that stable formulation could be developed by incorporating Carbopol – 934 for the sustained release of Nifedipine from mucoadhesive tablet with adequate bioadhesiveness and swelling properties without the risk of mucosal damage.

REFERENCES:

1. Asare.G.S Mucoadhesive gastrointestinal drug delivery system:An overview ,Pharmainfo.net ,2007.5:6.
2. Chien YW, Novel Drug Delivery Systems, 2nd edition, Marcel Dekker, Inc. New York, pp 1-42.
3. Hwang S J, Park H and Park K, “Gastric Retentive Drug-Delivery Systems”, Crit. Rev. Ther. Drug Carrier Syst. 1998, 15 (3), 243–284.
4. Whitehead L,. Fell, J. T and Collett J H,“Development of a Gastroretentive Dosage Form”, Eur. J. Pharma. Sci., 1996 4 (1)182.
5. Altermank,C,2007,a critical review of gastroretentive controlled drug delivery ,pharmaceutical develoement and technology,12,1-10
6. Wise DL, Handbook of Pharmaceutical Controlled Release Technology, Marcel Dekker Inc., New York, pp 329-344.

7. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. 2005. Floating drug delivery system: A Review, AAPS Pharm.sci.Tech, 6(3): E372-E390.
8. Rathbone JM, Hadgraft J, Michael SR, 2003, Modified Release Drug Delivery Technology, pp 1-11. Robinson JR, Lee Vincent HL, Controlled Drug Delivery-Fundamentals and Applications, 2nd edition, Marcel Dekker Inc., New York, pp 555-580.
9. Robinson JR, Lee Vincent HL, Controlled Drug Delivery-Fundamentals and Applications, 2nd edition, Marcel Dekker Inc., New York, pp 555-580.
10. Narendra.C, Srinath.M.S, Babu.G.2006.Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. AAPS Pharm.sci.Tech.7 (2):E1-E7.
11. Tripathi Kd.2000. Essential medical pharmacology, fourth edition. Jaypee brother's medical publisher (p) Ltd New Delhi pp .462-465.
12. Lachman L, Liberman HA, Kanig JL. 1987. The theory and practice of industrial pharmacy, 3 rd edition. Varghese publishing house Bombay pp.171-194.
13. Aulton ME .2002. Pharmaceutics the science of dosage form design, 2nd edition Churchhill livingstone pp. 16-32,114-138.