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Formulation and *In-vitro* Evaluation of Bio-Adhesive Gastroretentive System Using Nifidipine.

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ABSTRACT

The gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bio-adhesive systems and low-density systems. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease. Furthermore, improved bioavailability is expected for drugs that are absorbed readily upon release in the GI tract. Bio-adhesive system layer will adhere on gastric mucus which can provide significant of gastro-retentive system. Nifedipine- (anti-hypertensive drug) which is primarily absorbed from stomach and required more than three times a day but by using bio-adhesive layer it can be retain on stomach for more absorption and will reduce the frequency of dosing. The aim of study was to formulate and optimize the bio-adhesive gastro-retentive system of anti-hypertensive drug Nifidipine. Bio-adhesive layer will adhere to gastro mucous which can provide the significance of gastro-retentive system.

Key words: Bio-adhesive, Nifidipine, Gastro-retentive, Carbopol 394P, HPMC

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INTRODUCTION

Several approaches have been proposed to retain the dosage forms in the stomach. These methods include bio adhesive system, swelling system and expanding system and floating system [1]. In fact the buoyant dosage unit enhances gastric residence time (GRT) without affecting the intrinsic rate of emptying. From a pharmacokinetic point of view, the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached [2]. The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In case of bioadhesive drug delivery, the term bioadhesion is used to describe the adhesion between polymers, synthetic or natural and soft tissues or the gastrointestinal mucosa [3,10, 11].

The term "hypertension" literally means an abnormally raised arterial blood pressure. There are many conditions which elevate arterial pressure, including primary renal disease, pheochromocytoma, hyperthyroidism, hyperaldosteronism and coarctation of aorta, leading to secondary hypertension. In about 80 to 85 per cent of patients of hypertension, no specific cause is evident, and such a condition is labeled as primary or essential hypertension [6]. The most antihypertensive drugs can effectively reduce mildly elevated blood pressure, but their use is associated with many side effects. Thus the decision whether to use a drug to control borderline or mild hypertension is made on the basis of the benefit: risk ratio [5]. Nifedipine (anti-hypertensive drug) which is primarily absorb from stomach and required more than three times a day but by using bio-adhesive layer it can be retain on stomach for more absorption and will reduce the frequency of dosing [4].

The objectives of present studies are to formulate and evaluate Nifidipine bioadhesive layer by taken different polymer concentration (w/w). Another objective is to find out best formulation by data analysis.

MATERIALS AND METHODS

Materials

Nifidipine was procured from M/s Hi-Media Lab, Carbopol 934P and HPMC E15 were procured from Lobachem. All other ingredients used were of analytical grade.

Formulation of bio- adhesive layer

- 1000 mg of Nifedipine was dissolve in 15 to 20ml of ethanol.
- Amount of Carbopol 394P for particular preparation was mixed in 20 to 30ml of ethanol with constant string with the help of glass rod and to this required amount of HPMC was added as required for formulation.
- Solution of Nifedipine prepared in fist step was added to the mixture of Carbopol 394P and HPMC with constant string with the help of glass rod.
- Mixture of all ingredients was poured in a Petri-dish.
- Preparations were kept for two days at room temperature.

EXPERIMENT

Evaluation of bio-adhesive layer [7]

The production yield of bio-adhesive layer of various batches were calculated using the weight of final product after drying with respect to the initial total weight of the drug and polymer and polymer used for the production of bio-adhesive layer and % production yield were calculated as per the formula mentioned below-

Production yield (%) = (practical mass/ theoretical mass) ×100

Practical mass = weight of microspheres
Theoretical mass = drug + polymer

In vitro drug release study [8]

The drug release studies from bio-adhesive layer were carried out in vitro using a dissolution medium of HCl (0.1 N, pH 1.2) USP Type-2 (paddle) dissolution testing apparatus maintained at 37±0.5 °C with a rotation rate of 50 rpm. A 2cm×3cm piece of bio-adhesive layer was suspended in 900 ml of dissolution media with the help of high density mass which made layer suspended in media. At the preset time intervals, 5 ml aliquots were withdrawn and replaced by an equal volume of fresh dissolution media, maintaining the sink condition throughout the experiment. The amount of drug released at different time intervals was found by using a UV-Vis spectrophotometer (Shimadzu)

In-vitro Mucoadhesivity test [4]

The mucoadhesive property of bio-adhesive layer was evaluated in-vitro by modified physical balance for mucoadhesion. Pieces of mucosa (5cm×6cm) were mounted onto glass slides. About 2cm×3cm of bio-adhesive layer were attached at one arm of physical balance that was mounted above the mucosa. Modified physical balance was balance by adding water in required arm of before made them contract. Both layer and mucosa were wet with the help 0.1N HCl and made them in contract for 5minute. Water was added to the opposite arm until layer was removed.

A preload of 10 mg is placed on the slide for 5 min (preload time) After the completion of preload time, preload is removed from the glass slide and water is then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water is stopped when mucoadhesive dosage form is detached from the goat or rat stomach mucosa. The weight of water required to detach mucoadhesive dosage form from stomach mucosa is noted as mucoadhesive strength in grams.

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength}}{1000} \times 9.81$$

$$\text{Bond strength (N/m}^2\text{)} = \text{Force of adhesion (N)/ Surface area of tablet (m}^2\text{)}$$

Tensile strength

Taking a piece of about 4cm×5cm and fixed it between two rings of same diameter of about 3cm or less so that a weight of 10 gm can be put on it. 0.1N HCl was pouring at the layer, after five minute 10 gm weight was placed on it and the time at which layer brake was noted for each preparation.

Drug entrapment efficiency [9]

2×3cm of bio-adhesive layer was weighted accurately and drug was extracted from bio-adhesive layer by digesting for 24 hours in 10 ml of 6.8 pH phosphate buffer solution. During this period the suspension was agitated. After 24 hrs the suspension was centrifuged at 2000 rpm for about 3 minutes. The supernatant obtained was assayed spectrophotometrically for drug contents.

The drug entrapment efficiency (DEE) was determined as:

$$\text{DEE} = (Pc / Tc) \times 100$$

Pc is practical content,
Tc is the theoretical content.
All the experimental units were analyzed in triplicate (n=3).
Thickness: Thickness of each layer was measured with the help of Vanier calipers meter.

RESULTS AND DISCUSSION

The Bio-adhesive layer of Nifidipine was prepared by wet mixing process as per formula given in (table-1).

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Table 1: Composition of Bio-Adhesive Layer

Formulation No.	HPMC E15 (in mg)	CARBOPOL (in mg)	DRUG (in mg)
F1	100	1500	1000
F2	400	1500	1000
F3	600	1500	1000
F4	800	1500	1000
F5	1000	1500	1000
F6	600	2000	1000
F7	600	3000	1000
F8	-	1500	1000
F9	600	-	1000
F10	400	400	1000
F11	100	200	1000
F12	200	600	1000
F13	600	300	1000
F14	600	200	1000
F15	600	1500	1000
F16	1500	1500	1000

Evaluation of the Study

Production yield

Production yield was found to be good between 88 to 95% but best result was found 95% of preparation F5 in which the concentration of both polymer CP and HPMC was high 1000mg and 1500mg respectably.

Release profile

Good release was found in preparation (F6 from 0.13 to 91.56) and F7 (from 2.77 to 85.20) among all sixteen preparations.

Mucoadhesivity test

Formulations F1, F2, F3, F6 and F7 in contain high amount of cabopol 934P results high mucoadhesive strength to retain on mucous as compare to other preparations.

Tensile strength

Formulations F6, F7 and F16 show high tenstile strength as compare to rest of preparation to maintain their structure.

Drug entrapment efficiency

Good entrapment was found between 74 to 97% of bio-adhesive layers but highest entrapment was found of preparation F7 and F16 that was 97%.

Thickness

All the prepared layer was found 1.5 to 2 mm thick and uniformity was throughout of the layer.

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Production Yield in Percentage (%)

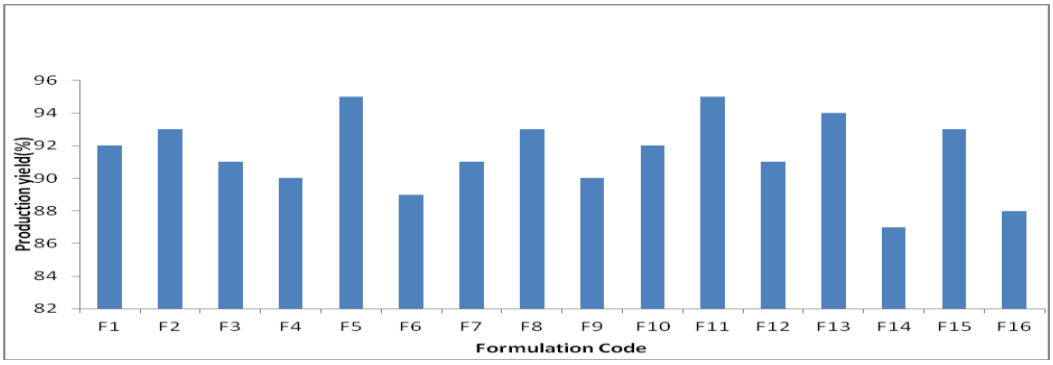

Figure 1: Formulation F5 shows best production yield with 95%

Table 2: Drug release Profile of prepared formulation (F1-F8)

TIME(In hrs)	F1	F2	F3	F4	F5	F6	F7	F8
1	0.09	0.18	-	-	-	0.13	2.77	96.08
2	0.12	0.14	0.002	-	-	1.17	5.16	96.12
3	7.2	0.17	0.008	-	-	3.41	8.01	96.89
4	7.4	1.3	0.091	-	-	15.49	18.67	96.89
5	7.49	5.52	0.186	-	-	28.39	33.83	96.91
6	7.82	5.64	3.256	0.024	-	40.18	46.64	97.01
7	8.12	5.67	3.875	0.037	-	53.11	60.13	97.00
8	8.14	5.69	4.392	0.039	0.019	66.82	75.10	97.03
9	8.18	6.01	15.30	0.012	0.028	79.90	88.90	97.05
10	8.26	6.04	16.13	0.043	0.034	81.81	90.50	97.13
11	8.32	6.9	16.92	0.012	0.046	90.03	92.60	97.58
12	8.42	7.02	16.98	1.05	0.973	91.56	85.20	97.61

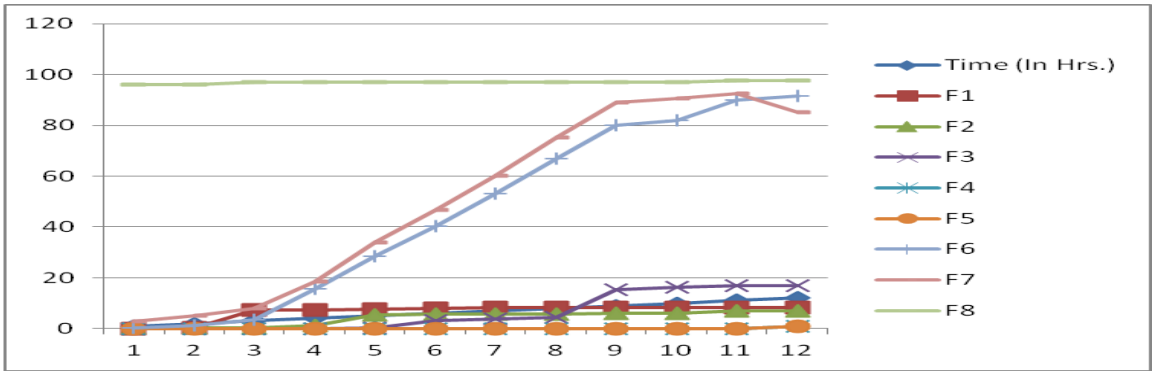

Figure 2: Graph showing Drug release profile of Formulation F1-F8

Table 3: Drug release Profile of prepared formulation (F9-F16)

TIME(In hrs)	F9	F10	F11	F12	F13	F14	F15	F16
1	-	0.21	1.08	0.13	0.22	1.26	28.19	0.24
2	-	0.32	2.19	0.18	0.23	1.29	54.17	0.02
3	-	5.47	3.23	1.58	13.13	2.56	69.13	0.03
4	-	20.42	4.32	3.43	13.19	8.58	78.94	0.06
5	-	20.48	5.44	12.09	13.21	13.16	88.96	0.06
6	-	20.49	6.89	25.48	13.27	13.19	96.01	0.71
7	-	20.58	8.71	35.18	13.29	13.21	96.04	1.14
8	-	20.62	9.92	51.42	20.19	20.19	96.09	1.16
9	-	20.64	12.37	63.91	27.34	27.34	97.08	2.01
10	0.40	21.13	15.46	78.84	30.44	30.44	97.82	2.04
11	0.80	21.15	25.82	89.03	36.45	36.45	97.84	2.53
12	1.56	22.19	33.68	90.04	56.07	56.07	97.85	2.56

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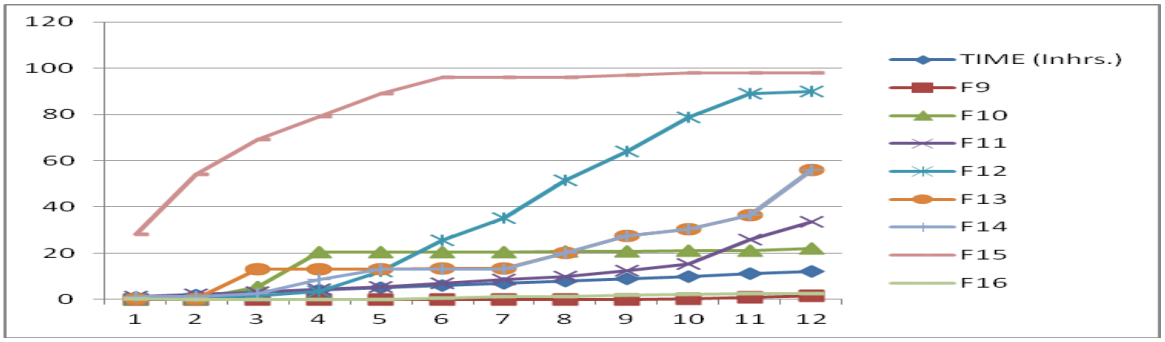

Figure 3: Graph showing Drug release profile of Formulation F9-F16

Mucoadhesive Strength

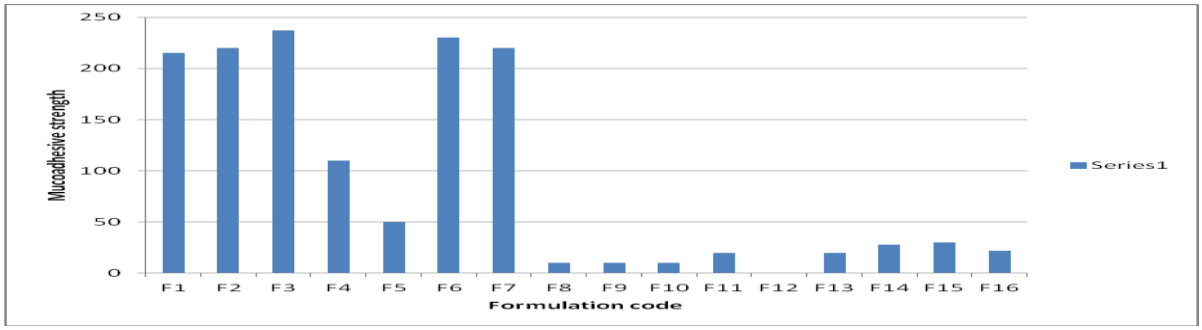

Figure 4: Formulation no.F1, F2, F3, F6, and F7 was found enough mucoadhesive strength to maintain their structure

Tensile Strength

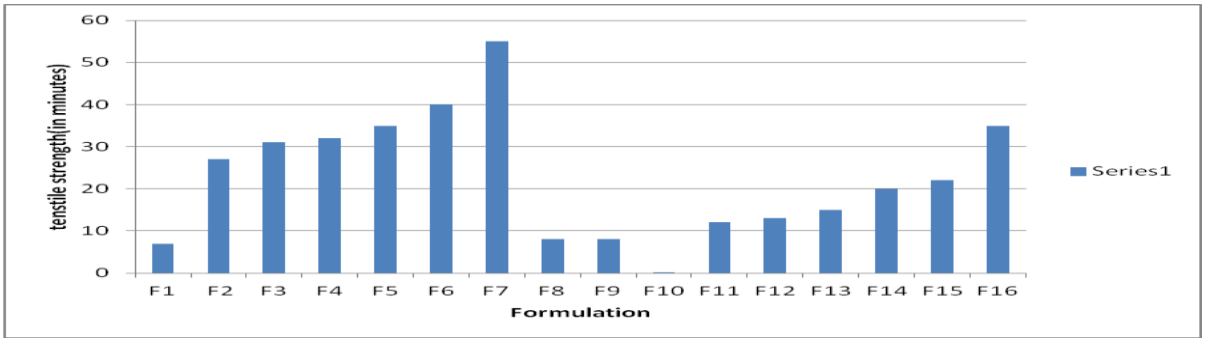

Figure 5: Formulation F6 and F7 was found to be high tensile strength as compare to rest of preparation.

Drug Entrapment Efficiency (%)

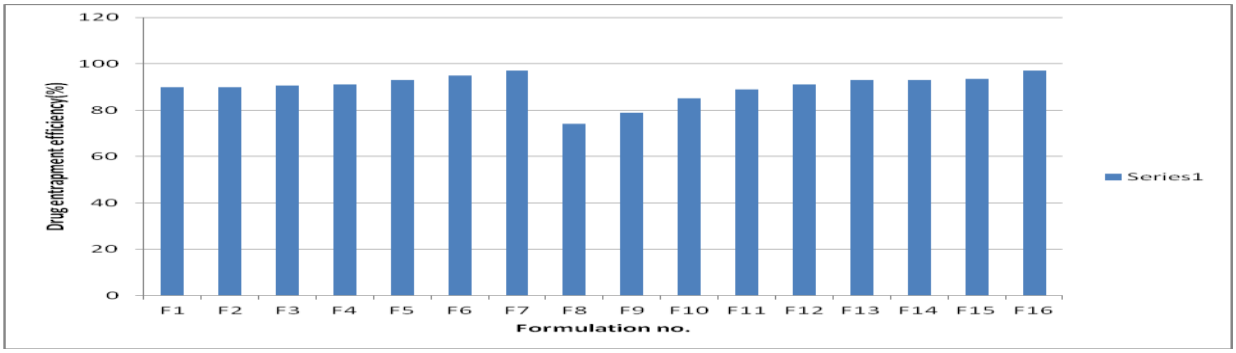

Figure 6: Formulation F7 and F16 show highest entrapment with 97% Entrapment efficiency

Table 4: Thickness of Bio-adhesive layer

Formulation No.	Thickness(mm)	Formulation No.	Thickness(mm)
F1	1.0±0.5	F9	1.0±0.5
F2	1.0±0.5	F10	1.0±0.5
F3	1.0±0.5	F11	1.0±0.5
F4	1.5±0.5	F12	1.0±0.5
F5	1.5±0.5	F13	1.5±0.5
F6	1.5±0.5	F14	1.5±0.5
F7	1.5±0.5	F15	1.5±0.5
F8	1.0±0.5	F16	1.0±0.5

CONCLUSION

Prepared layers were found to be uniform in thickness and smooth at optimum concentration ratio of polymer. Drug entrapment efficiency study was performed on each formulation and can be seen that the drug entrapment of all formulation was good, and found that it was increase with increase the concentration of both polymer (F16).Preparation no F6 andF7 had to be found high tensile strength as compare to rest of preparation in which polymer concentration was either high or low, it can concluded that at optimum ratio (1:5) of CP and HPMC layer show better tensile strength.

Mucoadhesivity strength of F1, F2, F3, F6 and F7 were found to be high as compare to other preparation. By observation of data it was concluded that mucoadhesive property was increased with increased concentration of both CP and HPMC up to a certain ratio after that it was decreased. In this research work we found that bioadhesive layer of Nifedipine can be formed by taken polymer CP and HPMC. Good Bioadhesion and release of drug were depending upon a proper combination of polymer.

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