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Novel site specific delivery system containing ofloxacin for the treatment of periodontal infection

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ABSTRACT

A Novel drug delivery system for the treatment of periodontitis was developed for site specific delivery of Ofloxacin which has excellent activity against anaerobic microorganism. Periodontal diseases are the conditions that affect the supporting structure of teeth leading to the formation of pocket due to which tooth loss occurs, for which site specific drug delivery systems are gaining importance. In the present investigation nine formulations of site specific mucoadhesive tablets were prepared and evaluated in order to achieve sustained release of drug. The tablets were prepared by direct compression method using Carbopol 934P, Hydroxy propyl methyl cellulose K4M, Sodium Carboxy Methyl Cellulose and Guar gum as mucoadhesive polymers in various ratios like 1:4, 2:3 and 4:1.The prepared tablets were evaluated for weight variation, thickness, hardness, friability, uniformity of active ingredient, surface pH, swelling studies, mucoadhesive strength, *Ex vivo* mucoadhesion time, *In Vitro* drug release study, Anti bacterial activity and then subjected to stability studies. The best mucoadhesive strength, mucoadhesive time and *In Vitro* drug release profile was observed in F4 containing Carpool 934P with Sodium Carboxy Methyl Cellulose in ratio of 1:4.The surface pH of tablets was found to be satisfactory, close to neutral pH; hence, no irritation would observe with these tablets. It was also observed that the optimized formulation follows peppas release kinetics.

Keywords: Ofloxacin, Mucoadhesive polymers, Surface pH, Mucoadhesive strength, *In Vitro* release.

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INTRODUCTION

Mucoadhesion is a topic of current interest in the design of drug delivery systems. Mucoadhesive drug delivery system prolong the residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the underline absorption surface and thus contribute to improved and or better therapeutic performance of the drug. In recent years many such mucoadhesive drug delivery systems have been developed for oral, mucoadhesive, nasal, rectal and vaginal routes for both systemic and local effects.

Extensive efforts have recently been focused on targeting a drug or drug delivery system in a particular region of the body for extended period of time, not only for local targeting of drugs but also for the better control of systemic drug delivery [1]. Oral mucoadhesive drug delivery systems offer many advantages over conventional systems such as ease of administration, rapid termination of therapy and administration to unconscious patients. Drugs which are destroyed by the enzymatic/alkaline environment of the intestines are unstable in the acidic environment of the stomach can be administered by this route. It permits localization of the drug to oral cavity for a prolonged period of time and significant reduction in the dose can be achieved, thereby reducing dose related side effects [2- 4]. Local delivery to the oral mucosa has a number of applications as treatment of toothache, treatment of periodontal infections, bacterial and fungal infections [4, 5].

Periodontal diseases are recognized as the major public health problem throughout the world. Daily oral hygiene plays a vital role in maintaining healthy teeth and gums. Periodontal disease can do occur in all age groups, ethnicities, races, genders and socioeconomic levels [6- 8]. Periodontal diseases are group of infections and inflammatory conditions, including gingivitis and periodontitis that affect teeth-supporting structures. These diseases occur when bacteria from dental plaque invade surrounding tissues and accumulation of plaque at the gingival margin induces inflammatory response. The result is the formation of pockets between gingiva and tooth that causes gingival margin retraction and the development of an ideal environment for anaerobic bacteria growth responsible for the disease. The progression of this destruction process can cause tooth loss [9, 10]. The therapeutic goal is the removing of bacteria responsible for the infection by mechanical cleaning and topical application of antimicrobial agents such as Tetracycline, Ofloxacin, Metronidazole, Clindamycin, Chlorexidine and Cetylpyridinium [11].

Antimicrobial agents are orally administered to produce a systemic effect, but this application induces some side effects like hypersensitivity, gastrointestinal intolerance, and development of bacterial resistance [12, 13]. Furthermore, it is reported that this kind of administration does not guarantee concentration at the action site because the active product is not retained locally for a sufficient period of time. A solution for these problems could be the local administration of the drug formulated in a controlled release delivery system to be placed directly on the action site [14].

The aim of this study is the preparation of site specific Mucoadhesive tablets in order to obtain sustained release of Ofloxacin. In planning this kind of formulation, the following characteristic are required: (i) small size, (ii) flexibility and adaptability to the mucosa, (iii) no irritation, no discomfort, no bad taste, (iv) no dry mouth, (v) no excessive salivation and heaviness in oral cavity.

MATERIALS AND METHODS

Ofloxacin IP was obtained as a gift sample from Goodman Pharmaceuticals Ltd., Pondicherry, India. Carbopol 934P, Hydroxyl Propyl Methyl Cellulose K4M, Sodium Carboxy Methyl Cellulose was procured as gift samples from Cipla Pvt Ltd., Mumbai. Spray dried lactose was obtained from Orchid Pharmaceuticals Pvt Ltd., Chennai, India. All other reagents and chemicals used were of analytical grade.

DRUG-POLYMERS COMPATIBILITY STUDIES:

Differential Scanning Calorimetry (DSC)

Any possible drug interaction can be studied by thermal analysis. The DSC study was performed on pure drug, drug + Carbopol 934P + HPMC-K4M, drug + Carbopol 934P + SCMC (DVP) and drug + Carbopol 934P + Guar gum. The study was carried out using a shimadzu DSC 60, (Japan). The 2 mg of sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300^{0}c at heating rate of 10^{0}c /min under nitrogen flow of 30ml/min.

Preparation of tablets

Mucoadhesive tablets, each containing 15 mg Ofloxacin, were prepared by direct compression method, using different combination of polymers Table 1. The tablets were prepared using Carbopol 934P as primary Mucoadhesive polymer and Hydroxyl Propyl Methyl Cellulose K4M, Sodium Carboxy Methyl Cellulose and Guar gum as secondary polymers. All the ingredients of tablets were blended in mortar with a pestle for 15 minutes to obtain uniform mixture. The blended powder was then compressed into 150 mg tablets (at 6 to 7.5 kg/cm^2) using 16 station rotary tablet machine (Cadmach, Ahmadabad, India) with 9 mm round shaped flat punch.

Determination of physicochemical parameters

The thickness and diameter of the tablets was determined using a vernier caliper. Three tablets from each type of formulation were used and average values calculated. Hardness of the tablets was measured by using the Monsanto hardness tester. It is expressed in kg/cm^2. Twenty tablets were weighed individually and the average weight was determined. Percentage deviation was calculated and checked for weight variation. Six tablets of each formulation were taken and amount of drug present in each tablet was determined. Each tablet was crushed

separately and 5% glacial acetic acid (about 70 ml) was added to extract the drug. Volume was made to 100 ml with 5%glacial acetic acid, and then filtered diluted and analyzed in spectrophotometer at 294 nm.

Surface pH study [15, 17]

The surface pH of the Mucoadhesive tablet was determined in order to investigate the possibility of any side effects in an oral cavity. As an acidic or alkaline pH may irritate the mucosa, attempt was made to keep the surface pH close to the mucosal pH. The tablets were allowed to swell for 2 h in 1 ml of distilled water (Ph 6.5 ± 0.05) at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min.

In vitro swelling study [20]

Three tablets were used from each formulation for the test. After recording the initial weights the tablets were placed over a 10 cm diameter wet filter paper disc soaked in purified water in a Petri dish at room temp. After the time interval of 1, 2, 4, 6 and 8 h., the tablets were removed and weighed individually. The percent water sorption was calculated using following formula

$$\% \text{ Swelling index} = [(w_2-w_1)/w_1] \times 100$$

Where,

W_2: weight of tablet after particular time interval
W_1: initial weight of tablet

In vitro bioadhesion study [21]

Measurement of adhesion strength was determined by using bovine mucosa which was obtained from slaughter house. The underlying tissues were separated and washed thoroughly with phosphate buffer solution (pH 6.6). The membrane was then tied to the bottom of the lower vial using rubber band. The vial was kept in glass bottle which was filled with phosphate buffer solution at 37 ± 1 ^{0}C in such way that buffer just reaches the surface of mucosal membrane and kept it moist. The tablet to be tested was stuck on the lower side of the hanging glass vial by using adhesive tape and the weight (2 gm) on the right pan was removed. This lowered the left side of the pan along with the tablet over the mucosa. It was kept undisturbed for three minutes and the weights are added on right side of pan till the tablet just separated from the membrane surface. The excess weight on the right pan i.e. total weight minus 2 gm was taken as measure of biooadhesive strength. Bioadhesive force was calculated by using following equation

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

Ex vivo mucoadhesion time

The *Ex vivo* mucoadhesion time was examined after application of the Mucoadhesive tablet on freshly cut bovine oral mucosa. The fresh bovine oral mucosa was tied on the glass slide and a mucoadhesive core side of each tablet was wet with 1 drop of phosphate buffer (pH 6.6) and pasted to the bovine oral mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer and kept at 37 ^{0}C ± 1^0 C. After 2 minutes, a slow stirring rate was applied to stimulate the oral mucosal cavity environment and tablet adhesion was monitored for 20 hours. The time for the tablet to detach from the bovine mucosa was recorded as the mucoadhesion time.

In vitro drug release study [18]

The influence of technologically defined condition and difficulty in simulating *In Vitro* conditions has led to development of a number of *In Vitro* release method for Mucoadhesive formulations; however no standard *In Vitro* method has been developed. Standard USP or BP dissolution apparatus have been used to study *In Vitro* release profile using rotating paddle and basket [18]. *In Vitro* release rate study of Mucoadhesive tablets of Ofloxacin was carried out using the veego dissolution test apparatus (USP I) rotating basket method. The dissolution medium consists of 500 ml of phosphate buffer (pH 6.6). The release was performed at 37^0±0.5^{0}C, with a rotation speed of 50 rpm. Samples (5ml) were withdrawn at predetermined time intervals (1, 2, 3, 8 hr) and analyzed after appropriate dilution by UV spectrophotometry at 288nm. The experiments for different formulations (F1 to F9) were conducted in triplicate and average values were recorded.

RESULTS AND DISCUSSION

Before designing various formulations, the drug-polymers compatibility studies were conducted by DSC studies. The results indicate that there was no incompatibility between drug and polymers. The results are shown in Figure 1.

Physicochemical parameters of all the tablets showed hardness, weight variation, friability and drug content as per the standards in I.P. The results are shown in Table 2.

The surface pH of all the prepared tablets was found closer to that of neutral pH and hence tablets should not cause any irritation to the oral mucosa. The results are shown in Table 3.

Table 3 shows the Bioadhesive performance of various tablets. The bioadhesive strength of the tablets was found to be a function of the concentration of polymer. As none of the tablets dislodged before complete erosion, the bioadhesive strength exhibited by all the tablets is satisfactory for maintaining them in the oral cavity. Among the formulations containing CP-934P in combination with different polymers, those containing CP-934P with SCMC (DVP) exhibited maximum bioadhesive strength followed by those containing CP-934P in combination with HPMC-K4M, which exhibited almost similar bioadhesive strength. The formulations containing CP-934P in combination with Guar gum showed the lowest bioadhesive strength.

The *In vitro* drug release from tablets prepared using different bioadhesive polymers is shown in Figures 4-6. The release of the drug seems to be dependent on the nature and concentration of the polymers used. The tablets F4 gave the maximum release in 8 h of the study. At higher concentration of polymers , the release of the drug as well as the adhesion time were found to be dependent on the type of polymers as well as the total composition of the tablets. The mechanism of drug release seems to be tablet erosion as observed visually during the release study. However, at higher concentration, the formulations containing CP-934P in combination with SCMC-DVP exhibited swelling which was predominant over erosion. Formulation F4 formed a swollen matrix which did not erode in 3 h.

Figures 4-6 shows the effect of CP-934P with HPMC-K4M, SCMC and Guar gum. The results showed that the concentration of CP-934P increased; the release rate decreased. The lowest release rate was observed with F9 containing 80% CP-934P with 20% of Guar gum (4:1) and the highest release rate was observed with F4 containing 20% CP-934P with 80% SCMC (1:4). The formulation F4 shows promising results by releasing 93.04% (r=0.9993, n=0.93) drug release by sustained manner at 8 h. This is due to 20% CP-934P with 80% of SCMC (DVP) absorbed water rapidly with maximum swelling at 4 h and start well erosion.

The advantage of these Mucoadhesive tablets was its erodible character as compared to the tablets prepared earlier which either dislodged or disintegrated during studies. Our system had better patient compliance because of the decrease in the frequency of administration as compared to the conventional tablets. The tablets released the drug in sustained manner over a period of 8 hours leaving no undisintegrated residual fragment. This was a significant achievement as patients did not have the necessity to remove the tablet after predetermined time intervals.

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Table 1: Composition of Site Specific Mucoadhesive Tablets

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ofloxacin	15	15	15	15	15	15	15	15	15
Carbopol 934P	15	30	45	15	30	45	15	30	45
HPMC K4m	60	45	30	-	-	-	-	-	-
SCMC (DVP)	-	-	-	60	45	30	-	-	-
Guar gum	-	-	-	-	-	-	60	45	30
Spray dried lactose	40	40	40	40	40	40	40	40	40
Mannitol	15	15	15	15	15	15	15	15	15
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Pine apple	1	1	1	1	1	1	1	1	1

Composition of nine formulations (F1 to F9) of site specific tablets of Ofloxacin obtained adding different polymers in varying ratios.

Table 2: Physicochemical parameters of Site Specific Mucoadhesive tablets

Code	Thickness (mm)*	Weight variation test (%)*	Hardness (kg/cm^2)*	Friability (%)*	Drug content (%)*
F1	2.10±0.01	1.16±0.83	7.58±0.37	0.15±0.05	93.85±0.87
F2	2.0±0.01	1.07±0.95	7.5±0.44	0.12±0.08	94.34±0.95
F3	1.99±0.01	0.93±0.79	7.5±0.44	0.10±0.03	91.59±0.62
F4	2.00±0.01	0.93±0.62	6.75±0.27	0.12±0.01	99.63±0.37
F5	2.01±0.02	0.93±0.66	7.25±0.27	0.18±0.08	97.91±0.43
F6	2.02±0.04	1.07±0.82	6.58±0.37	0.13±0.06	93.61±0.89
F7	2.01±0.03	0.93±0.73	6.41±0.37	0.13±0.03	100.1±0.69
F8	2.05±0.04	0.87±0.68	6.41±0.37	0.10±0.12	98.81±0.31
F9	2.00±0.02	0.93±0.85	7.25±0.27	0.12±0.10	99.49±0.59

*All the values are expressed as mean± SE, n=3.

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Table 3: Evaluation of site specific mucoadhesive tablets

Formulation code	Surface pH*	Bioadhesive Strength(g)*	Bioadhesive Force (N)*	Mucoadhesive time(hrs)*
F1	6.33±0.03	25.96±0.12	2.55±0.01	15.33±0.12
F2	6.35±0.02	24.50±0.21	2.40±0.02	13.20±0.16
F3	6.40±0.03	23.65±0.25	2.31±0.02	12.33±0.18
F4	6.58±0.02	30.93±0.09	3.03±0.09	16.25±0.16
F5	6.40±0.15	28.96±0.12	2.83±0.01	14.26±o.16
F6	6.48±0.03	27.53±0.20	2.69±0.02	13.21±0.16
F7	6.44±0.02	22.13±0.33	2.16±0.03	14.31±0.06
F8	6.32±0.02	21.20±0.33	2.05±0.04	12.33±0.14
F9	6.31±0.01	19.40±0.29	1.90±0.02	11.31±0.12

*All the values are expressed as mean± SE, n=3.

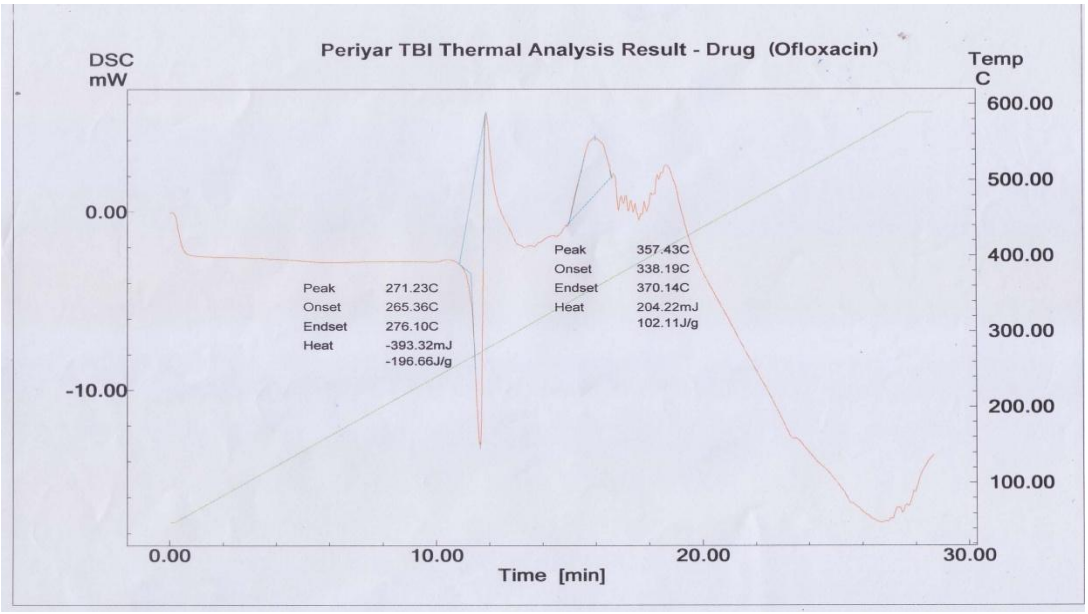

Figure 1(a): DSC thermal analysis of Ofloxacin

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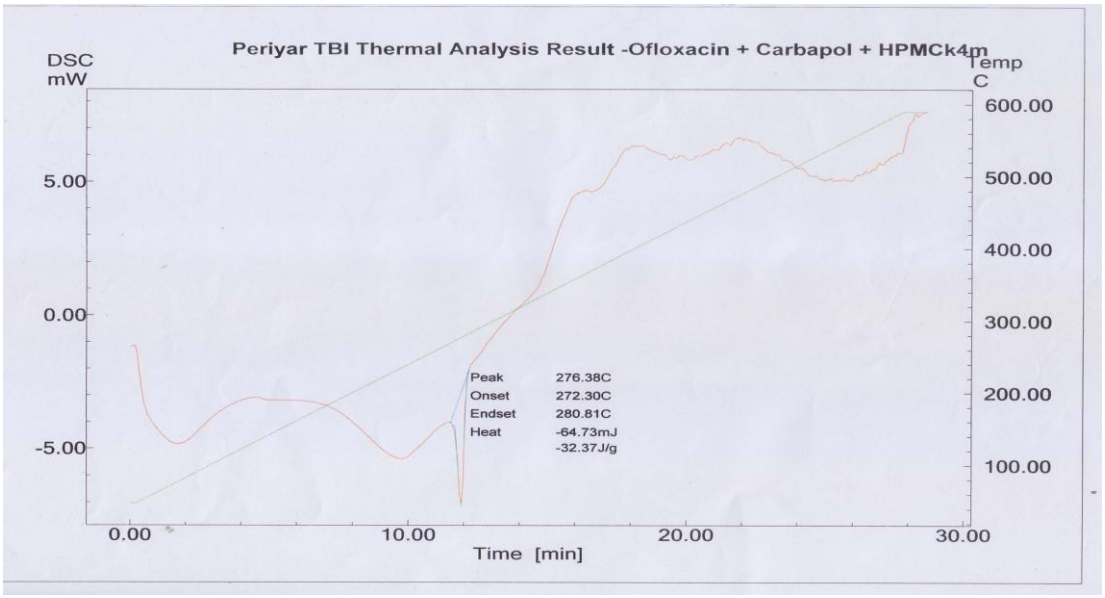

Figure 1(b): DSC thermal analysis of Ofloxacin + Carbopol 934P + HPMC K4M

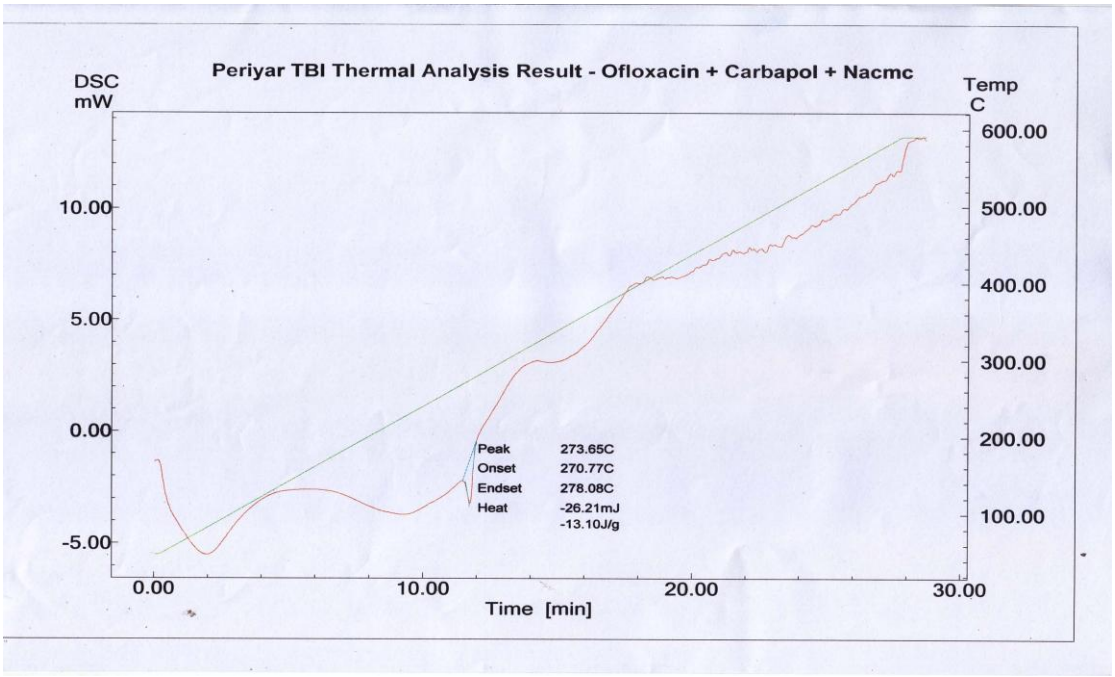

Figure 1(c): DSC thermal analysis of Ofloxacin + Carbopol 934P + Na CMC

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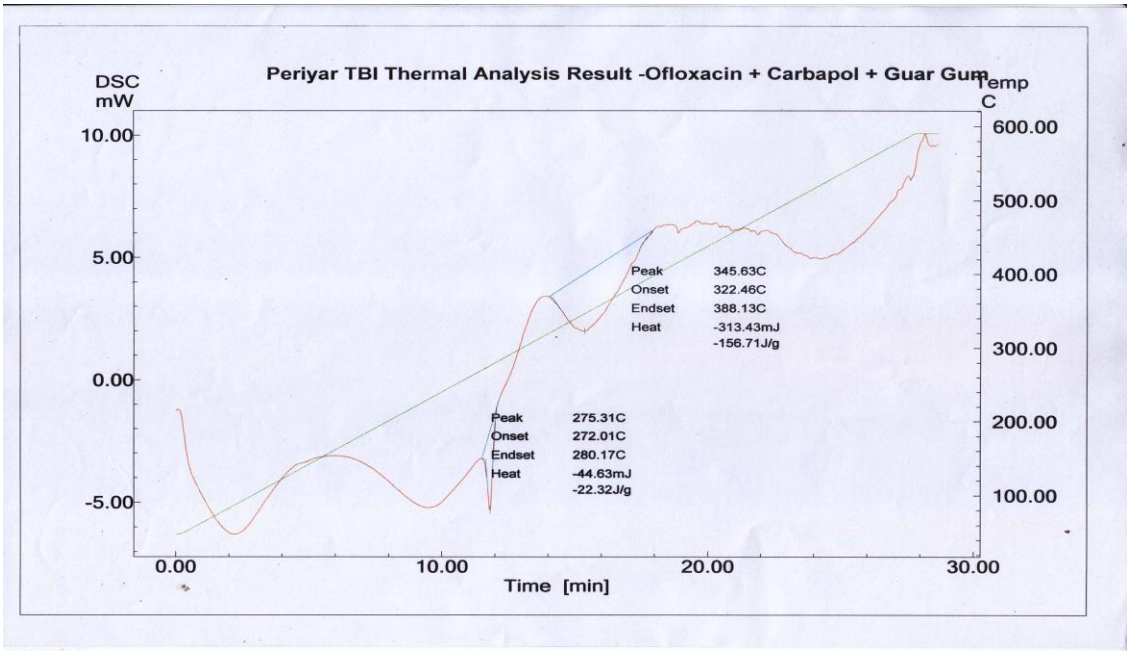

Figure 1(d): DSC thermal analysis of Ofloxacin + Carbopol 934P + Guar gum

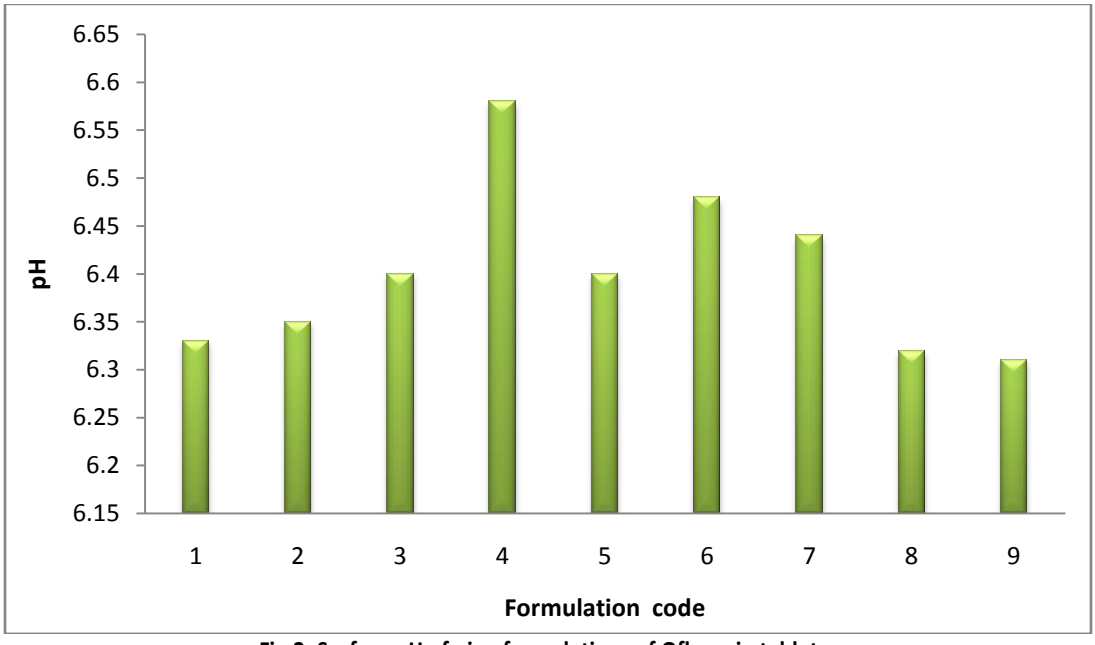

Fig.2: Surface pH of nine formulations of Ofloxacin tablets.

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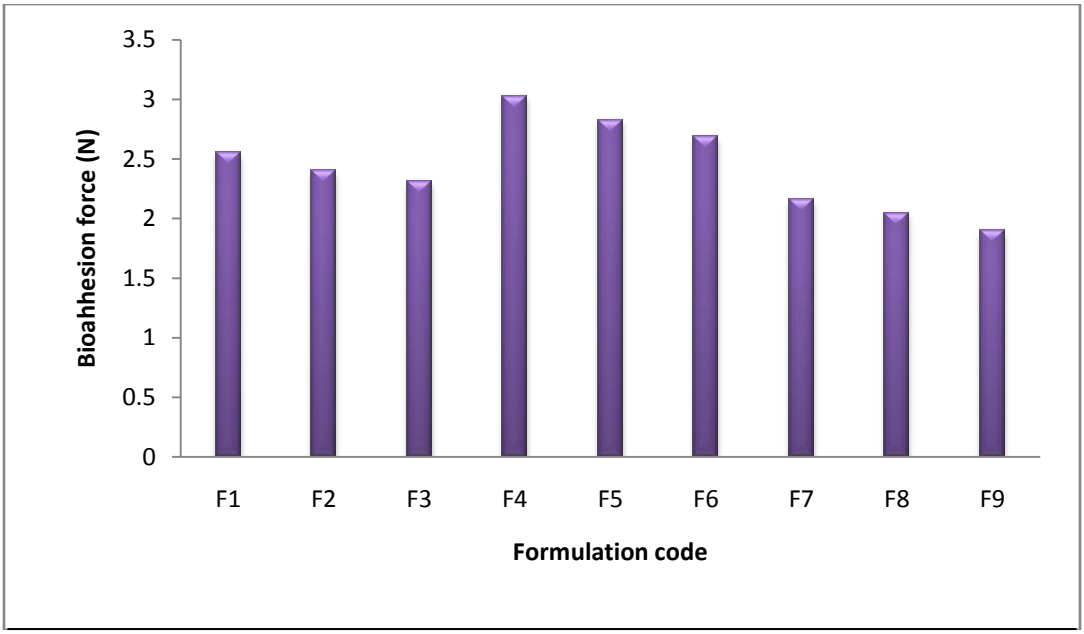

Fig.3: Effect of Bioadhesive polymers on Bioadhesive force

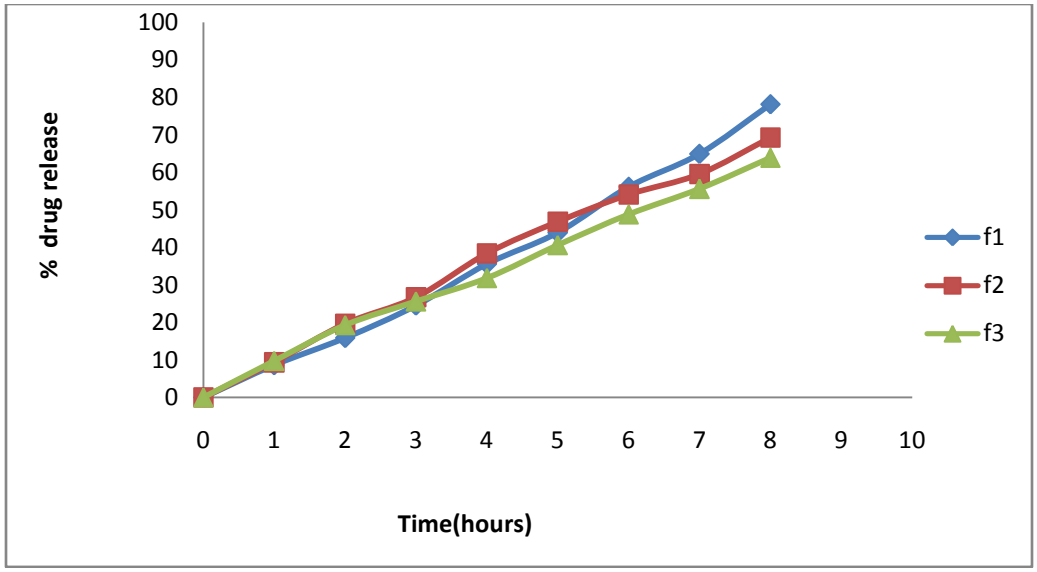

Fig.4: *In Vitro* drug release curves for tablets containing CP-934P with HPMC-K4M in various ratio i.e. 1:4, 2:3 and 4:1.

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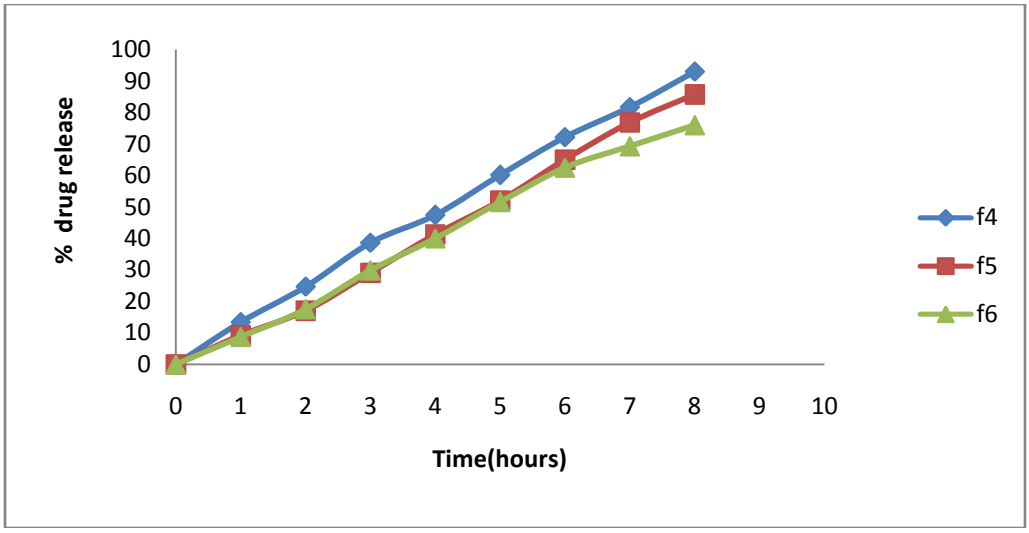

Fig.5: *In Vitro* drug release curves for tablets containing CP-934P with SCMC (DVP) in various ratio i.e. 1:4, 2:3 and 4:1.

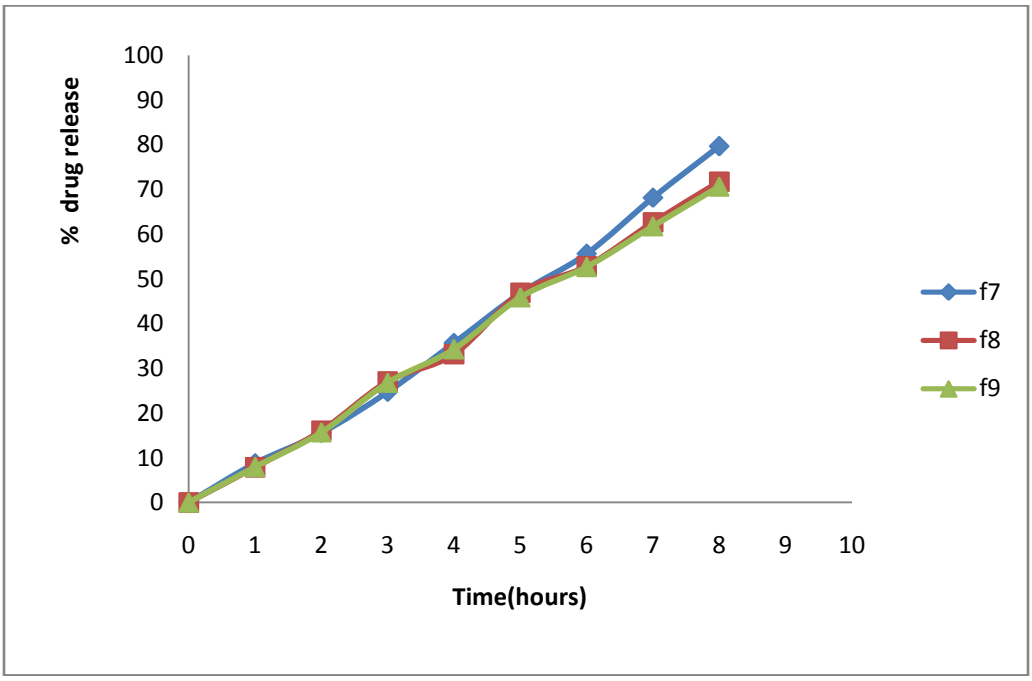

Fig.6: *In Vitro* drug release curves for tablets containing CP-934P with Guar gum in various ratio i.e. 1:4, 2:3 and 4:1.

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