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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MUCOADHESIVE TABLETS OF DILTIAZEM HYDROCHLORIDE FOR PROPHYLAXIS OF ANGINA PECTORIS

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ABSTRACT

The aim of the present study was to formulate and evaluate Gastroretentive sustained release mucoadhesive tablets of Diltiazem hydrochloride for the prophylaxis of Angina pectoris. The most common symptom of angina is feeling of pain or discomfort in chest caused by cardiac ischemia. Diltiazem is a potent calcium channel blocker acts by relaxing the muscles that make up the walls of the arteries, which increases blood supply to the heart. Preformulation studies showed excellent flow property. Tablets were prepared by direct compression method using Hydroxy Propyl Methyl Cellulose (HPMC) E 15 and HPMC K 15 as mucoadhesive polymers and Ethylcellulose (EC) as release retarding polymer. Uniformity of weight, hardness, thickness, diameter and friability were determined. Drug content for all the formulations was in the range of 90.66% to 99.83%w/w. *In vitro* release was performed in acid buffer pH 1.2. The drug release for the optimised batch (F4) was found to be 99.2% at the end of 23 hours. The sustained action was due to Ethylcellulose (10%). The swelling index was found to be 120%. The tablet swelled gradually and releases the drug slowly due to hydrophilic and high viscous nature of HPMC K15.

KEYWORDS: Diltiazem hydrochloride, Angina pectoris, Mucoadhesive tablets, Sustained release.

INTRODUCTION

A drug delivery system ideally should deliver a specified amount of drug to the site of action at an appropriate time and rate as dictated by the needs of body. Conventional pharmaceutical dosage forms now in use are unable to control either the rate or site specific delivery. As a result, the massive distribution of drugs in non-target tissues and body fluids necessitates therapeutic doses that far exceed the amount required in target cells, often leading to serious adverse effects during the treatment. The ultimate goal of Pharmacotherapeutics is to maximize the therapeutic efficacy of a drug while minimizing its adverse effects. This paved the way to the concept of rate controlled drug delivery systems to overwhelm the drawback of fluctuating drug levels associated with conventional dosage forms.[1]

Disadvantages of conventional systems[2]
- ❖ Frequency of dosing is high
- ❖ Significant fluctuation in drug levels
- ❖ Side effects are more common

Newer techniques capable of controlling the rate of drug delivery

- ➤ Sustaining the duration of therapeutic action
- ➤ Targeting the delivery of drug to a tissue.[2]

The sustained gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, floatation, sedimentation, expansion, modified shape system or by the simultaneous administration of pharmacological agent that delay gastric emptying rate. These advancements lead to development of several novel drug delivery systems, revolutionize the method of medication and provide number of therapeutic benefits.[3] The present work is to formulate Gastroretentive Mucoadhesive tablet (GRM) of Diltiazem (DZM) hydrochloride consisting of mucoadhesive polymers which adhere to the stomach mucosa and to increase the intimacy and duration of contact. Therefore the gastric retention of the drug can be prolonged. The absorption of DZM is in the upper part of the GI tract i.e., stomach. Formulation of gastroretentive mucoadhesive tablet improves the bioavailability of DZM. By controlling the release rate the saturation of absorption window can be overcome. Hence the Gastroretentive mucoadhesive tablet formulation is a suitable approach for the drug.[4] Angina pectoris is a very common disorder. It is not a disease in itself, but it is an important risk factor for cardio-vascular mortality

and morbidity. The most common symptom of angina is a feeling of pain or discomfort in chest. The pain can feel tight, dull or heavy. The pain can spread from chest to left arm, neck, jaw and back. The normal heart muscles or myocardium are supplied by healthy blood vessels like coronary arteries, the blood supply caries the oxygen and nutrition for the cardiac muscles. An abnormal amount of fats, platelets and blood clots start to deposit on the walls of the coronary arteries. This cause the blood vessels diameter to shrink and reduces the amount of blood that is able to pass through it. Treatment of angina aims to provide immediate relief from the symptoms, prevent future attacks, and reduce your risk of having a heart attack or stroke.

Drugs used in angina exploit two main strategies:
❖ Reduction of oxygen demand
❖ Increase of oxygen delivery to the myocardium.[5]

Calcium channel blockers (CCB) have been used for the treatment of Angina pectoris for many years. The mode of action is, CCB blocks the L type of calcium channels and delays their recovery. Calcium channel blockers work by relaxing the muscles that make up the walls of arteries, increasing blood supply to the heart.[5,6] Diltiazem Hydrochloride is a typical calcium channel blocker under Benzothiazepine derivatives. The drug comes under BCS Class I and has a short half-life of about 3-4.5 hours, hence requires frequent administration. The drug has a poor oral bioavailability of 40-60%. Thus, to reduce the frequency of administration and improve the patient compliance, the oral controlled release mucoadhesive tablets are formulated.[7,8]

MATERIALS AND METHODS

Materials
Diltiazem hydrochloride was obtained as a gift sample from Prim drugs and Pharmaceuticals Pvt. Ltd, Uttarakhand, India. HPMC E15 and HPMC K15 were procured as a gift sample from Samsung fine chemicals, Mumbai, India. Ethylcellulose was supplied by Caplin point, Puducherry, India. Lactose was obtained from Kniss laboratories, Chennai, India.

Method of preparation
Diltiazem Hydrochloride was mixed manually in polybag with Hydroxy Propyl Methyl Cellulose E15 (HPMC E15) and Hydroxy Propyl Methyl Cellulose K15 (HPMC K15), Ethyl cellulose and Lactose for 10 min. The blend was then compressed into tablets by direct compression method. Compositions of mucoadhesive tablet formulations were given in Table 1.1 Each tablet (300mg) contained 90 mg of Diltiazem Hydrochloride.

Table 1: Formulation of Diltiazem hydrochloride sustained release mucoadhesive tablets.

Ingre-dients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
Diltiazem HCl	90	90	90	90	90	90
HPMC E15	150	150	-	-	75	75
HPMC K15	-	-	150	150	75	75
Ethyl cellulose	9	30	9	30	9	30
Lactose	51	30	51	30	51	30

PREFORMULATION STUDIES

Physical compatibility[9]
Diltiazem hydrochloride was well mixed with excipient according to the formula selected for tablets and a small portion of this powder was kept in cleaned and dried vial in hot air oven at 40° C ± 2°C and at room temperature. Physical observation has been carried out visually for 7 days.

Chemical compatibility study[10]
A Fourier Transform-Infrared spectrophotometer was used to study the non-thermal analysis of Drug-Excipient compatibility. The spectrum of each sample was recorded over 450-4500cm^{-1}. Pure drug of Diltiazem hydrochloride with physical mixture compatibility studies were performed. Infra-red spectrum of Diltiazem hydrochloride was carried out using potassium bromide pellet dispersion method.

Derived properties of powder[11]
1. **Bulk density**
The bulk density was calculated using the following formula, $\rho_b = M/V_b$

2. **Tapped density**
Tapped density was calculated by the following formula, $\rho_t = M/V_t$

3. **Carr's compressibility index (CI)**
The % CI was calculated by using the formula:
$$CI = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

4. **Hausner's ratio (HR)**
It was determined by the ratio of tapped density and bulk density. It is calculated using the formula:
$$HR = \frac{\text{Tapped density}}{\text{Bulk density}}$$

5. **Angle of repose:**
Specified weight of the sample was slowly passed through funnel kept a height of 2cm from base. The powder was passed till it forms heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated by using the formula, $\tan \theta = h/r$

Post compression studies

1.   Uniformity of weight[12]
Twenty tablets were selected at random from each batch. The individual tablets were weighed and the average weight was calculated. The individual weights were compared with the average weight.

2.   Diameter and thickness[12]
Five tablets from each formulation were selected. The diameter and thickness of the tablets were measured using digital Vernier caliper.

3.   Hardness[12]
The resistance of tablets to chipping or breakage during storage, transportation and handling before usage depends on its hardness. Five tablets were selected randomly and the hardness was measured by Monsanto hardness tester.

4.   Friability[12]
Ten tablets were weighed and then placed in the chamber. The friabilator was set for 100 revolutions and the tablets were subjected to the combined effects of shock and abrasion because the plastic chamber drops the tablets at a distance of six inches during every revolution. The tablets were redusted to remove the powder and reweighed. The friability is given by the formula,

$$F = (1-W/W_o) \; X \; 100$$

Where, W_o - Weight of the tablet before the test, W - Weight of the tablet after the test

5.   Drug content[13]
Accurately weighed sample of the tablet powder equivalent to 100 mg of Diltiazem Hydrochloride was dissolved and then made up to 100 ml with acid buffer pH 1.2. 10 ml of the solution was diluted with acid buffer pH 1.2. Further 10 ml of the solution was diluted with acid buffer pH 1.2. The absorbance of the solution was measured at the maximum at about 237nm. The drug content was calculated.

6.   Surface pH[14]
The Gastroretentive tablets were allowed to swell in distilled water for 2 h at room temperature. The surface pH of the swollen Gastroretentive tablets was measured by bringing the electrode in contact with the surface pH of the tablet allowing it to equilibrate for 1 minute using pH meter.

7.   Swelling index[13]
The swelling of the tablet involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle results in saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through the pores and bind to large molecule; breaking the hydrogen bond and results in the swelling of particle. One tablet from each batch was weighed and placed in petri dish containing 25 ml of acid buffer pH 1.2. At regular intervals the tablet was removed, excess of buffer was removed using filter paper and weighed again. The swelling index was calculated by using the formula,

$$\text{Swelling index (S.I)} = (W_t-W_o)/W_o \; X \; 100$$

Where, W_t = Weight of tablet at time t, W_o = Weight of tablet before placing in the petri dish.

8.   *In vitro* dissolution studies[15]
The drug dissolution profile was determined using USP Type II (Paddle Type) dissolution test apparatus. 900 ml of acid buffer pH 1.2 was used as the dissolution medium. The release was performed at 37°C ± 0.5°C, with a rotation speed of 100 rpm. 10 ml of sample was withdrawn accurately at half an hour intervals for 24 hours. The dissolution medium was replenished with the same amount of the fresh medium. Samples were filtered through Whatmann filter paper and analysed spectrophotometrically at 237 nm using UV/Visible double beam spectrophotometer.

Kinetic analysis of Diltiazem hydrochloride release data[16]
The *in vitro* drug release data were tested with the following mathematical model. The goodness of fit was found out to describe the kinetics of drug release.

Zero order release model
Zero order models describe the systems where the drug release rate is independent of its concentration. The equation assumes that the cumulative amount of drug release is directly related to time. $C = k_o t$

First order release model
First order models describe the systems where the release rate is dependent on the concentration. The release behaviour of first order equation is expressed as log cumulative percentage of drug remaining vs time. The equation is as follows,

$$\text{Log } C = \text{log } C_o - k \; t \; / \; 2.303$$

Higuchi square root law model
The Higuchi model describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of release is related to the rate of drug diffusion. This model describes the cumulative percentage of drug release vs square root of time.
The equation is as follows, $Q = kt^{1/2}$

Hixson-Crowell release model
The Hixson-Crowell cube root model describes the release from systems where there is a change in surface area and diameter of the tablets or particles.

$$Q_o^{1/3} - Q_t^{1/3} = K_{HC} \; t$$

Korsmeyer and Peppas model
Korsemeyer and Peppas Model derive a simple relationship which describes the drug release from a polymeric system equation. The equation is, $M_t/M_\alpha = K \; t^n$

RESULTS AND DISCUSSION

Physical compatibility study

The physical compatibility study was performed visually. The results show that the drug and the excipients are physically compatible with each other.
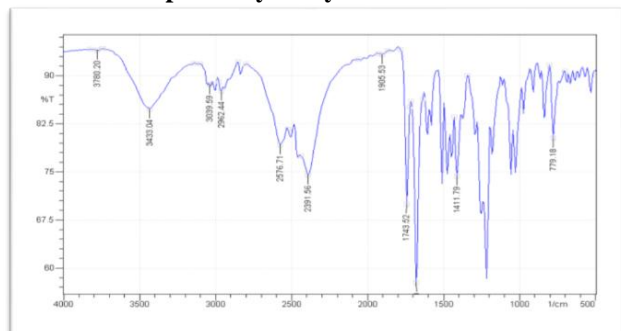
Chemical compatibility study- FTIR studies

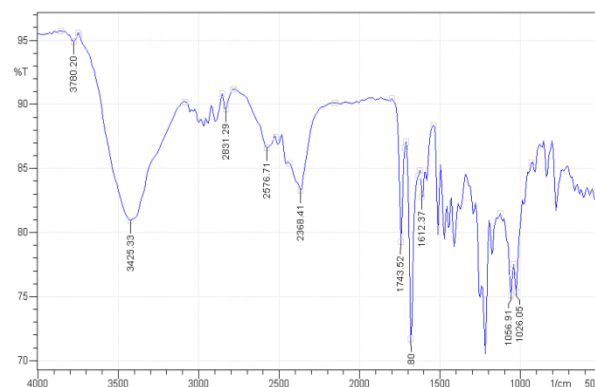
Figure 1: FTIR spectra of Diltiazem hydrochloride.

Figure 2: FTIR spectra of optimised batch (F4).

Preformulation studies of the drug and blends

Table 2: Preformulation studies on various formulation blends.

S.No	Formulation code	Bulk density(g/ml)	Tapped density(g/ml)	Carr's index (%)	Hausner's ratio (HR)	Angle of repose(θ)
1	F1	0.4666	0.5333	12.51	1.14	27.13±1.7845
2	F2	0.4830	0.5555	13.05	1.15	28.19±0.2969
3	F3	0.4908	0.5645	13.06	1.15	29.31±1.3961
4	F4	0.4708	0.5381	12.51	1.14	26.55±1.9442
5	F7	0.4788	0.5471	12.48	1.14	25.07±0.0531
6	F8	0.4939	0.5680	13.04	1.15	27.43±1.0418

Preformulation studies for all the formulations were performed. The bulk density of the various formulation blends ranged from 0.4666 to 0.4939 g/ml. The tapped density of the various formulation blends ranged from 0.5381 to 0.5680 g/ml. The Carr's index (CI) ranged from 12.51 to 13.06%. The Hausner's ratio (HR) of the various formulation blends ranged from 1.14 to 1.15. The powder blends showed good flow property. The angle of repose of the various formulation blends ranged from 25.07 to 29.31. All the powder blends showed excellent flow property.

Evaluation of diltiazem hydrochloride tablets – post compression studies.

Table 3: Post compression study data.

Formulation code	Average weight (mg)	Hardness (kg/cm²)	Thickness (mm)	Diameter (mm)	Friability (%)	Drug content (%w/w)	Surface pH
F1	296.0	11±0.00	5±0.00	8±0.00	0.1	96.86	6.5±0.008
F2	297.0	13±0.00	5±0.00	8±0.00	0.1	90.66	5.9±0.005
F3	300.5	11.6±1.85	5±0.00	8±0.00	0.13	99.83	6.7±0.00
F4	288.9	11±0.00	5±0.00	8±0.00	0.14	97.49	6.5±0.008
F5	303.8	8±0.00	5±0.00	8±0.00	0.13	96.81	6.9±0.009
F6	301.4	8.6±0.73	5±0.00	8±0.00	0.23	92.4	6.8±0.00

The tablets are uniform in weight and the weight ranged from 296 to 303.8mg. The tablets of all formulations (F1 to F6) comply with the official standards. The hardness of tablets was ranged from 8 to 10.5 kg/cm². The tablets can withstand the stress during handing and transport. The thickness for all the formulations was found to be 5mm. The tablets have uniform thickness. The diameter for all the formulations was found to be 8mm. The tablets have uniform diameter. The % friability of various formulations ranged from 0.1 to 0.23. Hence the % friability complies with the official standards. The percentage drug content of all the formulations ranged from 90.66%w/w to 99.83%w/w. All the formulations comply with the official standards. The surface pH of the various formulations ranged from 5.99 to 6.87.

Swelling study

Table 4: Percentage Swelling of Tablets.

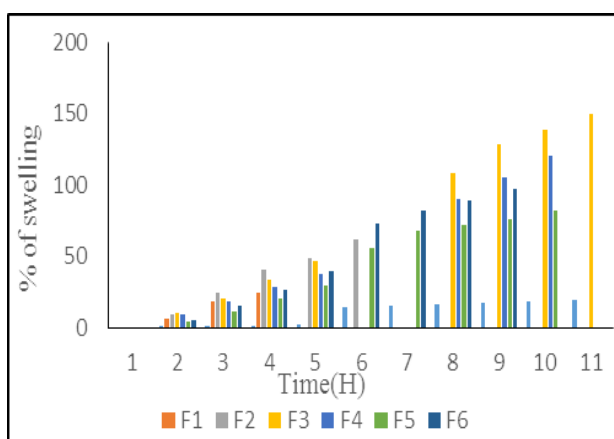| Time (H)	Percentage swelling of various formulations (%)					
	F1	F2	F3	F4	F5	F6
0.5	6.1	9.6	9.9	9.6	4.2	5.6
1	18.0	24.2	20.2	18.0	11.7	14.9
1.5	24.8	40.2	33.8	28.2	20.5	26.8
2	-	48.8	46.3	37.4	29.7	39.8
14	-	61.8	-	-	56.2	73.2
15	-	-	-	-	67.6	81.9
16	-	-	108.8	90.1	72.1	89.4
17	-	-	128.3	105.0	75.7	97.7
18	-	-	139.1	120.2	81.6	-
19	-	-	150.2	-	-	-

Figure 3: Swelling index of various formulations.

The swelling index for all the formulations was performed and the percentage swelling ranged from 24.8% to 150.2%. The maximum and minimum swelling index was observed in the formulation F3 & F1 containing HPMC K15 and HPMC E15 respectively at highest concentration of about 50% each. F3 showed maximum swelling upto 19 hours. HPMC K15 is a high grade viscosity polymer and highly hydrophilic in nature. Thus the swelling may be due to the high viscous nature of the polymer HPMC K15.

In vitro release study of the tablets

Table 5: *In vitro* release of various formulations – Comparison data.

Time (H)	Cumulative percentage drug release (%)					
	F1	F2	F3	F4	F5	F6
0.5	19.9	14.5	9.1	12.3	15.9	11.7
1	35.2	24.8	13.9	14.2	20.0	14.5
1.5	46.2	34.1	17.6	22.4	24.2	19.8
2	56.0	39.9	21.5	24.4	26.9	23.3
3	81.9	56.0	29.5	-	-	-
4	98.3	67.4	32.7	-	-	-
5	104.3	83.4	-	-	-	-
6	-	93.6	-	-	-	-
7	-	99.9	-	-	-	-
14	-	-	-	-	86.4	78.9
14.5	-	-	-	-	-	-
15	-	-	77.5	-	91.3	84.2
15.5	-	-	-	-	-	-
16	-	-	85.1	-	95.1	90.1
16.5	-	-	-	-	-	-
17	-	-	90.8	-	99.8	97.9
17.5	-	-	-	80.55	-	-
18	-	-	92.4	-	105.7	103.3
18.5	-	-	-	82.0	-	-
19	-	-	98.8	-	-	-
19.5	-	-	-	85.9	-	-
20	-	-	101.6	-	-	-
20.5	-	-	-	89.8	-	-
21	-	-	-	-	-	-
21.5	-	-	-	95.3	-	-
22	-	-	-	-	-	-
22.5	-	-	-	99.2	-	-
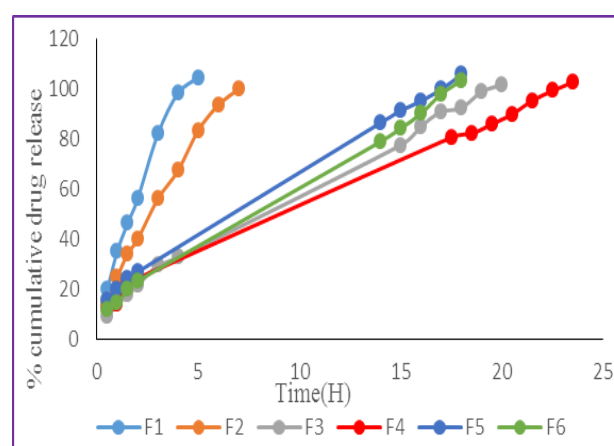
Figure 4: Comparative *in vitro* drug release study.

The drug release for all the formulations was performed. Formulations were made using HPMC E15, HPMC K15 as mucoadhesive polymers, individually and in combination. Ethyl cellulose was used as a release retarding polymer. Various concentrations of ethyl cellulose was employed. The drug release for all the formulations was obtained in the range of 99.9% to 105.7%. Formulation F4 showed drug release of about 99.2% at the end of 23 hours. The drug was released in

the sustained manner upto 23 hours due to the highest concentration of ethyl cellulose (10%) in F4. F3 showed 101.6% at the end of 20 hours. F3 & F4 had EC concentration of 3% & 10% respectively. Increasing the concentration of ethyl cellulose decreases the rate of drug release due to the water insoluble nature of the polymer. F4 had increased EC concentration than F3. It is concluded ethyl cellulose is used to release the drug in a sustained manner. F4 may be considered as the optimised formulation.

Release Kinetics of the Optimized Formulation

Table 6: Release kinetics of the Optimised Formulation (F4).

| Time (H)	Log time (H)	Sq. root of time (H)	Cum % drug release	Cum % drug remaining	Log cum % drug release	Log cum % drug remaining	Cube root of cum % drug remaining
0	∞	0	0	100	∞	2	4.64
0.5	-0.30	0.71	12.3	87.7	1.090	1.943	4.44
1	0	1	14.2	85.8	1.152	1.933	4.41
1.5	0.18	1.22	22.4	77.6	1.350	1.890	4.26
2	0.30	1.41	24.4	75.6	1.387	1.878	4.23
17.5	1.24	4.18	80.5	19.5	1.906	1.299	2.69
18.5	1.27	4.30	82.0	18	1.914	1.255	2.62
19.5	1.29	4.42	85.9	14.1	1.934	1.149	2.42
20.5	1.31	4.53	89.8	10.2	1.953	1.009	2.17
21.5	1.33	4.64	95.3	4.7	1.979	0.672	1.67
22.5	1.35	4.74	99.2	0.8	1.996	-0.097	0.93
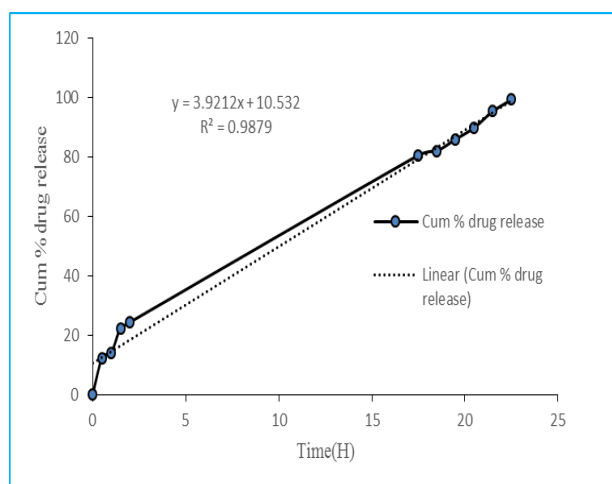
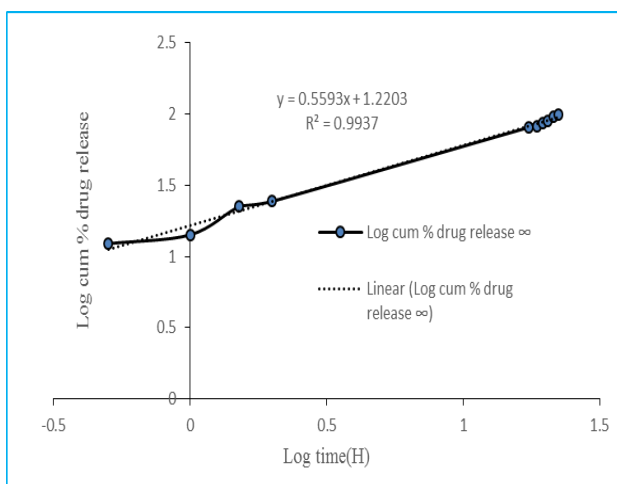**Figure 5: A plot of Zero order kinetics.**

Figure 6: A plot of Korsemeyer and Peppas kinetics.

The coefficient of determination (R^2) was taken as criteria for choosing the most appropriate model. Among the various plots, zero order showed the highest linearity in which the R^2 value was found to be close to 1(0.9879). Thus it is concluded that the drug release follows zero order kinetics. The release mechanism was determined on the basis of n value in the Korsemeyer Peppas model. If the value is <0.5, the drug release follows diffusion mechanism and if the value is >0.5, the drug release follows non-fickian diffusion mechanism. Here, the value of n was found to be >0.5 (0.5593). Thus it is concluded that the drug release follows Non-fickian diffusion mechanism.

CONCLUSION

The present study was to formulate and evaluate sustained release mucoadhesive tablets of Diltiazem hydrochloride by direct compression method. *In vitro* dissolution study showed the drug release upto 23 hours. Increasing the concentration of Ethylcellulose retard the release of drug in a sustained manner. For the sustained release of drug, maximum concentrations of polymers are required. Thus the development of sustained release mucoadhesive tablets of Diltiazem hydrochloride is effective in the treatment of Angina pectoris.

ACKNOWLEDGEMENT

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