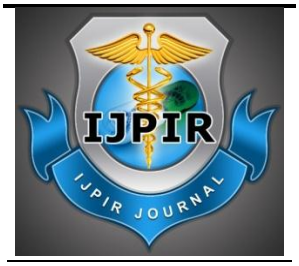
Research Article



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Formulation and invitro evaluation of diltiazem hydrochloride tablets for buccal drug delivery system by using various polymers

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ABSTRACT

Diltiazem hydrochloride is a calcium channel blocker used to treat high blood pressure, angina, and certain heart arrhythmias. It may also be used in hyperthyroidism if beta blockers cannot be used. . The aim of the present study was to develop buccal formulation of Diltiazem hydrochloride to maintain constant therapeutic levels of the drug for over 12 hrs. Methocel K15M, Methocel K100M and Locust bean gum were employed as polymers. Diltiazem hydrochloride dose was fixed as 60 mg. Total weight of the tablet was considered as 300 mg. Polymers were used in the concentration of 30 mg, 45mg and 60 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F2) showed better and desired drug release pattern i.e.,97.83 % in 12 hours. It followed zero order release kinetics mechanism.

Keywords: Diltiazem hydrochloride, Buccal Tablets.

INTRODUCTION

Buccal Delivery System

The unique environment of the oral cavity offers its potential as a site for drug delivery. Because of the rich blood supply and direct access to systemic circulation, the oral mucosal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extentensively metabolized in the liver (first pass effect) [1-5].

Delivery through Buccal Mucosa

Administration of a drug via the buccal mucosa (the lining of the cheek) to the systemic circulation is defined as buccal delivery. Despite, the buccal mucosa is significantly less permeable than the sublingual mucosa and usually not able to provide rapid drug absorption or good bioavailability; it is relatively more permeable than the skin and also offers other advantage over alternative delivery routes. The fact that the buccal mucosa is less

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permeable than sublingual floor makes it more desirable site for sustained drug delivery. Apart from avoiding enzymatic degradation and first pass metabolism, the non acidic conditions and lipophilic nature of the buccal tissue provide potential and promises for successful delivery of peptide and proteins [6-10].

METHODOLOGY

Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 1. The tablets were prepared as per the procedure given below and aim is to prolong the release of Diltiazem hydrochloride. Total weight of the tablet was considered as 300mg [11-15].

Procedure

1) Diltiazem hydrochloride and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method [16-18].

Table 1: Formulation composition for tablets

Formulation No.	Diltiazem hydrochloride	Methocel K 15M	Methocel K100M	Locust bean gum	Mag. Stearate	Talc	MCC pH 102
F1	60	30	-	-	4	4	QS
F2	60	45	-	-	4	4	QS
F3	60	60	-	-	4	4	QS
F4	60	-	30	-	4	4	QS
F5	60	-	45	-	4	4	QS
F6	60	-	60	-	4	4	QS
F7	60	-	-	30	4	4	QS
F8	60	-	-	45	4	4	QS
F9	60	-	-	60	4	4	QS

All the quantities were in mg

In vitro drug release studies

Dissolution parameters

Apparatus -- USP-II, Paddle Method
Dissolution Medium -- 6.8 ph phosphate buffer
RPM -- 50
Sampling intervals (hrs) -- 0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature -- 37°c + 0.5°c

As the preparation was for drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c + 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated 6.8 ph phosphate buffer was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 237 nm using UV-spectrophotometer.

RESULTS AND DISCUSSION

The present study was aimed to developing buccal tablets of Diltiazem hydrochloride using

various polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

Analytical Method

Graphs of Diltiazem hydrochloride was taken in buccal pH that is in p H 6.8 phosphate buffer at 237 nm

Table 2: Observations for graph of Diltiazem hydrochloride in p H 6.8 phosphate buffer (237 nm)

Conc [µg/l]	Abs
0	0
2	0.121
4	0.265
6	0.434
8	0.565
10	0.721
12	0.901

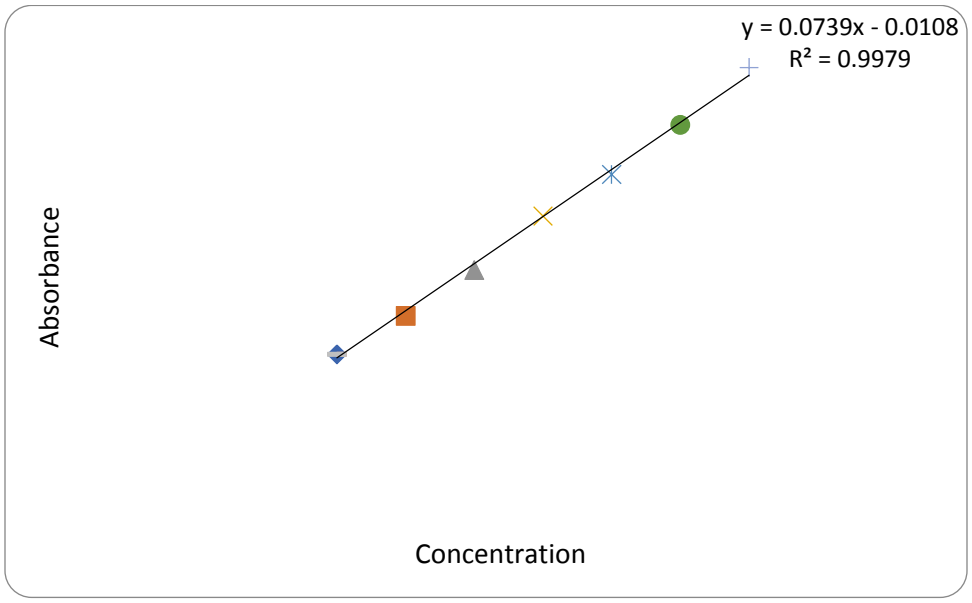

Figure 1: Standard graph of Diltiazem hydrochloride in pH 6.8 phosphate buffer (237 nm)

Preformulation parameters of powder blend

Table 3: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	23.16	0.46	0.58	16.19	0.99
F2	24.64	0.57	0.59	16.83	0.97
F3	24.54	0.56	0.59	17.65	0.67
F4	23.46	0.54	0.65	17.09	1.17
F5	25.37	0.45	0.59	18.00	1.21
F6	24.21	0.46	0.65	17.76	0.97
F7	24.19	0.58	0.69	16.42	0.84
F8	25.21	0.55	0.57	17.94	1.11
F9	25.07	0.57	0.58	18.00	1.19

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43 to 0.58 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the formulation of tablet.

Table 4: Post compression parameters

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	298.5	4.4	0.48	2.6	99.12
F2	301.4	4.5	0.47	2.8	98.03
F3	298.6	4.3	0.46	2.9	99.17
F4	300.6	4.5	0.48	2.7	98.24
F5	299.4	4.4	0.53	2.8	99.15
F6	300.7	4.5	0.55	2.9	98.23
F7	302.3	4.4	0.56	2.5	98.16
F8	301.2	4.5	0.58	2.7	99.15
F9	298.3	4.4	0.55	2.8	99.16

Invitro quality control parameters for tablets

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

In-Vitro Drug Release Studies

Table 5: Dissolution Data of Diltiazem hydrochloride Tablets (F1, F2, F3 formulations).

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F1	F2	F3
0	0	0	0
0.5	2.41	3.08	6.13
1	11.44	11.18	12.32
2	17.62	18.26	18.64
3	24.75	26.16	27.45
4	35.61	35.67	34.11
5	41.37	47.23	39.46
6	48.53	55.13	45.11
7	55.51	64.53	56.17
8	63.87	68.55	65.12
9	72.11	77.58	68.44

10	77.94	86.43	71.82
11	83.92	92.99	77.35
12	87.03	97.83	82.62

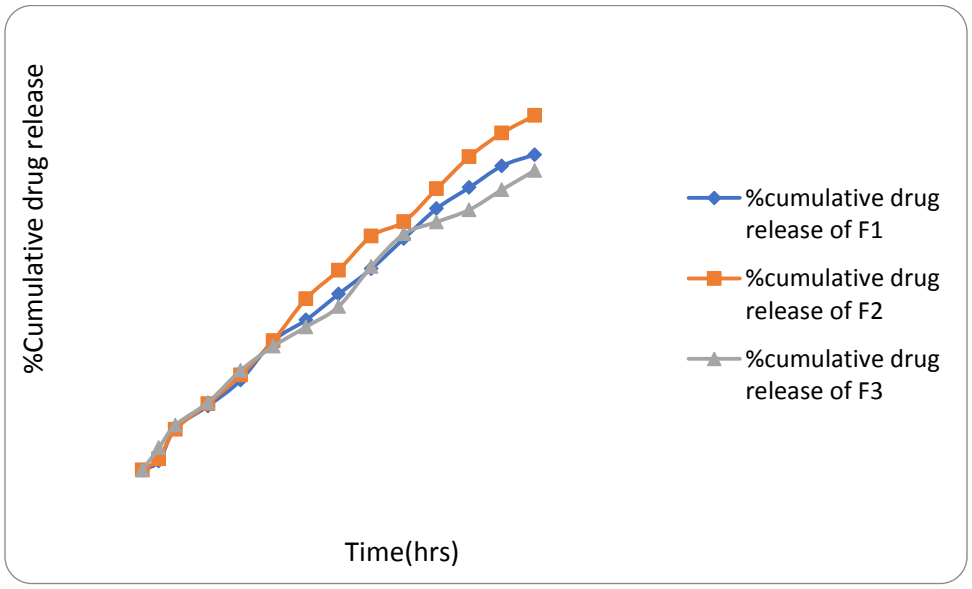

Fig 2: Dissolution profile of Diltiazem hydrochloride (F1, F2, F3 formulations).

Table 6: Dissolution Data of Diltiazem hydrochloride Tablets (F4, F5, F6 formulations)

TIME	**CUMULATIVE PERCENT DRUG RELEASED**		
(hr)	**F4**	**F5**	**F6**
0	0	0	0
0.5	3.59	6.59	5.61
1	9.14	11.65	11.75
2	15.85	17.88	23.12
3	22.32	25.45	35.87
4	30.57	32.73	44.64
5	37.84	37.56	47.96
6	44.54	45.89	56.44
7	51.66	58.65	68.95
8	57.73	66.07	77.62
9	64.93	75.23	80.72
10	74.82	83.62	83.68
11	83.97	89.55	86.21
12	88.94	93.04	91.04

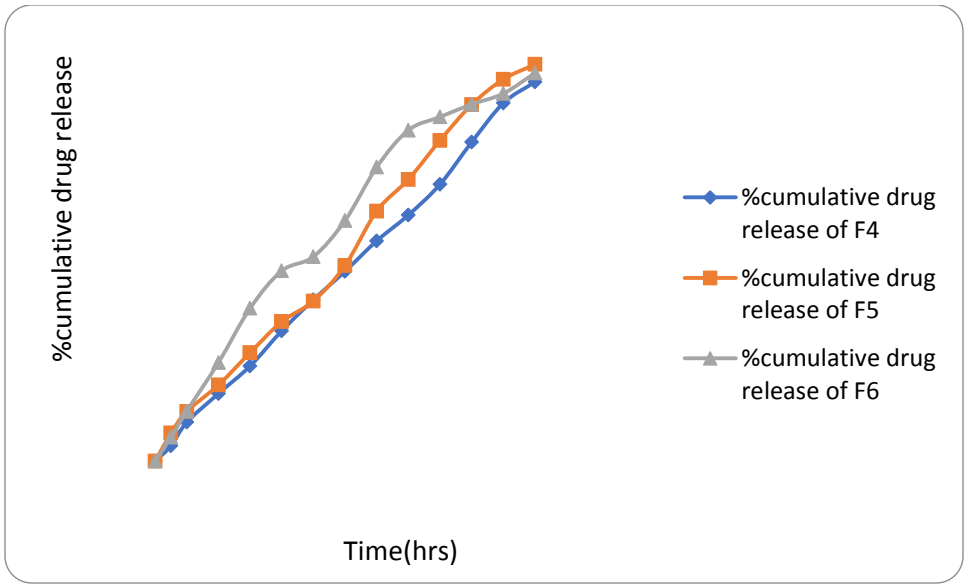

Fig 3: Dissolution profile of Diltiazem hydrochloride (F4, F5, F6 formulations)

Table 7: Dissolution Data of Diltiazem hydrochloride Tablets (F7, F8, F9 formulations)

TIME	CUMULATIVE PERCENT DRUG RELEASED		
(hr)	F7	F8	F9
0	0	0	0
0.5	6.31	5.11	4.10
1	14.65	14.15	10.55
2	19.72	22.76	17.77
3	26.76	29.71	26.55
4	30.74	35.41	34.44
5	36.79	48.81	42.33
6	45.85	55.76	51.36
7	57.36	65.61	59.67
8	65.74	69.45	61.94
9	74.98	74.16	68.33
10	83.64	80.09	77.52
11	87.96	82.38	82.59
12	91.75	88.75	86.02

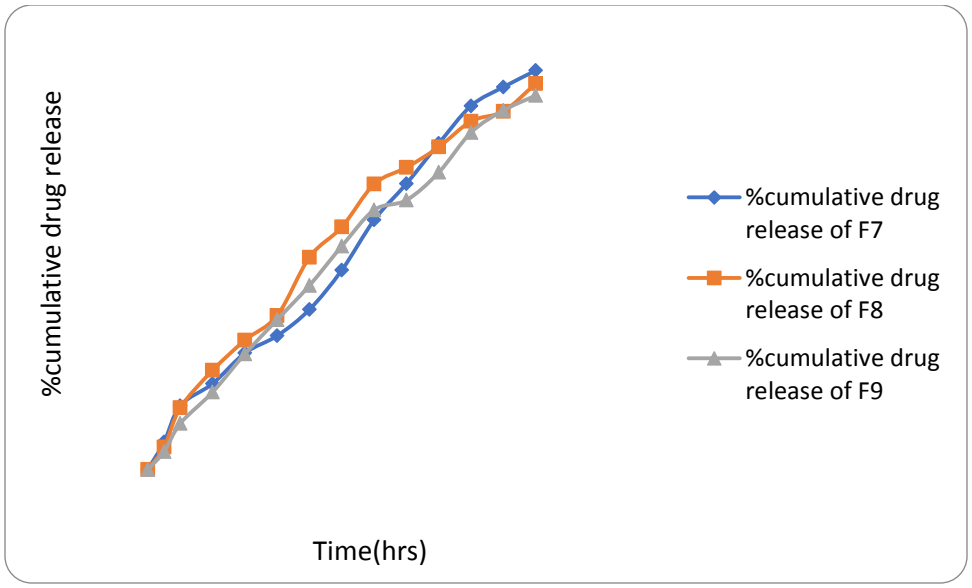

Fig 4: Dissolution profile of Diltiazem hydrochloride (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with Methocel 100M as polymer were unable to retard the drug release up to desired time period i.e., 12 hours. Whereas the formulations prepared with Methocel K15M retarded the drug release in the concentration of 45 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 97.83% in 12 hours with good retardation. The formulations prepared with Locust bean gum showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 8: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)
0	0	0.707106781		
3.08	0.5	0.707	1.048	0.000
11.18	1	1.414	1.262	0.000
18.26	2	1.414	1.418	0.301
26.16	3	1.732	1.552	0.477
35.67	4	2.000	1.674	0.602
47.23	5	2.236	1.741	0.699
55.13	6	2.449	1.810	0.778
64.53	7	2.646	1.836	0.845
68.55	8	2.828	1.890	0.903
77.58	9	3.000	1.937	0.954
86.43	10	3.162	1.968	1.000
92.99	11	3.317	1.990	1.041
97.83	12	3.464	1.991	1.079

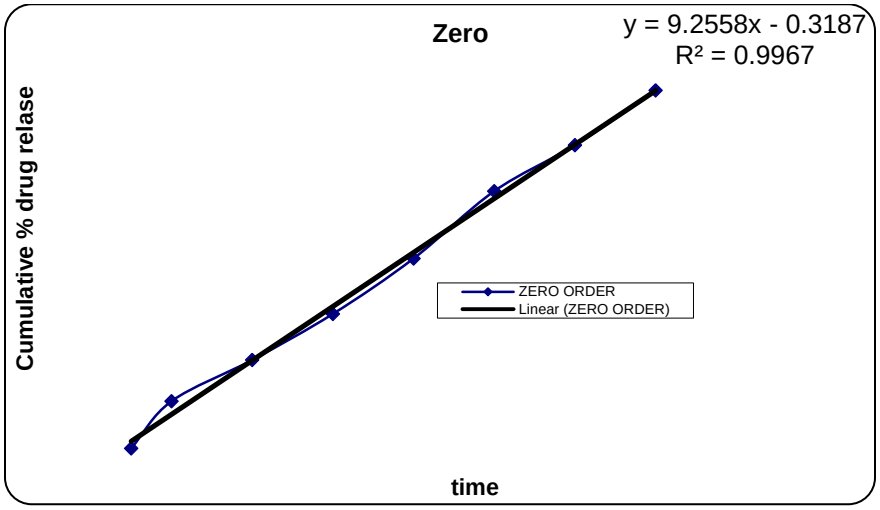

Fig 5: Zero order release kinetics graph

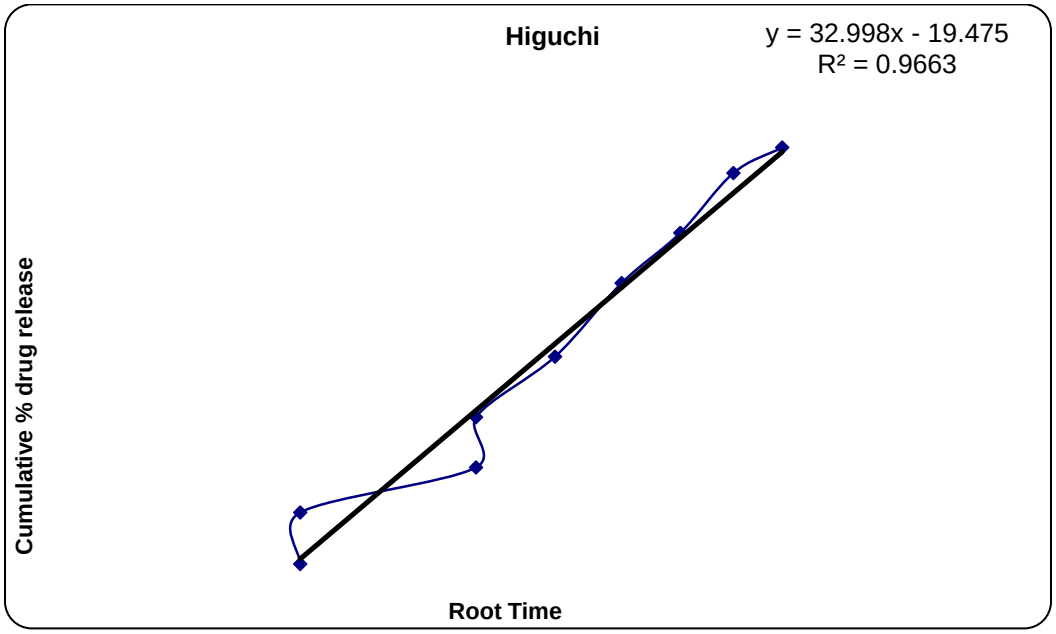

Fig 6 : Higuchi release kinetics graph

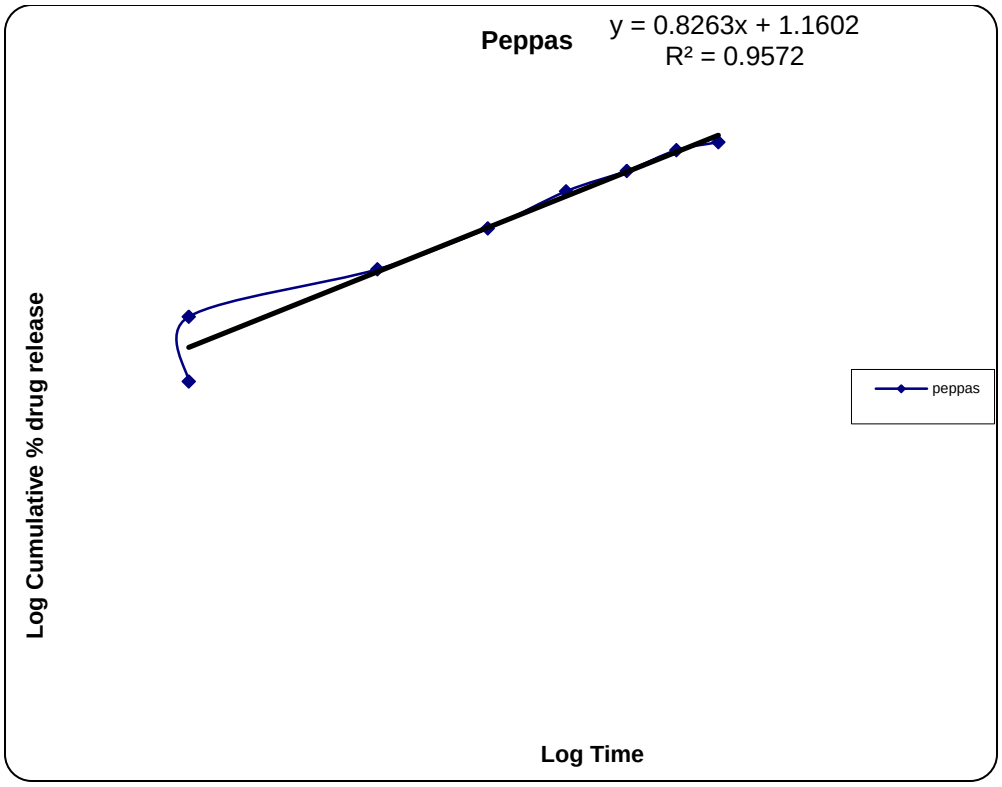

Fig 7: Kars mayer peppas graph

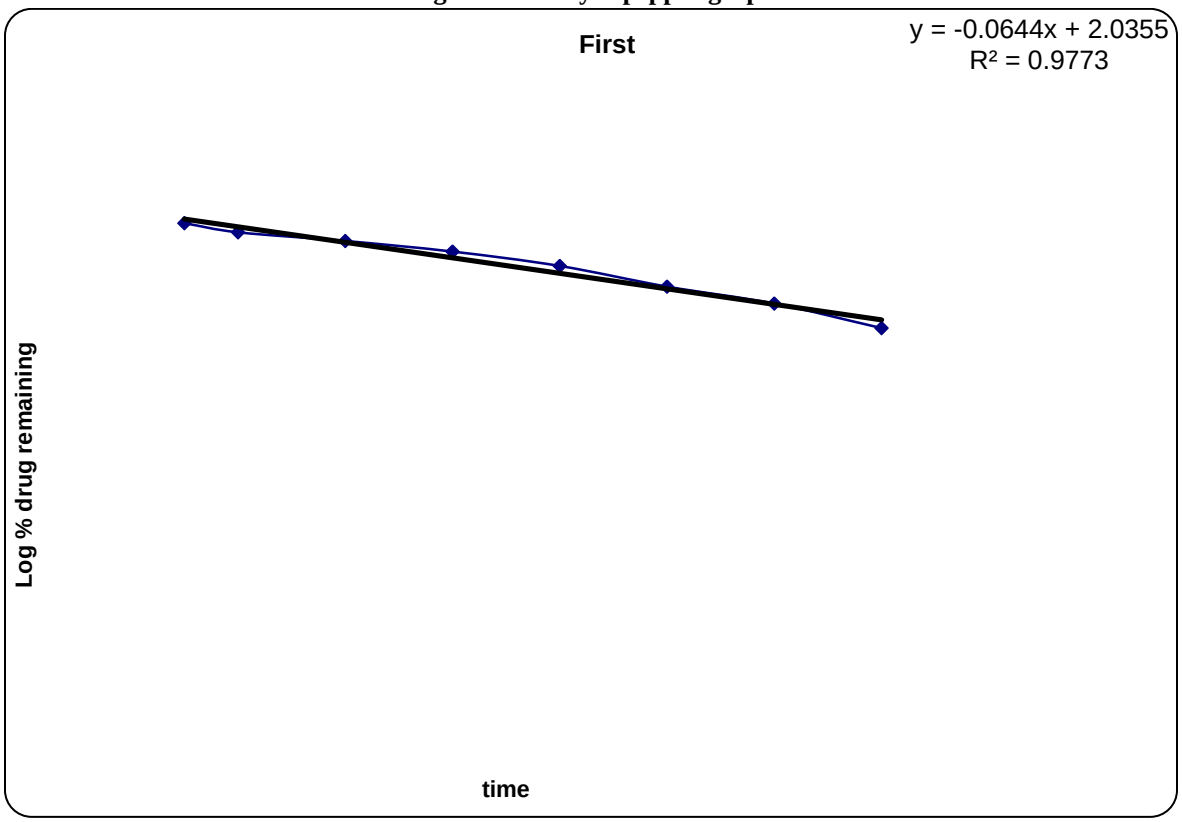

Fig 8: First order release kinetics graph

From the above graphs it was evident that the formulation F2 was followed Zero order release kinetics.

Drug and excipient compatability studies

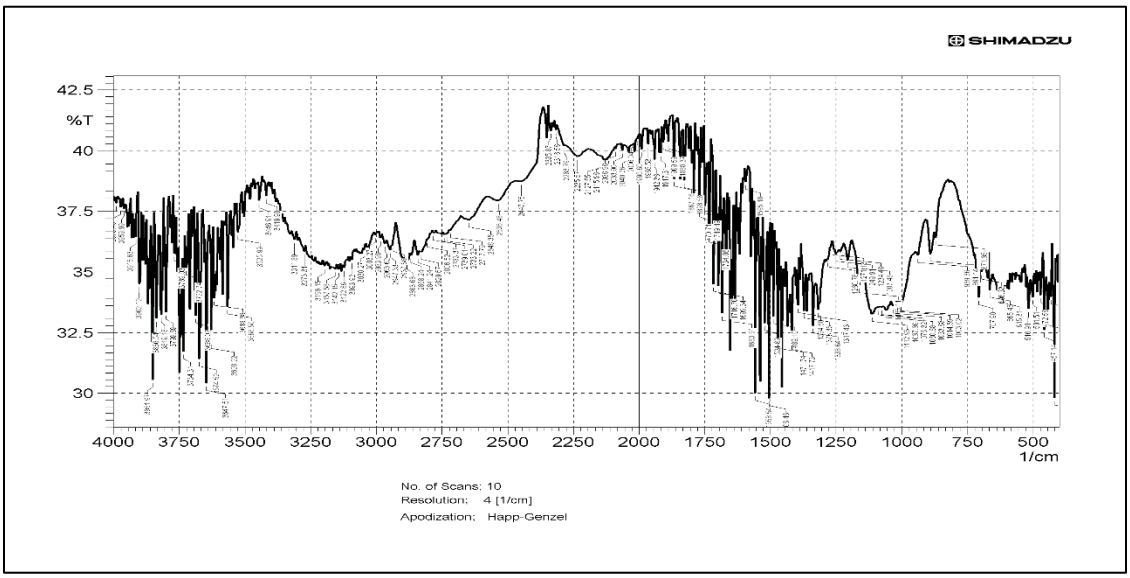

Fig 9: FTIR spectrum of pure drug

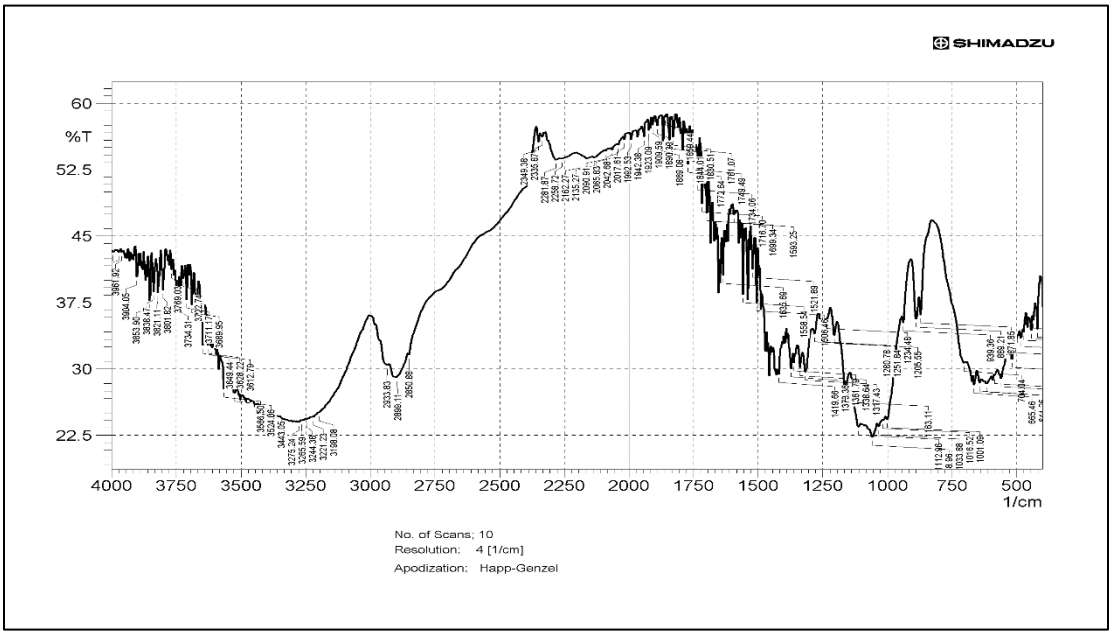

Fig 10: FTIR spectrum of optimised formulation

CONCLUSION

The aim of the present study was to develop buccal formulation of Diltiazem hydrochloride to maintain constant therapeutic levels of the drug for over 12 hrs. Methocel K15M, Methocel K100M and Locust bean gum were employed as polymers. Diltiazem hydrochloride dose was fixed as 60 mg. Total weight of the tablet was considered as 300 mg. Polymers were used in the concentration of 30 mg, 45mg and 60 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F2) showed better and desired drug release pattern i.e.,97.83 % in 12 hours. It followed zero order release kinetics mechanism.

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