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Research Article

Development, Characterisation and Invitro Evaluation of Buccoadhesive Bilayered Tablets for the Treatment of Hypertension

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ABSTRACT

Ramipril is a prodrug belonging to the class of angiotensin-converting enzyme (ACE) inhibitor, which undergoes extensive hepatic first pass metabolism. The aim of the present study is to develop buccoadhesive bilayered tablet of ramipril to achieve the greater therapeutic efficacy, to increase the bioavailability, to overcome the first pass hepatic metabolism of the drug. A UV spectrophotometric method has been employed for the estimation of Ramipril at 219 nm. Buccal tablets of Ramipril were prepared by direct compression method using ethyl cellulose as a polymer. The precompression parameters like bulk density, tapped density, carr's index and angle of repose were determined. The post compression parameters like hardness, thickness, friability, weight variation, in vitro dissolution, FTIR studies were carried out to check if any interactions had occurred, results were promising. The optimized formulation was selected based on results and percentage drug release was found to be 92.95 and followed First order, peppas model with Fickian release mechanism.

Keywords: Ramipril, buccoadhesive tablets, invitro drug release, Ethyl cellulose

INTRODUCTION[1,2,3,4]

In recent years, there has been a growing interest in the use of delivery of therapeutic agents through various transmucosal routes to provide a therapeutic amount of drug to the proper site in body to achieve and maintain the desired concentration. Drug delivery via buccal mucosa by using bioadhesive polymers offers a novel route of drug administration. It provides direct entry of drug molecules into systemic circulation, thus avoiding hepatic first pass effect. The ease of administration and ability to terminate drug delivery when required makes it a potential and attractive route of drug delivery. Buccoadhesive drug delivery system prolong the residence time of the dosage form at the site of absorption and facilitate an intimate contact of the dosage form with the absorption surface and thus contribute to improved therapeutic efficacy of the drug [5,6]. Ramipril is an ACE inhibitor which undergoes extensive hepatic first pass metabolism (80%), with an oral bioavailability of 28% and half life of 2-4hrs [7]. The present study is carried out in order to increase the bioavailability and to decrease the hepatic metabolism of the drug Ramipril.

MATERIALS AND METHODOLOGY

Ramipril was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad. Ethyl cellulose was obtained from Colorcon Asia Pvt. Ltd., Goa. Other excipients were procured from SD Fine Chemicals.

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PHARMATUTOR
PHARMACY INFOPEDIA
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SACNNING OF THE DRUG FOR THE DETERMINATION OF λmax[8]

10mg of Ramipril was weighed and dissolved in 100 ml phosphate buffer pH 6.8. Standard solution having concentration of 10 µg/ml was prepared. The absorption maxima of the standard solution was scanned between 200-400 nm on UV Spectrophotometer against blank. The absorption maxima was found to be 219nm.

STANDARD CALIBRATION CURVE OF RAMIPRIL [8]

The calibration curve for Ramipril was prepared in phosphate buffer pH 6.8. Accurately weighed sample of 50 mg of Ramipril was dissolved in 100 ml of phosphate buffer pH 6.8. 1 ml of each of this solution was diluted to 100 ml with phosphate buffer pH 6.8. The resulting stock solution was of 5µg/ml. From this stock solution, serial dilutions 5-25 µg/ml of Ramipril concentration were made using phosphate buffer pH 6.8. The prepared solutions of Ramipril were analyzed by UV spectrophotometer by measuring the absorbance at 219 nm against phosphate buffer pH 6.8 as blank.

FORMULATION OF BUCCOADHESIVE BILAYERED TABLETS OF RAMIPRIL[9,10,11]

Buccoadhesive bilayered tablets are prepared in 3 stages:

STAGE 1: PREPARATION OF IMMEDIATE RELEASE LAYER

Weigh accurate quantity of Ramipril , polymers (preferred polymer and their different concentrations) and lubricant (2% w/w) were blended homogeneously for 15 minutes by trituration using glass mortar and pestle. The mixture was used for compression of core layer. The composition of the core tablets is tabulated in table no 1.

STAGE 2: PREPARATION OF SUSTAINED LAYER

Weigh accurate quantity of Ramipril , polymers (preferred polymer and their different concentrations) and lubricant (2% w/w). Small quantity of methanol is added to Ethyl cellulose to dissolve ethyl cellulose. To this mixture other ingredients are added except Magnesium stearate and talc and dough is made. This dough is passed through sieve #44 to get granules. These granules are further dried in a oven at a temperature of 40ºC. Magnesium stearate and talc is added to the granules. The mixture was used for compression of backing layer. The composition of the core tablets is tabulated in Table 2.

STAGE 3: COMPRESSION[12,13]

Core layer and backing layer were sequentially compressed by indigenously developed and standardised dies and punches on tablet compression machine. An accurately weighed 25 mg drug-polymers mixture was compressed initially. The upper punch was removed and backing layer composition 25 mg was added over the core layer and again compressed.

EVALUATION PARAMETERS

PRECOMPRESSIONAL PARAMETERS[14,15,16]

1.Bulk density[14]:-Bulk density was determined by pouring gently 20 gm of sample (Albendazole) through a glass funnel into 50 ml graduated cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as:

Bulk density *= weight of sample in gram /volume occupied by the sample*

2.Tapped density[14]:

Tapped density was determined by using Electro lab density tester. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

noted and taped density is calculated using following formula.

Tapped density = Wt. of sample in gm / Tapped volume

3. Carr's index[14]:

Based on the poured density and tapped density, the percentage compressibility of the granules was computed using the Carr's compressibility index by the formula

$$\text{Carr's index (\%)} = \frac{\text{tapped density} - \text{poured density}}{\text{tapped density}} \times 100$$

4.Hausner's ratio:

Hausner's ratio was calculated using the formula,

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{poured density}}$$

5.Angle of Repose[14]:

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

$$\tan\theta = h / r$$

$$\theta = \tan^{-1} h / r$$

Where,
θ = angle of repose,
h = height,
r = radius.

A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed .Determine the angle of repose by measuring the height of the cone of powder and radius of the heap of powder.

POSTCOMPRESSION PARAMETERS [17]

All the prepared matrix tablets were evaluated for the following official and unofficial parameters.

a)General appearance:

The mucoadhesive tablets morphological characterization includes size, shape, colour, presence or absence of odour, taste surface texture was determined.

b) Thickness:

Thickness of the prepared buccal tablets was tested using calibrated vernier calipers.
This test was done in triplicate and average was calculated.

c)Hardness:

The prepared buccoadhesive tablet hardness was measured using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

d)Friability[14,15]:

The friability of the tablets was determined using electrolab friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into the friabilator.

PHARMATUTOR
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The friabilator was operated at 25rpm for 4min. After 4min the tablets were weighed again. The friability was then calculated using the formula,

Friability (%) =

$$\frac{initial\ \ weight - final\ \ weight}{initial\ \ weight} x\,100$$

e)Weight variation test[15,16,17]:

Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 10 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the percentage shown in table 9 and none deviate by more than twice the percentage shown.

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	10.0
130-324	7.5
More than 324	5.0

Weight variation tolerance for uncoated tablets

f) Drug content[15]:

Ten tablets were randomly taken and triturated using a glass mortar and pestle. An accurately weighed quantity of triturated powder equivalent to 10 mg of drug was taken into 100 ml volumetric flask and dissolved in phosphate buffer pH 6.8. 1 ml of above solution was withdrawn and made to 10 ml with phosphate buffer. Thus the corresponding concentration was determined using uv spectrophotometer at 219 nm.

g) *In vitro* drug release studies [14]:

USP type II rotating paddle method was used to study the drug release from the bilayered tablet. The dissolution medium consisted of 900 ml phosphate pH 6.8. The release study was performed at 37 ±0.50ºC, with a rotation speed of 50 rpm. The samples were analyzed after appropriate dilution using UV double beam spectrophotometer at 219nm.

h) Drug Release Kinetics: [18]

To analyse the drug release kinetics and mechanism, the data obtained were fitted into zero order, first order, Higuchi model and Kosmeyer peppas model. The criteria for selecting the most appropriate model were selected on the basis of correlation coefficient values.

RESULTS AND DISUSSION

The FTIR studies showed that there is no drug-polymer incompatibility. The pure drug of Ramipril was scanned over a range of 200 to 400nm and λmax was observed at 219nm (Figure 3). The standard calibration curve of ramipril in Phosphate buffer pH 6.8 was obtained and R^2 was found to be 0.999 (figure 4).

The tablets were evaluated for postcompressional parameters general appearance, weight variation, friability, hardness and invitro dissolution study. The hardness, thickness and friability was found to be in the range of 4 to 4.03kg/cm^2, 2.00 ± 0.01 to 2.02±0.01 and 0.08 to 1.79%. (table 4). From the above results it is clear that the formulated tablets have good mechanical strength and mechanical resistance.

The drug content was found to be in the range of 90.01% to 99.25%. the invitro drug

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

dissolution studies were performed in PH 6.8 phosphate buffer for 6hrs at 50rpm. All the formulations showed more than 70% to 92.25% drug release. The drug release data was fitted into different kinetic models i.e Zero order, First order, Higuchi model, kosmeyer's and peppas model. (Figure no:) The interpretation of data was done based on the value of correlation coefficient. The drug release followed First order & kosmeyer's and peppas model indicating fickian drug release (Table 5)

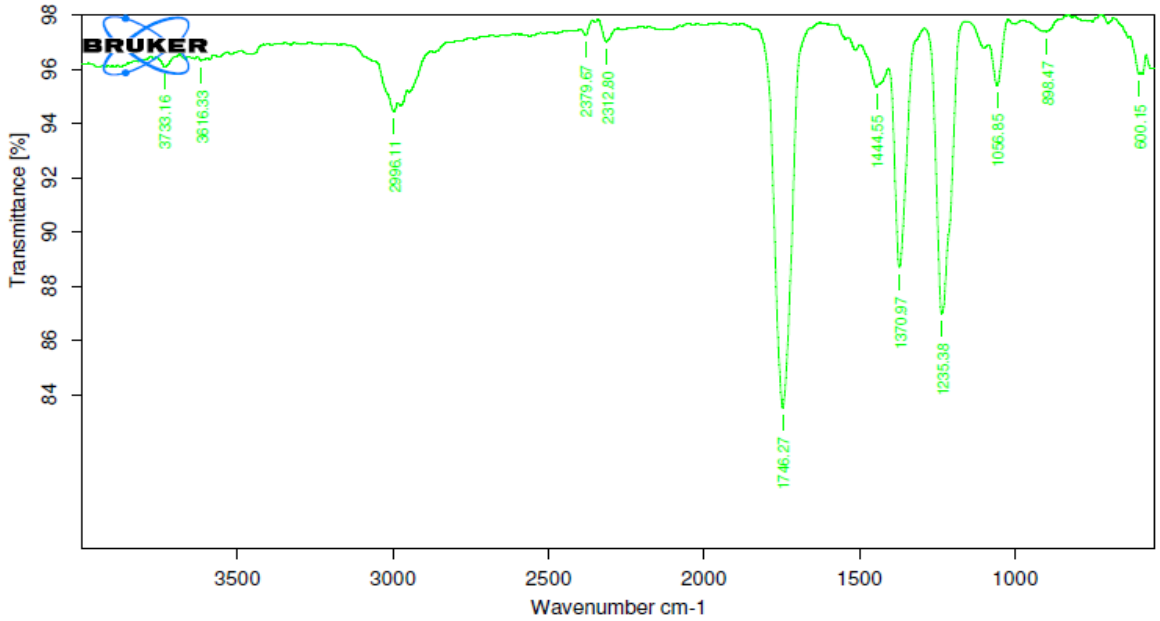

FIGURE : 1 FTIR SPECTRUM OF PURE DRUG RAMIPRIL

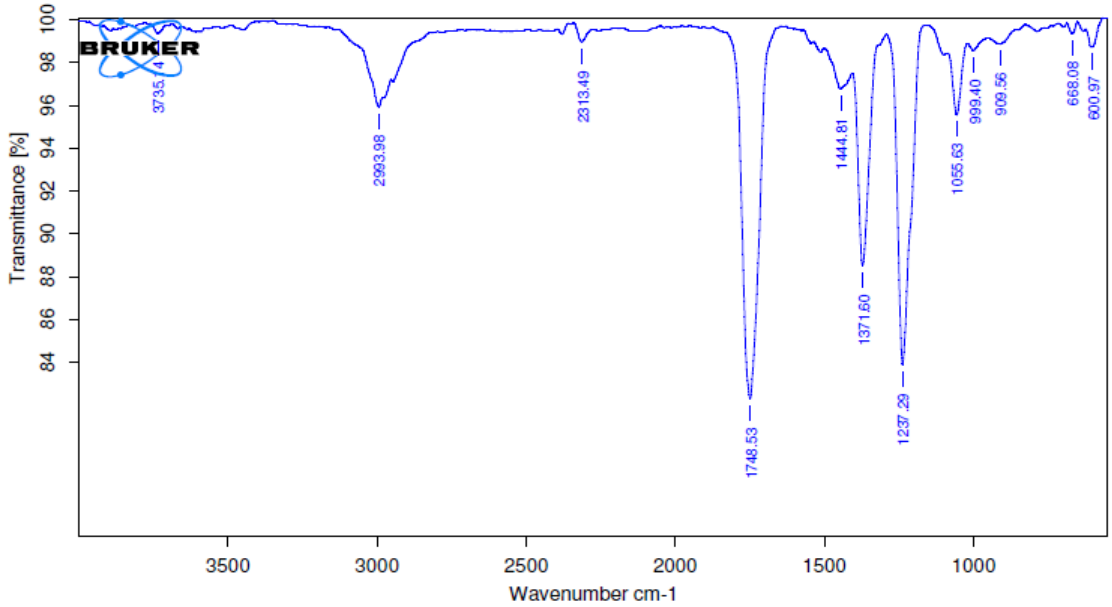

FIGURE 2: FTIR SPECTRUM OF PURE DRUG RAMIPRIL AND EXCEPIENTS

PHARMATUTOR
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ISSN: 2347-7881

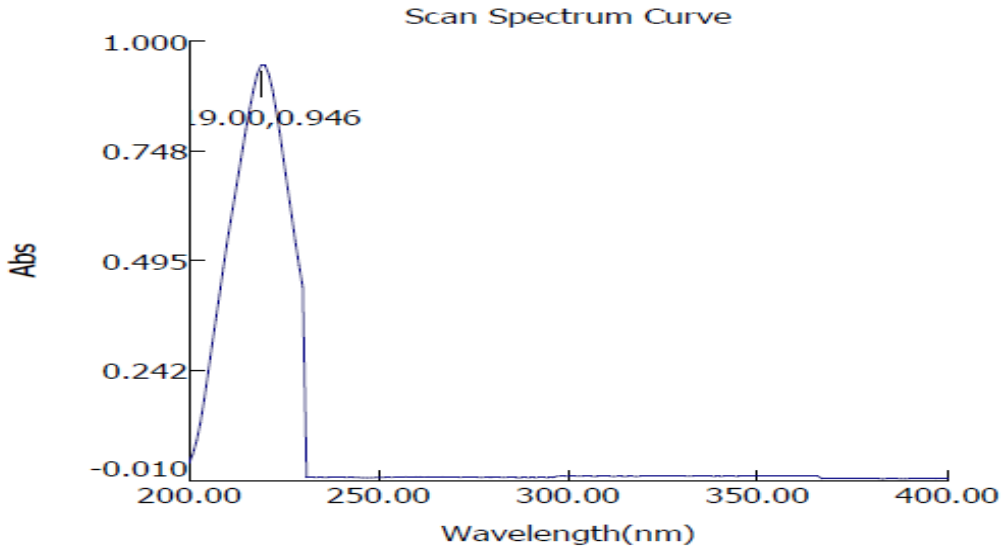

FIGURE: 3 SCAN SPECTRUM CURVE OF RAMIPRIL

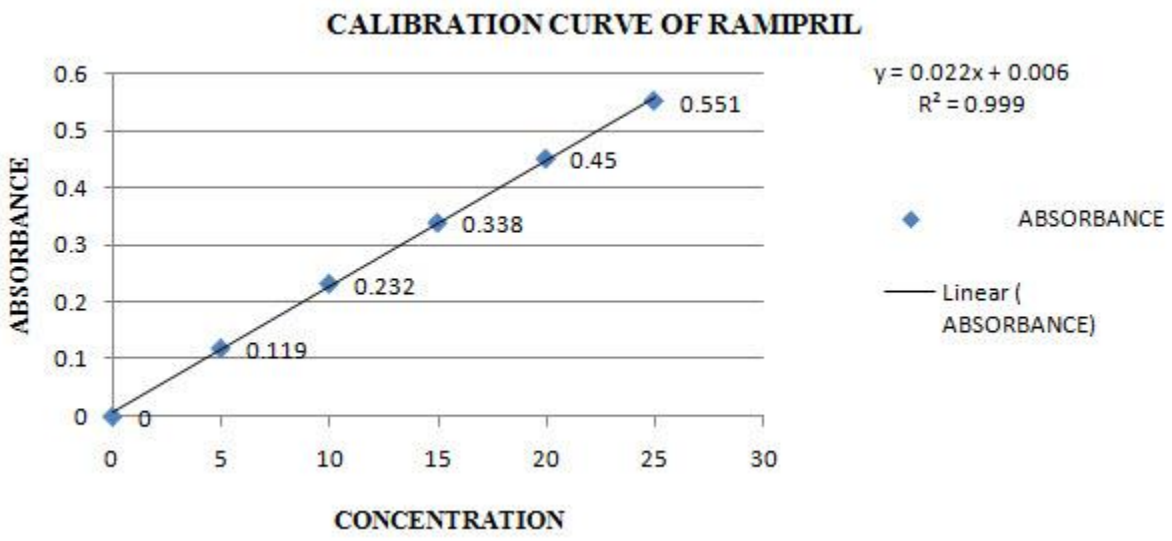

FIGURE: 4 STANDARD CALIBRATION CURVE OF RAMIPRIL

INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)
RAMIPRIL	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
SODIUM STARCH GLYCOLATE	1.52	1.49	1.50	1.25	1.32	1.42	1.00	1.60
CROSS CARMELLOSE	0.85	0.80	0.86	0.82	0.85	0.85	0.83	0.85
LACTOSE	18.88	20.085	20.015	20.305	20.205	20.105	20.545	19.93
CALCIUM STEARATE	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
TALC	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25

PHARMATUTOR
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ISSN: 2347-7881

TABLE 1: COMPOSITION OF IMMEDIATE RELEASE LAYER

INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)
RAMIPRIL	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
ETHYL CELLULOSE	2.75	4.00	3.20	3.00	4.50	4.10	4.30	4.50
GUAR GUM	0.70	1.15	0.75	1.25	0.50	1.25	0.85	1.12
GUGGUL	0.50	0.5	0.50	0.50	0.50	0.5	0.50	0.50
LACTOSE	17.05	15.35	16.55	16.25	15.5	15.15	15.35	14.88
MAGNESIUM STEARATE	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
TALC	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75

TABLE 2: COMPOSITION OF SUSTAINED RELEASE LAYER

BATCH	F1	F2	F3	F4	F5	F6	F7	F8
ANGLE OF REPOSE	24.84	22.81	23.41	23.89	24.33	24.81	24.89	25.2
BULK DENSITY	0.629	0.635	0.624	0.615	0.620	0.622	0.628	0.632
TAPPED DENSITY	0.74	0.745	0.747	0.732	0.751	0.729	0.730	0.723
COMPRESSIBILTY INDEX	15	14.765	16.465	13.797	18.109	14.95	15.06	13.13
HAUSNER'S RATIO	1.17	1.173	1.197	1.16	1.22	1.175	1.176	1.151

TABLE 3: PRECOMPRESSION EVALUATION OF POWDER BLEND OF ALL FORMULATIONS

FORMULATION	WEIGHT VARIATION AVERAGE WEIGHT IN mg	THICKNESS	HARDNESS Kg/cm^2	FRIABILITY	DRUG CONTENT%
F1	49.8	2.00	4.2	0.08	99.25
F2	50.1	2.00	4.1	0.04	95.65
F3	49.9	2.01	4.0	0.179	91.325
F4	50	2.02	4.3	0.155	97.20
F5	50	2.01	4.0	0.178	90.18
F6	50	2.01	4.0	0.120	94.5
F7	49.7	2.00	4.2	0.132	93.18
F8	50	2.00	4.0	0.031	95.40

TABLE 4: POST COMPRESSION EVALUATION OF PREPARED TABLETS

FORMULATION	CUMMULATIVE % DRUG RELEASE	ZERO ORDER R^2	FIRST ORDER R^2	HIGUCHI R^2	KOSMEYER PEPPAS R^2
F1	87.349	0.821	0.9567	0.9561	0.9671
F2	92.95	0.9336	0.9749	0.9855	0.9901

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ISSN: 2347-7881

F3	85.71	0.8474	0.9732	0.9726	0.9942
F4	75.24	0.8052	0.8704	0.9345	0.9845
F5	70.49	0.7355	0.8797	0.8891	0.9914
F6	82.44	0.8175	0.9509	0.9372	0.9863
F7	77.36	0.8834	0.972	0.9765	0.9768
F8	75.89	0.8591	0.9593	0.9765	0.9966

TABLE 5: MODEL FITTING OF DRUG RELEASE PROFILE OF FORMULATED TABLETS

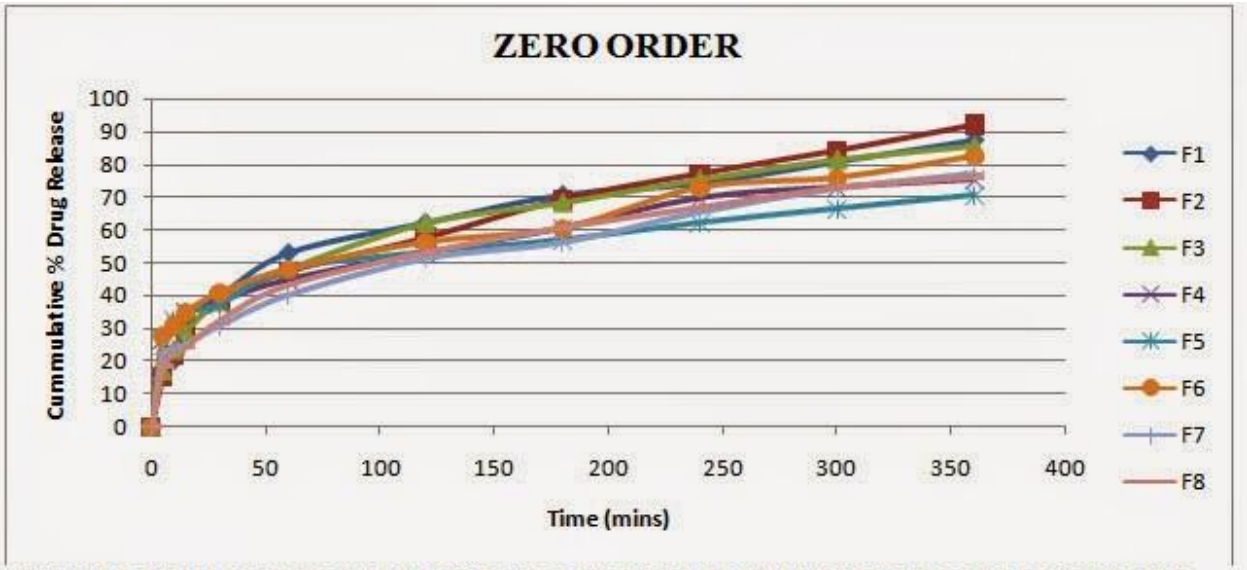

FIGURE 5: PLOTS OF CUMMULATIVE % DRUG RELEASE AS A FUNCTION OF TIME FOR FORMULATED RAMIPRIL BUCCOADHESIVE BILAYERES TABLETS (F1-F8)

FIGURE 6: FIRST ORDER PLOT FOR FORMULATED RAMIPRIL BUCCOADHESIVE BILAYERED TABLETS (F1-F8)

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

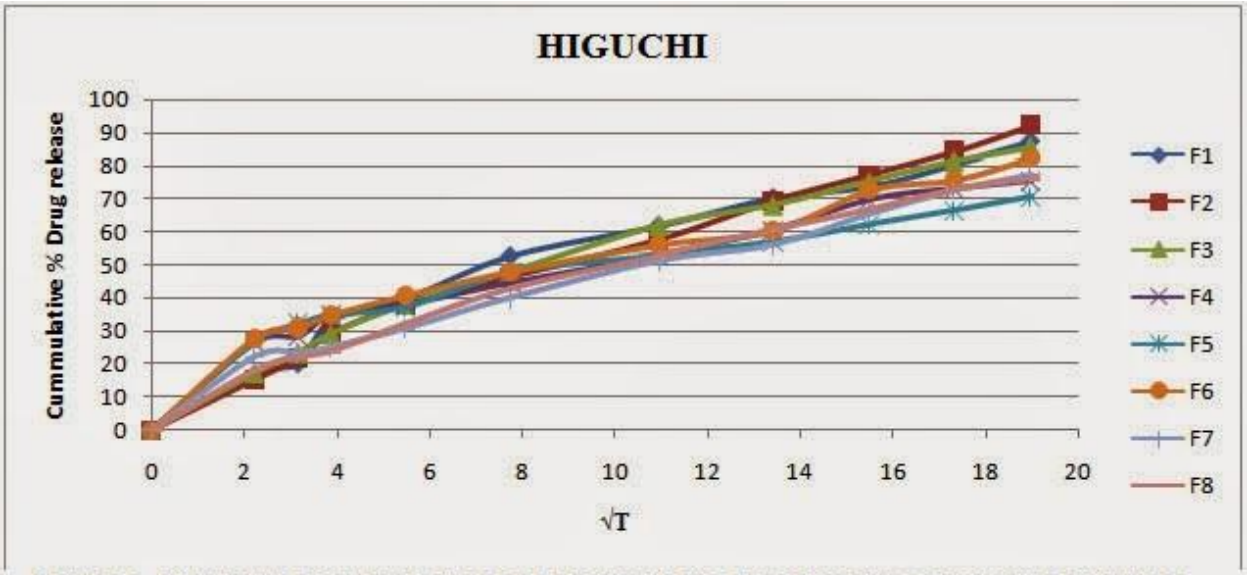

FIGURE 7: HIGUCHI'S DIFFUSION PLOT FOR FORMULATED RAMIPRIL BUCCOADHESIVE BILAYERED TABLETS (F1-F8).

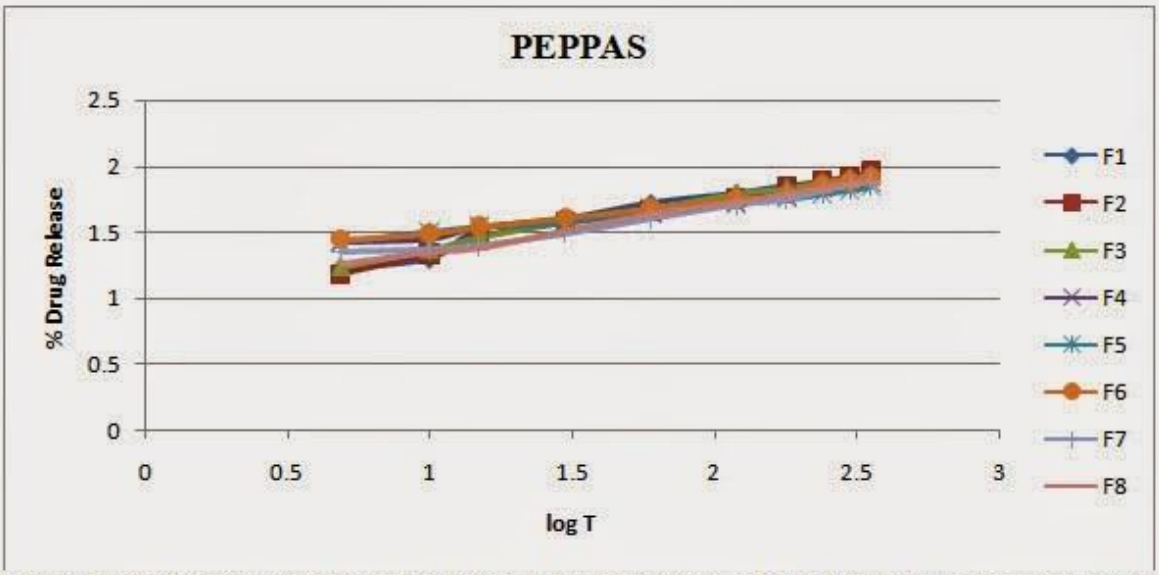

FIGURE 8: KOSMEYERS AND PEPPAS MODEL PLOT FOR FORMULATED RAMIPRIL BUCCOADHESIVE BILAYERED TABLETS (F1-F8).

CONCLUSION

From the results obtained in the present study, it can be concluded that, IR studies showed no significant Drug- Excipient interaction. So it can be concluded that drug and other excipients are compatible with each other. The formulated tablets were satisfactory in terms of physical parameters (hardness, thickness, weight variation), drug content and *invitro* drug release. Although all buccal tablets exhibited satisfactory drug release, the best results were obtained with tablet formulation F2. *In- vitro* dissolution studies of the optimized formulation indicated the drug release followed first order

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

Korsmeyer-Peppa's Model. The release of Ramipril from the buccal tablets followed fickian release kinetics which is indicative of drug release mechanism.

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