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Bioavailability Enhancement of Curcumin via Mucoadhesive Drug Delivery System

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ABSTRACT

The main aim of this study was to improve the bioavailability of curcumin through buccal route using mucoadhesive drug delivery. Curcumin is practically insoluble in water. After oral administration, most part of the drug was metabolism in liver .Therefore an attempt has been made to improve the bioavailability by using different concentration of sodium lauryl sulphate as bioenhancer. Buccal bilayer tablets were prepared by direct compression with different ratio of HPMC.K4M.as bioadhesive polymer and ethyl cellulose as backing layer. The formulation were characterized for various physiochehimical parameter such as weight variation, thickness, hardness, fribality, mucoadhisive strength, drug content, swelling studies and in vitro diffusion studies. The best mucoadhesive performance and *In vitro* drug release profile exhibited by tablets containing hydroxyproply methylcellulose K4M (5%) and Sodium louryl sulphate (0.1%).To conclude that the formulated unidirectional, bilayered, buccoadhesive tablet for curcumin using HPMC as mucoadhesive agent is superior to oral conventional tablet, as it has the potential to bypass the first pass metabolism and improve the bioavailability of curcumin.

Keywords: Curcumin, Ethyl cellulose, Sodium Lauryl Sulphate, HPMC.

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INTRODUCTION

The requirement for research and development of new pharmaceuticals molecules. The safety and potency of particular treatment may be improve if its administration rate or delivery rates, targeting, monitoring of site is controlled. [1]. There are different route of administration of drug into the body like oral, sub mucosal, parenteral, transdermal, pulmonary etc. Among this route of administration oral route is broadly preferred. This route is very simple, most economical and noninvasive, now a day scientist are trying to develop various technologies to incorporate in oral formulations.; a small change in drug delivery method can make tremendous difference in patient acceptability and bioavailability. [2]. However, this route offers several disadvantages as well like: Sometimes inefficient, First pass effect, Irritation to gastric environment, Unpleasant taste of drug, Not suitable in case of emergency [3]

Difficulties associated with parenteral delivery and poor oral availability promoted the impetus for exploring another routes for the delivery of those drugs. As a result, other absorptive mucosa is considered as effective site for drug delivery. There are different types of route for drug delivery for example mucosal linings of nose, vaginal, ocular, rectal and oral cavities this proposes distinctive advantage over per-oral administration for systemic effects. Among the different buccal mucosa, mucosal routes shows better acceptability over smooth muscles and immobile mucosa, so it is appropriate for giving in controlled release dosage forms [4].

Curcumin [1, 7-Bis (4-hydroxy-3- methoxyphenyl)-1,6-

heptadiene 3,5-dione] is the naturally derived therapeutic products, in the current scenario it is very popular in respect of research , due to it has various properties. Curcumin is the main biologically active curcuminoid of *Curcuma longa*-a herbaceous perennial herb family (Zingiberaceae) [5]. Curcumin produce a wide variety of physiologic activities, like anti-inflammatory activity by inhibiting NF-kB; induced apoptosis shows antineoplastic activity by arresting cell cycle it also inhibit angiogenesis .It possess anti-oxidant activity by excluding free radicals and an increasing intracellular concentration of glutathione. curcumin also shows anti viral and anti hepatotoxic activity. [6].

The pharmacokinetic studies of animals shows that 40-85 percent of oral dose of curcumin passes unchanged through the GIT.It is mainly absorbed flavanoid metabolized in the intestinal mucosa and liver. It has slow rate of absorption due to which is often given in combination with bromelain to increase absorption and to enhanced anti inflammatory activity [7]. The main disadvantage associated with oral administration of curcumin is high metabolic instability and less aqueous solubility due to which its systemic

bioavailability is limited. In addition, to this the patient shows non compliance for oral curcumin at the high doses (>8 g/day) to overcome these difficulties, new strategies for delivery of curcumin are being studied [8]. The present study was planned with the aim to formulate mucoadhesive buccal tablets of curcumin to improve the solubility and dissolution profile.

MATERIALS AND METHODS

Methodology

Pre-compressional Studies

Curcumin and the selected polymers were subjected to pre-compressional studies. Identification and purity of curcumin was determined by measuring the solubility, melting point, determination of $\lambda_{max.}$ Compatibility of curcumin and polymers was examined by the help of FTIR.

Formulation of Curcumin Buccal Tablets

All the ingredients except ethyl celluose are passed through sieve 80 and gently mixed together in an air tight plastic container. Then mixture is lubricated by adding magnesium stearate and talc and again blended for 2 min. The mixed ingredients are evaluated for precompression parameters, followed by direct compression. The weight of the tablets is adjusted to 200mg and coated by ethyl cellulose 60 mg to keep the unidirectional flow of drug.

Table 1: Formulation Table

Batch Code	F1	F2	F3	F4
Curcumin	100	100	100	100
Guar gum	10	20	30	40
Microcrystalline cellulose (MCC)	15	15	15	15
PEG – 6000	11	11	11	11
Piperine	2	2	2	2
Magnesium Stearate	3	3	3	3
Talc	2	2	2	2
Lactose	57	47	37	27
Ethyl cellulose	60	60	60	60
Total Weight	260	260	260	260

Curcumin Buccal Tablet evaluation

Uniformity of Weight

Twenty tablets were selected at a random and weighed individually. The average weight was calculated. The percentage deviation of tablets was calculated and compared with the standard specifications.

Table 2: Standards for calculating uniformity of weight

S.No.	Average weight of a tablet	% Deviation
1.	80 mg or less	±10
2.	80-250 mg	±7.5
3.	More than 250 mg	±5

Thickness

The thickness was measured to determine the uniformity of size and shape. Thickness of the Curcumin buccal tablets was measured using vernier caliper.

Hardness

Hardness is defined as the force required for breaking a tablet at diametric compression test and it is termed as tablet crushing strength. Hardness of the prepared formulations was determined using a tablet hardness tester. It was expressed in kp.

Friability

Friability of the prepared formulations was determined by using a friability tester. Pre- weighed tablets sample was placed in the friability tester, which was then operated for 25 revolutions for 4 min, tablets were dusted and reweighed. The friability of the tablets was calculated using the formula mentioned below.

$$\%\text{Friability} = \frac{Initial\ weight - Final\ weight\ of\ Tablets}{Initial\ weight\ of\ Tablets} \times 100$$

Drug Content

Ten tablets were randomly taken, weighed and powdered. The powder weight equivalent to 140 mg of curcumin was weighed out and put in 150 ml of methanol and placed in an ultra sonicator for 5 min. The sonicated solution was then filtered out using a Whatman No. 1 filter paper. The filtered solution was then made-up to 250ml using methanol. 5ml from the above solution was taken and diluted to 100ml with methyl alcohal. The final solution was analyzed using U.V. Visible spectrophotometer at 325 nm.

Swelling Index

The, previously weighed (w1), tablets were placed individually in a petri-dish containing 10ml of distilled water. The weight of the tablet (w2) after 30min was noted down after wiping the excess water from the tablet using a filter paper. The swelling index was calculated using the formula.

$$\text{Swelling Index} = \frac{W2-W1}{W1} \times 100$$

Wash –off Test

The mucoadhesive properties of the tablets were evaluated by wash-off method. buccal mucosa pieces of goat were mounted on the glass slides provided by suitable support. After fixing two tablets to this glass slide by pressing them onto the pre-wet tissue for 30sec, it was attached to the arm of tablet disintegration test apparatus (with the cylindrical drug chambers removed) and was run at 37°C in pH 6.8 buffer. Time taken for the detachment of both the tablets was noted down.

In vitro drug release study

The dissolution study was carried out by dissolution apparatus. The dissolution medium consisted of 900ml of pH 6.8 phosphate buffer. The temperature was set at 37 ± 0.5°C with a revolving speed of 50 rpm. The curcumin buccal tablet was allowed to sink to the base of the vessel. Samples of 10ml were withdrawn at 10 min interval, filtered and analyzed by UV at 425 nm.

Drug Release Kinetics

The release of drugs from the tablet can be characterized using various kinetic models [9].

- **Zero order equation**
- **First order equation**
- **Higuchi Kinetics**
- **Korsmeyer Peppas equation**
- **Hixson and Crowell erosion equation**

Table 3: Release mechanism based on n-value

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45< n > 0.89	Anomalous (non-fickian) diffusion
0.89	Case – II tranport
N	Super case – II transport

Table 4: Parameters of release kinetics

Release mechanism	Y - axis	X - axis
Zero order Kinetics	% Cumulative drug release	Time in min
First order kinetics	Log % cumulative drug remaining	Time in min
Higuchi Kinetics	% Cumulative drug release	Square root of time
Korsmeyer-Pappas Equation	Log cumulative % of drug release	Log time
Hixson and crowell equation	Cube root of % drug remaining	Time in min

RESULTS AND DISCUSSION

The curcumin buccal tablet were successfully made – (direct compression method) by using guar gum and piperine as excipient.

Pre-compression Evaluations

Buccal Tablet Evaluations

Table 5: Pre-compression parameters

Code	Bulk Density (g/cm3)	Tapped density (g/cm3)	Carr's index	Hausner's ratio	Angle of repose
F1	0.559	0.722	21.56	1.289	25.000
F2	0.541	0.689	18.79	1.240	28.594
F3	0.536	0.693	20.68	1.252	26.215
F4	0.524	0.697	21.33	1.271	21.371

Pre-compression specifications played an important role in enhance the properties of pharmaceuticals preparation especially in tablet formulation. This includes Bulk and Tapped density/ Carr's index, Angle of repose and Haaunser's ratio. Before the tablets formulations the drug were tested for above mentioned parameters, it was observed that all the results found as per prescribed limits in IP as shown in table 5. For all the formulations bulk density was stated to be ranging from (0.524-0.559)gm/cm^3, tapped density was between (0.689-0.722) gm/cm^{3}and angle of repose was found in between (21.371 to 28.594) gm/cm^3. Carr's index - (18.79 to 21.56) and Hausner's - (1.240 to 1.289).

Post-Compression Evaluation

Weight variation

According USP twenty tablets were selected randomly from every batch; weighed individually by using analytical weighing balance. The average and standard deviation were calculated. The average weight of 20 tablets was observed in between ***379.88 ± 0.287 mg to 380.86 ± 1.096 mg*** as showed in table 6**.** Weight variation analysis of all batches was found within the pharmacopoeial limits; ±7.5% of the weight.

Table 6: Weight Variation Data

Code	Weight variation
F1	379.33±1.258
F2	381.50±1.322
F3	380.34±0.577
F4	380.50±0.500

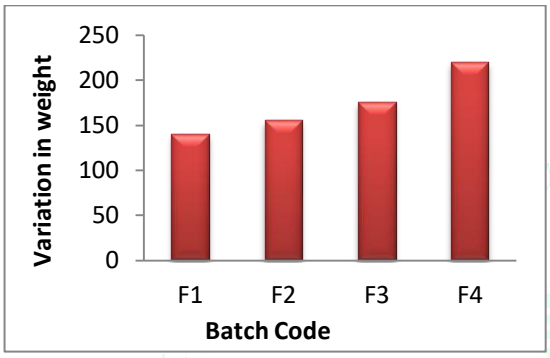

Fig 1: Weight variation

Thickness

The thicknesses of tablet are important for its uniformity of tablet size. Tablet width was measured by using (Caliper Vernier). 3 tablet average of was taken. The tablet thickness must be within ± 5 variation of standard value. The width of tablets for every batch ranged in between 3.7±0.054 to 3.9±0.035 mm (Table 7). This shows proper handling characteristics for all batches.

Table 7: Thickness Testing Data

Batch Code	Thickness
F1	3.8±0.019
F2	3.7±0.054
F3	3.9±0.035
F4	3.8±0.047

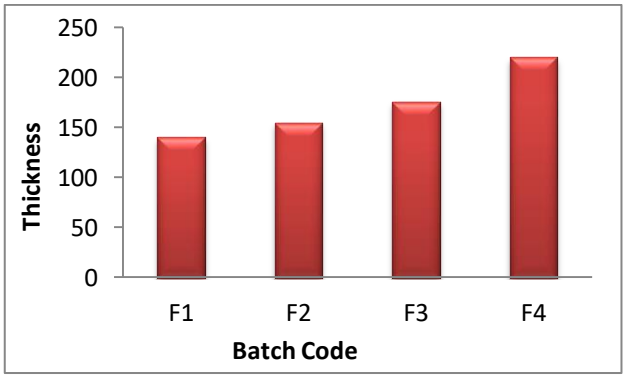

Fig 2: Thickness testing interpretation

Hardness

Tablet hardness indicate that the ability of the tablet to face mechanical shocks while handling. It is measured by using Monsanto hardness tester. Its unit expressed in kilo gram/cm^2. Average of 6 tablet was taken as per USP norms from each formulation. Hardness of tablets of every batch (ranged between 4.0±0.179 to 5.0±0.196 kg/cm^2 (Table No.8). Its confirm that good mechanical strength for all batches.

Table 8: Hardness Testing Data

Batch Code	Hardness (kg/cm^2)
F1	4.0±0.163
F2	4.0±0.115
F3	5.0±0.179
F4	4.0±0.142

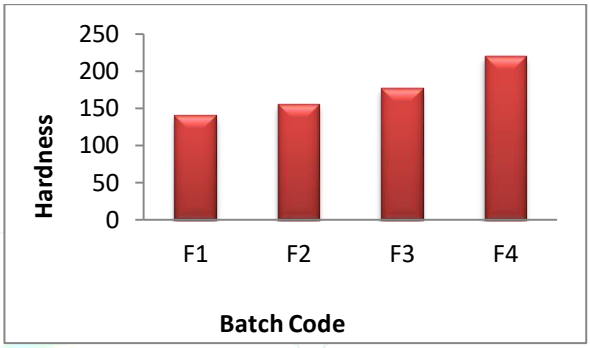

Fig 3: Hardness testing interpretation

Friability

Friability test is used to determine the loss in weight of tablets in container for the duration of transportation. 20 tablets were initial weight was recorded and load in Roche friabilator. It rotates at 25 rpm for 4 minutes. After that loaded tablet was taken out and again weight, the difference between the weights was recorded .The friability result for formulated tablets was observed-(0.41 ± 0.013 to 0.68 ± 0.012 %) as showing table 9**.** All the formulated tablets showed the percentage friability not more than 1%.

Table 9: Friability Testing Data

Batch Code	Friability (%)
F1	0.53±0.011
F2	0.41±0.013
F3	0.59±0.014
F4	0.68±0.012

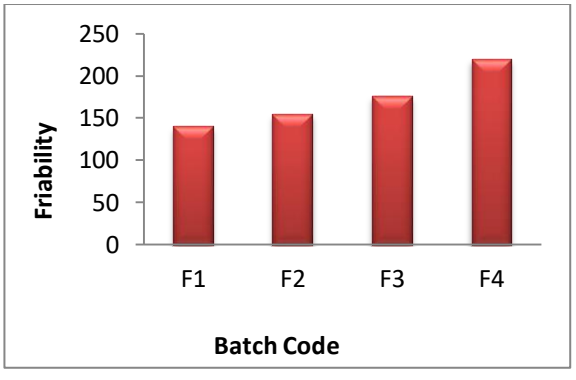

Fig 4: Friability testing interpretation

Drug content

Five tablets from each formulation were taken, crushed and mixed. From the mixture of 100mg ;equivalent mixture was extracted carefully within range of pH 6.8 phosphate buffer and 3% tween 80.The quantity of drug present in each extract wascalculated by using UV spectrophotometer at wavelength 425 nm against blank. All the formulated mucoadhesive buccal tablets are tested for uniformity of drug content.

Drug content in formulation was observed (96.00±1.410 to 97.14±1.332 %) which is shown in table 10.

Table 10: Drug Content Testing Data

Batch Code	Drug Content (%)
F1	97.14±1.332
F2	96.24±1.390
F3	96.00±1.410
F4	96.11±1.782

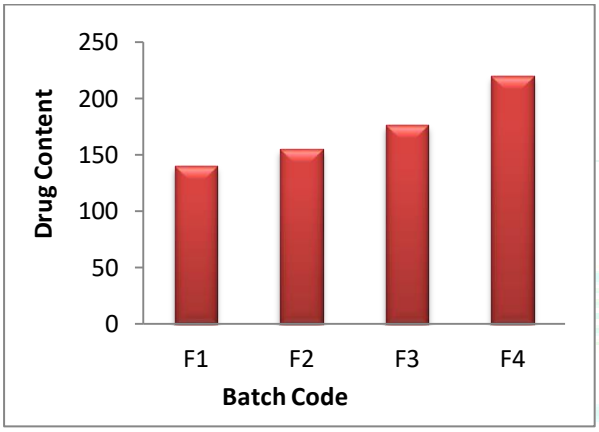

Fig 5: Drug content testing interpretation

Swelling Index

The curcumin mucoadhesive buccal tablets initial weight exactly and taken into a petri dish which contains 5ml of pH 6.8 phosphate buffer, temperature maintained at 37±0.5°C. After f 3 hour the tablets were removed from the Petri dish and swollen tablets were reweighed (final weight). The swelling index was calculated by means of mathematical expression .The swelling index of buccal tablets was observed in between (8.78±0.874 to 53.70±0.854), at the end of 3 hours as showed in table 11.

Table 11: Swelling index Testing Data

Batch code	Swelling index
F1	19.66±0.341
F2	25.48±0.288
F3	34.17±0.322
F4	46.89±0.641

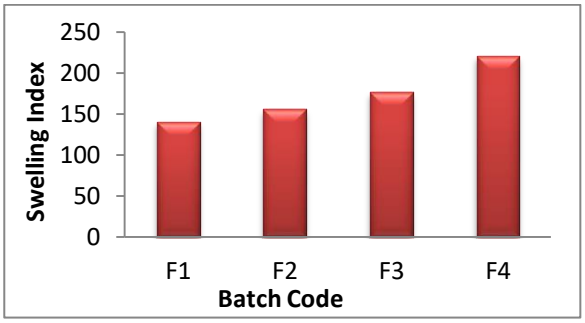

Fig 6: Swelling Index testing interpretation

Retention time (*In vitro*)

In vitro retention time is determined by goat buccal mucosa in modified magnetic stirrer. The buccal mucosa of goat was attached with glass slide and the curcumin mucoadhesive tablet was press on buccal mucosa of goat for 30 seconds, which is dip in beaker containing 500ml of pH 6.8 phosphate buffer, the temperature maintained at 37±0.5ºC. The magnetic beat was rotated at 25 rpm, the experiment was continuing till the buccal tablet detached from the goat buccal mucosa. The *In-vitro* residence time of buccal tablets was observed (140 minutes to 220 minutes) that is considered as good retention time as shown in table 12.

Table 12: *In vitro* Retention time

Batch Code	*In vitro* retention time (min)
F1	140
F2	155
F3	176
F4	220

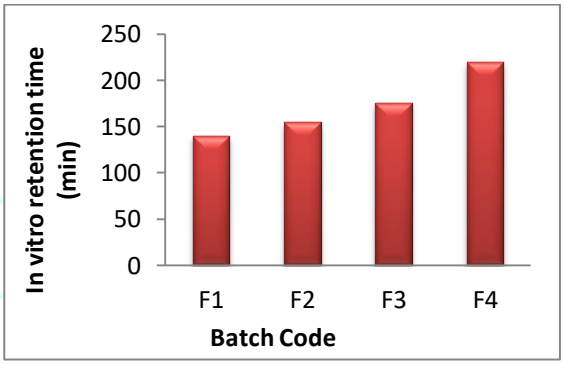

Fig 7: *In vitro* retention time interpretation

***In-vitro* Drug release**

The drug release studies were performing by using USP II dissolution test apparatus (paddle type).the tablet was formulated in such manner that drug is release from one side only, because it is design for unidirectional released.Now, all tablet were placed in 900ml in phosphate buffer (pH 6.8) containing 3% tween 80 ,The temperature maintain at 37±0.5°C; 4.0 hours. Now start the machine and set the paddle on 100 rpm. After every 30 min take 5 ml sample .Maintained dissolution medium with fresh buffer for analysis of drug content. Now check on UV spectrophotometer at 425nm. The drug release by formulated tablets is (82.02±0.33**%)** which is showed by formulation F3 within 4.0 hours.

Note-UV spectrophotometer is used for drug release here because there is no specific dissolution test available for curcumin mucco adhesive tablets.

Table 13: Drug release data (*In vitro*)

S.No.	Time (min)	Cumulative % drug release			
		F1	F2	F3	F4
1	0	0	0	0	0
2	30	24.52±0.72	26.74±0.46	12.07±0.29	19.21±0.12
3	60	59.26±0.28	39.07±0.22	25.94±0.71	23.01±0.25
4	90	76.05±0.34	46.31±0.53	36.08±0.66	32.84±0.14
5	120	94.19±0.87	62.92±0.91	42.15±0.85	38.29±0.16
6	150	-	80.62±0.35	57.33±0.22	44.59±0.38
7	180	-	92.25±0.57	68.79±0.11	49.60±0.65
8	210	-		72.48±0.95	57.03±0.28
9	240	-		82.02±0.33	67.22±0.91

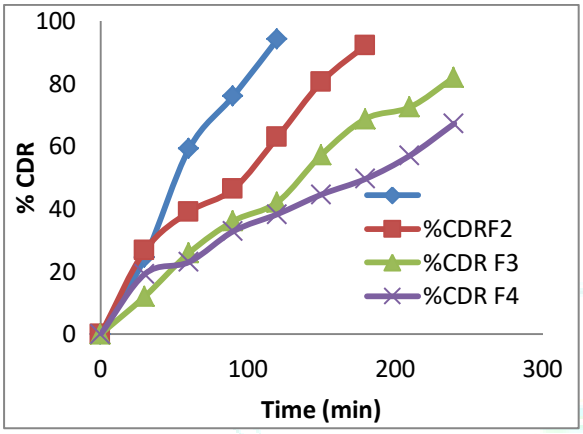

Fig 8: *In vitro* drug release interpretation

Mathematical expression for kinetic assessment of drug release mechanism

The release data obtained from *in vitro* dissolution studies were fitted to five different mathematical models namely, 0 order, 1st order, Higuchi's model, Korsmeyer peppas & Hixson-crowell to find mechanism of drug release. Correlation coefficients (R^2) obtained from regressed plots of different kinetic models such as 0 order, 1st order, Higuchi's model, Korsmeyer peppas and Hixson-crowell model are also mentioned. The correlation coefficients (R^2) were used as an indication of the best fit, for each of the models considered. The correlation coefficients (R^2) was obtained in 0 order, 1st order, Higuchi model, Korsmeyer peppas and Hixson-crowell model of formulation F3 shown in fig. 6.13-6.17 were 0.989, 0.969, 0.939, 0.996, 0.786. In this formulation Korsmeyer peppas model best explain in vitro drug release ,because best linearity was found in Korsmeyer peppas model equation plot (R^2 = 0.998) shown in fig. 9.

Table 14: *In vitro* release data of F3: Zero order kinetics

Time (min)	Percentage cumulative drug release
0	0
30	12.07
60	25.94
90	36.08
120	42.15
150	57.33
180	68.79
210	72.48
240	82.02

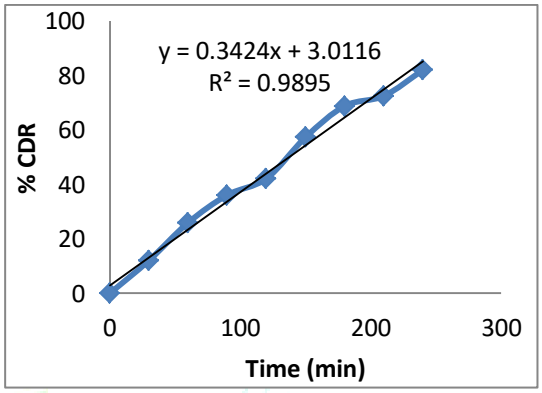

Fig 9: Plot for zero order kinetic

Table 15: release data of formulation F3: First order kinetics (*In vitro*)

Time (min)	Log % cumulative drug remaining
0	2
30	1.94
60	1.86
90	1.80
120	1.76
150	1.63
180	1.49
210	1.43
240	1.25

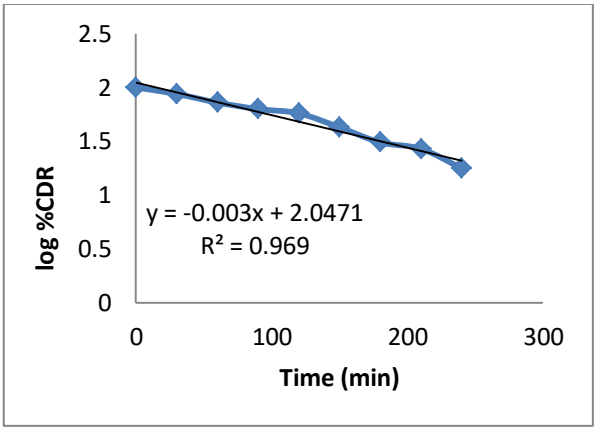

Fig 10: Plot for first order kinetics

Table 16: *In vitro* release data of F3: Higuchi model release kinetics

% Cumulative drug release	SQRT
0	0
12.07	5.47722
25.94	7.74596
36.08	9.48683
42.15	10.95445
57.33	12.24744
68.79	13.41640
72.48	14.49137
82.02	15.49193

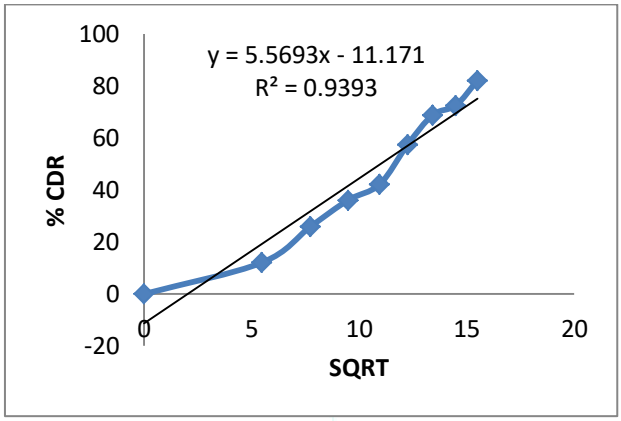

Fig 11: Plot of Higuchi model release kinetics

Table 17: *In vitro* release data of F3: Koresmeyer Peppas model

Log Time	Log % CDR
0	0
1.477	1.081
1.778	1.406
1.954	1.557
2.079	1.624
2.176	1.758
2.255	1.837
2.322	1.860
2.380	1.913

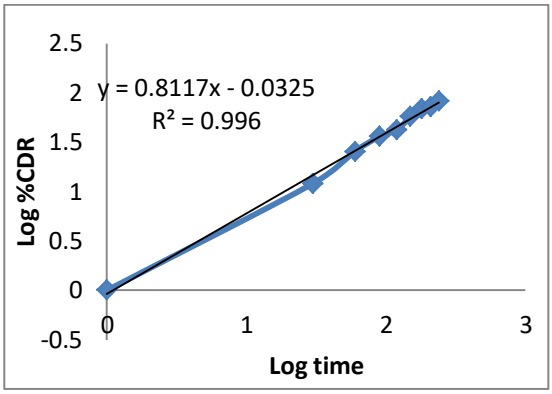

Figure 12: Plot of Korsmeyer peppas model release kinetics

Table 18: *In vitro* release data of F3: Hixson Crowell model

Time (min)	Cube root of % cumulative drug release
0	0
30	2.29
60	2.96
90	3.30
120	3.48
150	3.85
180	4.09
210	4.16
240	4.64

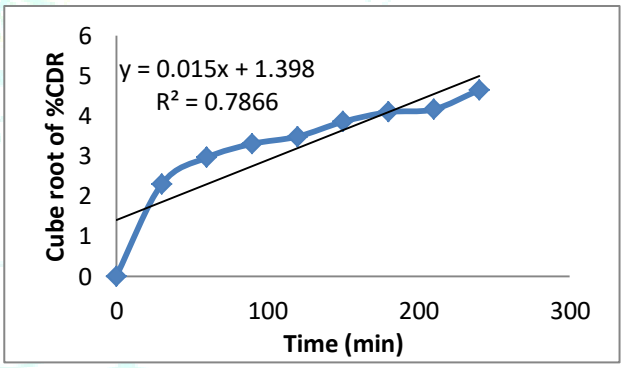

Figure 13: Plot of Hixson crowell model release kinetics

Table 19: Kinetic assessment of dissolution data of curcumin mucoadhesive buccal tablet formulation

Zero order model	First order model	Higuchi model	Koresmeyer peppas	Hixson crowell
R^2	R^2	R^2	R^2	R^2
0.989	0.969	0.939	0.996	0.786

CONCLUSION

On the basis of this research work we can conclude that, delivery through buccal route is a promising way to enhance the bioavailability of poorly water soluble/ water insoluble drugs. Buccal drug delivery helps in eliminating the first pass metabolism of various drugs and directly provides the drug to the systemic circulation. Incorporation of hydrophilic polymer enhances the efficacy of this system. This opens an extensive area for research in this field which will be beneficial in overcoming the bioavailability problems of existing drugs as well as new molecules because as per statistics 70% of new developed compounds are facing the problem of poor bioavailability due to which they cannot reach the development pipeline. Therefore, further research needs to be done to study this area extensively.

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