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Research

Formulation And Characterization Of Bilayered Buccal Tablets Of Diacerein

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Abstract

Buccoadhesive Bilayer buccal tablets of Diacerein were prepared by using Cashew nut tree gum, Xanthan gum and Karayagum as mucoadhesive polymers. Nine formulations were developed with varying concentrations of polymers F1 to F9 formulations were composed of Cashew nut tree gum, Xanthan gum and Karayagum in ratios of 1:1, 1:2 and 1:3. The formulated mucoadhesive buccal tablets were assessed for quality attributes like weight variation, hardness, thickness, friability, drug content, moisture absorption, surface pH and *in vitro* drug release studies. Optimized formulation F4 showed maximum release of the drug (99.59%). The FTIR results showed no evidence of interaction between the drug and polymers. All the evaluation parameters given the positive result and comply with the standards. The results indicated that the mucoadhesive buccal tablets of Diacerein may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in bioavailability of Diacerein through buccal mucosa.

Keywords: Diacerein, Cashew nut tree gum, Xanthan gum and Karayagum and Buccal tablets.

INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing. Problems such as first pass metabolism and drug degradation in the GIT environment can be circumvented by administering the drug via buccal route. Moreover, the oral cavity is easily accessible for self-medication and be promptly terminated in case of toxicity by removing the dosage form from buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally via this route Successful buccal drug delivery using buccal adhesive system requires at least three of the following (a) A bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa (b) A vehicle the release the drug at an appropriate rate under the conditions prevailing in

the mouth and (c) Strategies for overcoming the low permeability of the oral mucosa. Buccal adhesive drug delivery stem promotes the residence time and act as controlled release dosage forms.

The use of many hydrophilic macromolecular drugs as potential therapeutic agents is there in adequate and erratic oral absorption. However, therapeutic potential of these compounds lies in our ability to design and achieve effective and stable delivery systems. Based on our current understanding, it can be said that many drugs cannot be delivered effectively through the conventional oral route.

The main reasons for the poor bio-availability of many drugs through conventional oral route are:

- ✓ Pre-systemic clearance of drugs.
- ✓ The sensitivity of drugs to the gastric acidic environment which leads to gastric irritation. Limitations associated with gastro intestinal tract like variable absorption characteristics.

Buccal mucosa composed of several layers of different cells. The Epithelium is similar to stratified squamous epithelia found in rest of the at least one of which is biological nature are held together by means of interfacial forces.[1]

Buccal drug delivery is a type of bioadhesive drug delivery especially it is a mucoadhesive drug delivery system is adhered to buccal mucosa.

- ➢ The term bioadhesion is commonly defined as an adhesion between two materials where at least one of the materials is of biological origin. In the case of bioadhesive drug delivery systems, bioadhesion often refers to the adhesion between the excipients of the formulation (i.e. the inactive media) and the biological tissue.
- ➢ The term mucoadhesion can be considered to refer to a sub group of bioadhesion and, more specifically, to the case when the formulation interacts with the mucous layer that covers a mucosal tissue.

The mucosal layer lines a number of regions of the body including gastrointestinal tract, urogenital tract, airway, ear, nose and eye. Hence mucoadhesive drug delivery system includes the following:

1. Buccal delivery system
2. Oral delivery system
3. Ocular delivery system
4. Vaginal delivery system
5. Rectal delivery system
6. Nasal delivery system[2]

Overview of the Oral Mucosa Structure The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer18, 19 can be seen in figure 1. The epithelium of the buccal mucosa is about 40- 50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The turnover time for the buccal epithelium has been estimated at 5-6 days[3], and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 μm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized[4]. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, nonkeratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramides and only have small amounts of ceramide [5-7]. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

Mechanism Of Mucoadhasive

Several theories have been put forward to explain the mechanism of polymer–mucus interactions that lead to mucoadhesion. To start with, the sequential events that occur during bioadhesion include an intimate contact between the bioadhesive polymer and the biological tissue due to proper wetting of the bioadhesive surface and swelling of the bioadhesive. Following this is the penetration of the bioadhesive into the tissue crevices, interpenetration between the mucoadhesive polymer chains and those of the mucus. Subsequently low chemical bonds can become operative. Hydration of the polymer plays a very important role in bioadhesion. There is a critical degree of hydration required for optimum bioadhesion. If there is incomplete hydration, the active adhesion sites are not completely liberated and available for interaction. On the other hand, an excessive amount of water weakens the adhesive bond as a result of an overextension of the hydrogen bonds. During hydration; there is a dissociation of hydrogen bonds of the polymer chains. The polymer–water interaction becomes greater than the polymer-polymer interaction, thereby making the polymer chains available for mucus penetration. Following polymer hydration intermingling between chain segments of the mucoadhesive polymer with the mucus occurs. The factors critical for this model of mucoadhesion are the diffusion coefficient of the polymer, contact

time and contact pressure. The polymer diffusion coefficient is influenced by the molecular mass between cross-links, and is inversely related to the cross-linking density. [11-14]

Advantages Of Buccal Drug Delivery System

1) Bypass the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism. In addition the drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
2) Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications.
3) Sustained drug delivery.
4) A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.
5) Increased ease of drug administration.
6) Though less permeable than the sublingual area, the buccal mucosa is well vascularized, and drugs can be rapidly absorbed into the venous system underneath the oral mucosa.
7) In comparison to TDDS, mucosal surfaces do not have a stratum corneum. Thus, the major barrier layer to transdermal drug delivery is not a factor in transmucosal routes of administration.
8) Transmucosal delivery occurs is less-variable between patients, resulting in lower intersubject variability as compared to transdermal patches.
9) The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.

Disadvantages Of Buccal Drug Delivery System

1) Low permeability of the buccal membrane: specifically when compared to the sublingual membrane.
2) Smaller surface area. The total surface area of membranes of the oral cavity available for drug absorption is 170 cm2 of which ~50 cm^2 represents non-keratinized tissues, including the buccal membrane.
3) The continuous secretion of saliva (0.5–2 l/day) leads to subsequent dilution of the drug.
4) Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form.

These are some of the problems that are associated with buccal drug delivery.

Limitations Of Buccal Drug Administration

1) Drugs which are unstable at buccal pH cannot be administered.
2) Eating and drinking may become restricted.
3) There is an ever present possibility of the patient swallowing the dosage form.
4) Over hydration may leads to slippery surface and structural integrity of the formulation may get disrupted by this swelling and hydration of the bioadhesive polymers.
5) Drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odor cannot be administered by this route.
6) Only drug with small dose requirement can be administered.
7) Only those drugs which are absorbed by passive diffusion can be administered by this route. 8) Drugs contained in the swallowed saliva follow the pre-oral and advantages of buccal route are lost.[15,16]

MATERIALS AND METHODS

Diacerein- Procured From Lark laboratories, Bhiwadi, India. Provided by SURA LABS, Dilsukhnagar, Hyderabad.
Bulk density Apparatus- Cintex industrial corporation, Mumbai.
Tapped Density Apparatus- Electrolab, India
Hardness Tester (Monsanto)- Monsanto
UV/Visible-spectrophotometer- Lab India
Dissolution Apparatus (U.S.P)- Lab India
Franz diffusion cell- Borosil Glass Works Ltd
Modified 2- arm balance- Remi equipments Ltd
Digital pH meter- Lab India
FT-IR spectrophotometer- Bruker, Germany

METHODOLOGY

Preformulation studies

Analytical method used in the determination of Diacerein

Preparation of 0.2M Potassium Dihydrogen Orthophosphate Solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 mL of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution: Accurately weighed 8 gm of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed

Preparation of pH 6.8 phosphate buffer: Accurately measured 250 mL of 0.2M potassium dihydrogen ortho phosphate and 112.5 mL of 0.2M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

Preparation of pH 7.4 phosphate buffer: Accurately measured 250 mL of 0.2M potassium dihydrogen ortho phosphate and 195.5 mL of 0.2M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

Formulation development of tablets

Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. Cashew nut tree gum, Xanthan gum and Karaya gum are the mucoadhesive polymers used in this preparation of buccal mucoadhesive drug delivery systems.

Diacerein was mixed manually with different ratios of Cashew nut tree gum, Xanthan gum and Karaya gum, Ethyle cellulose and MCC as diluent for 10 min the blend was mixed with talc and magnesium stearate for 3-5 min.

Evaluation of pre-compression blend

The quality of tablet, once formulated, by rule is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characterization of blends produced. Prior to compression, granules were evaluated for their characteristic parameter such as Tapped density, Bulk density, Carr's index, Angle of repose, Hausner's ratio. Compressibility index was calculated from the bulk and tapped density using a digital tap density apparatus. The various characteristics of blends tested are as given below:

Preparation of Tablets

Then the powder blend was compressed into tablets by the direct compression method using 8mm flat faced punches. The tablets were compressed using a ten station LAB PRESS rotary tablet-punching machine. The weight of the tablets was determined using a digital balance and thickness with digital screw gauge. Composition of the prepared bioadhesive buccal tablet formulations of Diacerein were given in Table 8.4.

Table 1: Formulation Chart

INGREDIENTS (MG)	FORMULATION CODES								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diacerein	50	50	50	50	50	50	50	50	50
Cashew nut tree gum	25	50	75	-	-	-	-	-	-
Xanthan gum	-	-	-	25	50	75	-	-	-
Karaya gum	-	-	-	-	-	-	25	50	75
Ethyle cellulose (Backing Layer)	40	40	40	40	40	40	40	40	40
MCC	61	36	11	61	36	11	61	36	11
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	5	5	5	5	5	5	5	5	5
Saccharin sodium	15	15	15	15	15	15	15	15	15
Total weight	200	200	200	200	200	200	200	200	200

Evaluation Of Buccal Tablets

Physicochemical characterization of tablets

The prepared Diacerein buccal tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

A. Weight variation

B. Tablet Thickness

C. Tablet Hardness

D. Friability

E. Assay

***In vitro* release studies**

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 8 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 252nm.

Drug-excipient compatibility studies

Fourier Transform Infrared spectroscopic studies

A Fourier Transform – Infra Red spectrophotometer was used to study the non-thermal analysis of drug-excipient (binary mixture of drug: excipient 1:1 ratio) compatibility. The spectrum of each sample was recorded over the 450-4000 cm^{-1}. Pure drug of Diacerein with physical mixture (excipients) compatibility studies were performed.

RESULTS AND DISCUSSION

Standard graph in phosphate buffer pH 6.8 (λ_{max} 252 nm)

Standard graph of Diacerein was plotted as per the procedure in experimental method and its linearity is shown in Table 9.2 and Fig 9.1**.** The standard graph of Diacerein showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

Table 2: Standard graph values of Diacerein in pH 6.8 phosphate buffer

Concentration (µg/mL)	Absorbance
0	0
2	0.143
4	0.259
6	0.378
8	0.511
10	0.629

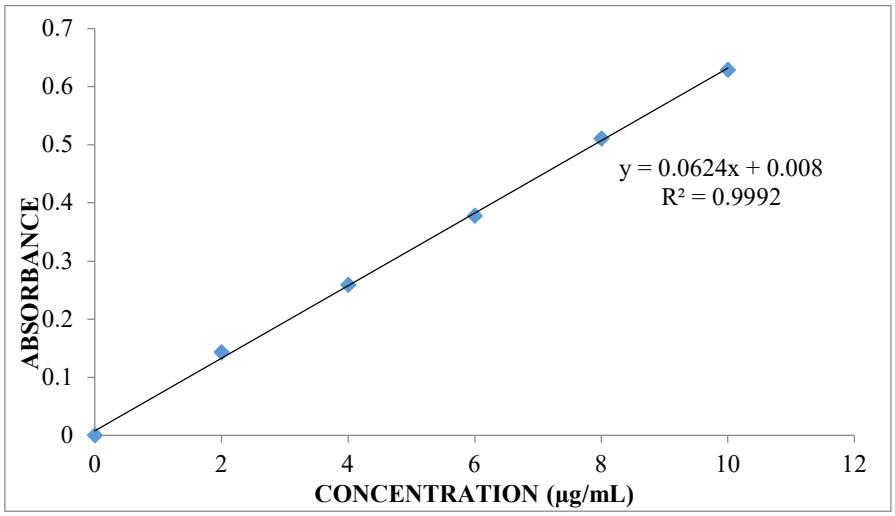

Fig 1: Standard graph of Diacerein in pH 6.8 phosphate buffer

Standard graph in phosphate buffer pH 7.4 (λ_{max} 255 nm)

Standard graph of Diacerein was plotted as per the procedure in experimental method and its linearity is shown in Table 9.3 and Fig 9.2. The standard graph of Diacerein showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

Table 3: Standard graph values of Diacerein in pH 7.4 phosphate buffer

Concentration (µg/mL)	Absorbance
0	0
2	0.122
4	0.234
6	0.369
8	0.478
10	0.596

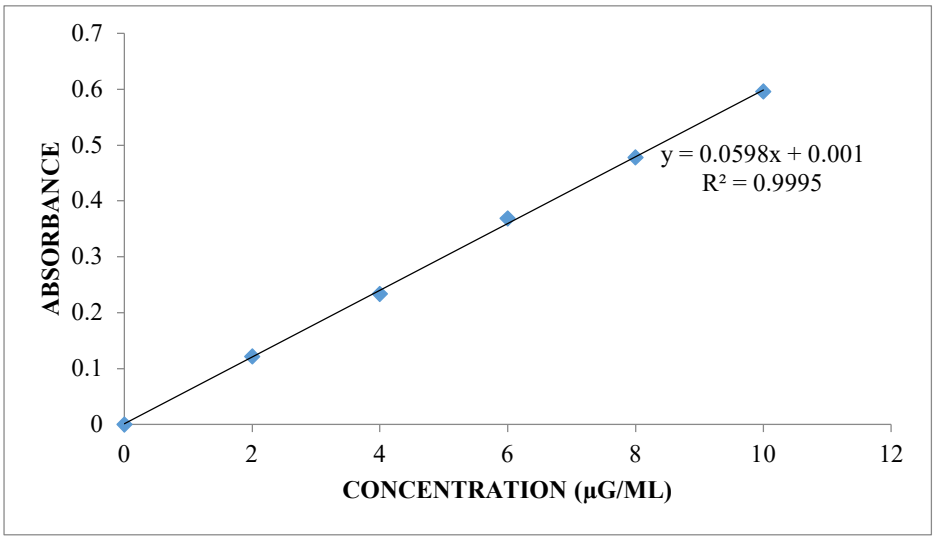

Fig 2: Standard graph of Diacerein in pH 7.4 phosphate buffer

Evaluation

Characterization of pre-compression blend

The pre-compression blend of Diacerein bilayer buccal tablets were characterized with respect to angle of repose, bulk density, tapped density, carr's index and hausner's ratio**.** Angle of repose was less than 29.58º, Carr's index values were less than 16.07 for the pre-compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.19 for all the batches indicating good flow properties.

Table 4: Physical properties of pre-compression blend

Formulation Code	Angle of repose (Ɵ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
F1	28.75	0.481	0.572	15.90	1.18
F2	27.33	0.475	0.566	16.07	1.19
F3	25.38	0.524	0.599	12.52	1.14
F4	26.43	0.412	0.483	14.69	1.17
F5	24.77	0.488	0.537	9.12	1.10
F6	26.42	0.439	0.521	15.73	1.18
F7	28.19	0.559	0.649	13.94	1.16
F8	29.58	0.331	0.393	15.77	1.18
F9	28.73	0.362	0.428	15.42	1.18

Evaluation of buccal tablets

Table 5: Physical evaluation of Diacerein buccal tablets

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)
F1	198.47	4.01	4.9	0.56	96.10
F2	196.92	4.92	4.0	0.36	98.65
F3	199.30	4.35	5.3	0.24	99.10
F4	197.12	4.87	4.1	0.68	97.34
F5	198.82	4.28	5.2	0.59	98.58
F6	199.27	4.13	5.6	0.32	96.14
F7	200.04	4.79	4.1	0.77	99.82
F8	198.75	4.35	5.0	0.62	95.38
F9	197.80	4.60	4.8	0.43	98.76

***In vitro* release studies**

Table 6: *In vitro* dissolution data for formulations F1 – F9

TIME (H)	CUMULATIVE PERCENTE OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	22.89	17.72	19.90	26.12	14.82	13.92	15.05	13.53	11.58
1	26.32	35.50	28.35	32.83	24.73	20.03	23.19	18.92	20.16
2	38.58	45.93	32.17	41.51	35.90	27.51	30.27	28.60	26.09
3	52.91	61.46	38.26	49.15	47.17	35.99	36.59	37.18	34.10
4	67.54	67.59	46.83	56.99	58.34	46.42	49.01	46.82	53.23
5	78.73	78.98	59.41	67.31	64.10	55.60	55.39	52.99	57.42
6	90.15	82.42	63.96	74.65	70.09	63.17	75.53	67.76	65.99
7	96.21	86.18	74.63	82.09	75.37	70.96	85.89	77.14	76.37
8		91.13	87.57	99.59	87.24	75.12	93.73	87.34	81.83

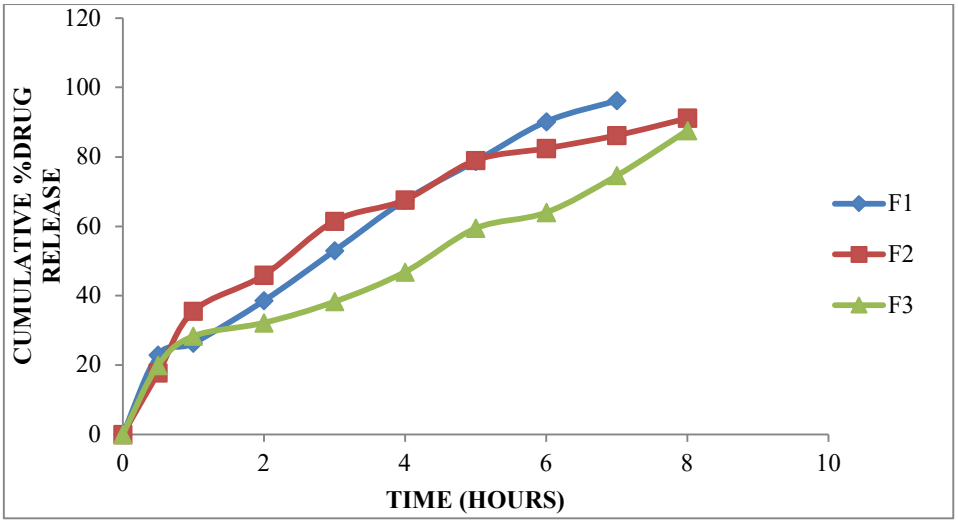

Fig 3: *In vitro* dissolution data for formulations F1 – F3 by using Cashew nut tree gum polymer

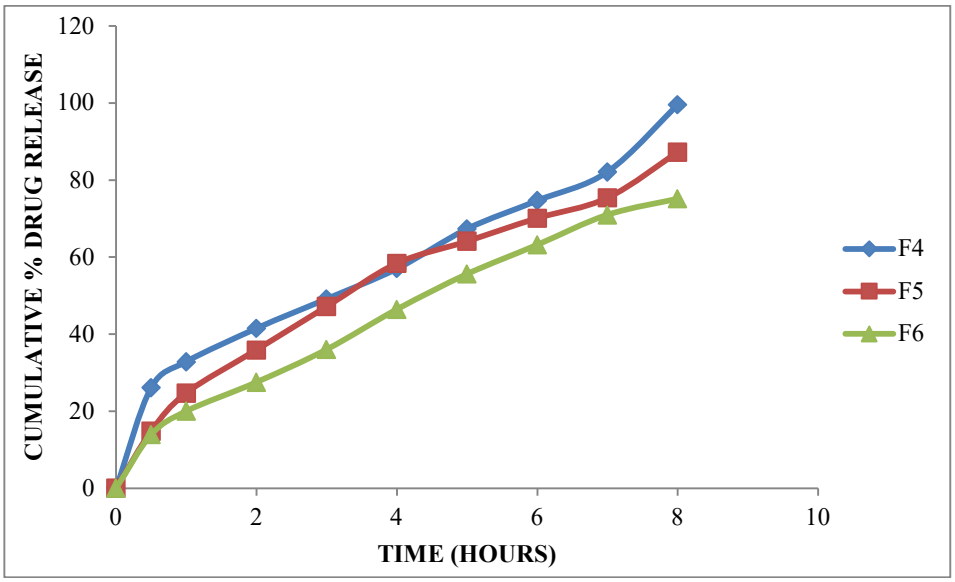

Fig 4: *In vitro* dissolution data for formulations F4 –F6 by using Xanthan gum polymer

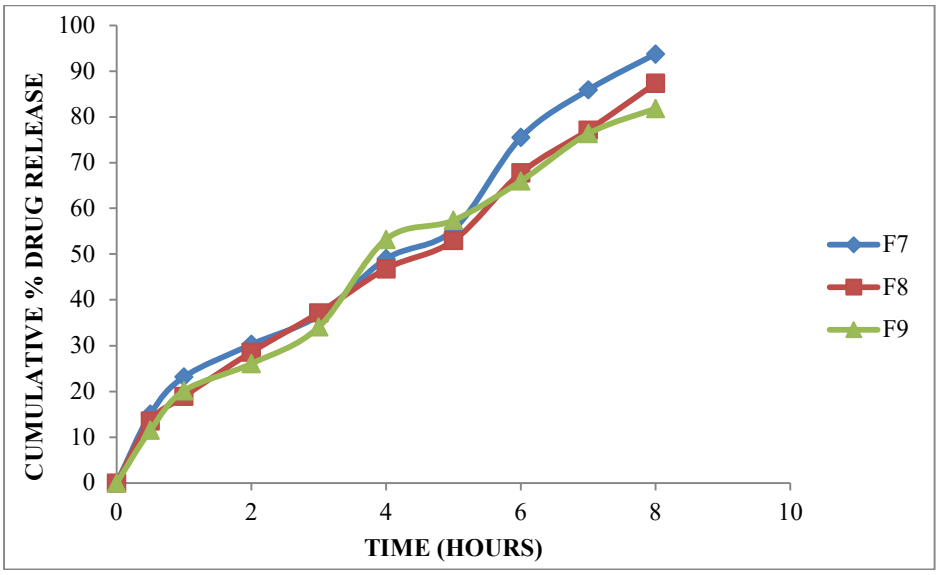

Fig 5: *In vitro* dissolution data for formulations F7- F9 by using Karaya gum polymer

From the above graphs it was evident that Cashew nut tree gum in the concentration of 50mg of polymer of the total tablet weight (F2) drug with other Two Formulations F1, F3. Where as in F2 formulation the quantity of polymer was less hence it showed more drug retardation with more drug release that is 91.13 % in 8 hrs. From the above graphs it was evident that Xanthan gum in the Polymer concentration of 20mg (F4) is showing better result 99.59% drug release when compared with other two formulations F5, F6, as the concentration of polymer increases the retarding of drug release decreased. From the above graphs it was evident that Karayagum in the Polymer concentration 20mg formulation (F7), is showing better result 93.73% drug release when compared with other two formulations. Where as in F8, F9 formulations the concentration become high and the drug release was less

Release kinetics

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Diacerein release from buccal tablets. The data was fitted into various kinetic models such as zero, first order kinetics, higuchi and korsmeyer peppas mechanisms and the results were shown in below table.

Table 7: Release kinetics and correlation coefficients (R^2)

Cumulative (%) Release Q	Time (T)	Root (T)	Log(%) Release	Log (T)	Log (%) Remain	Release Rate (Cumulative % Release / T)	1/Cum% Release	Peppas Log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
26.12	0.5	0.707	1.417	-0.301	1.869	52.240	0.0383	-0.583	73.88	4.642	4.196	0.446
32.83	1	1.000	1.516	0.000	1.827	32.830	0.0305	-0.484	67.17	4.642	4.065	0.577
41.51	2	1.414	1.618	0.301	1.767	20.755	0.0241	-0.382	58.49	4.642	3.882	0.760
49.15	3	1.732	1.692	0.477	1.706	16.383	0.0203	-0.308	50.85	4.642	3.705	0.937
56.99	4	2.000	1.756	0.602	1.634	14.248	0.0175	-0.244	43.01	4.642	3.504	1.138
67.31	5	2.236	1.828	0.699	1.514	13.462	0.0149	-0.172	32.69	4.642	3.197	1.444
74.65	6	2.449	1.873	0.778	1.404	12.442	0.0134	-0.127	25.35	4.642	2.938	1.704
82.09	7	2.646	1.914	0.845	1.253	11.727	0.0122	-0.086	17.91	4.642	2.616	2.025
99.59	8	2.828	1.998	0.903	-0.387	12.449	0.0100	-0.002	0.41	4.642	0.743	3.899

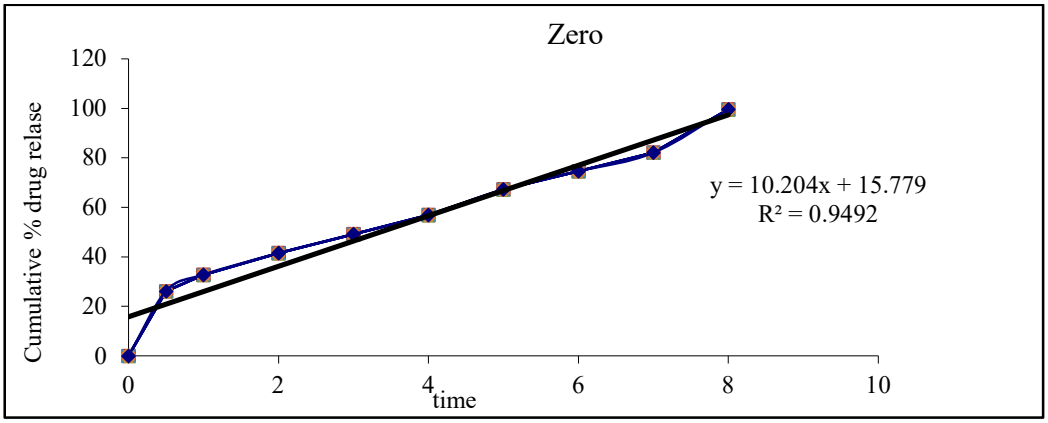

Fig 6: Zero order plot of optimized formulation

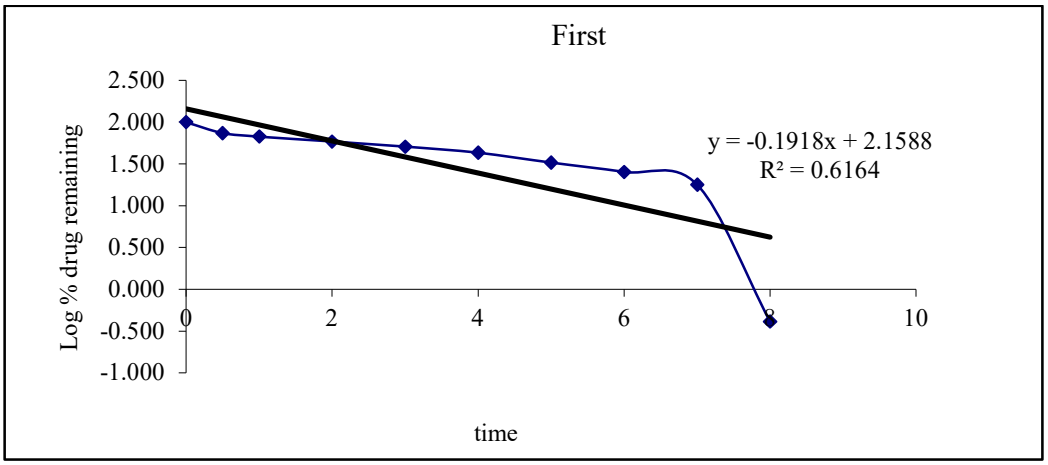

Fig 7: First order plot of optimized formulation

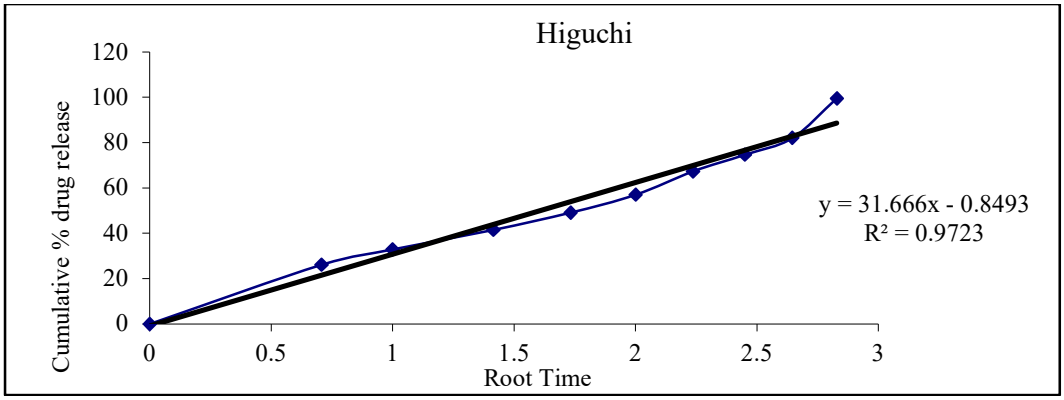

Fig 8: Higuchi plot of optimized formulation

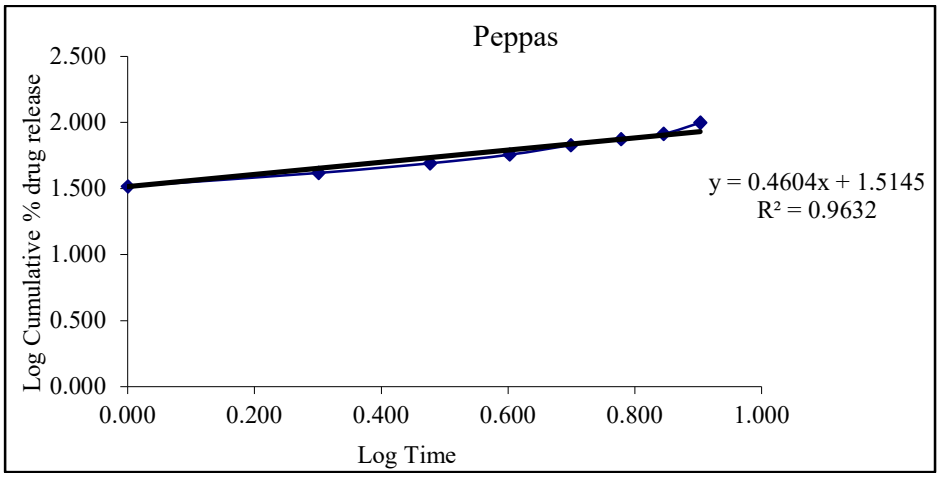

Fig 9: Koresmeyer-peppas plot of optimized formulation.

This formulation was following Higuchi release mechanism with regression value of 0.972.

Drug – excipient compatibility studies by physical observation

Diacerein was mixed with various proportions of excipients showed no color change at the end of two months, proving no drug-excipient interactions.

FTIR

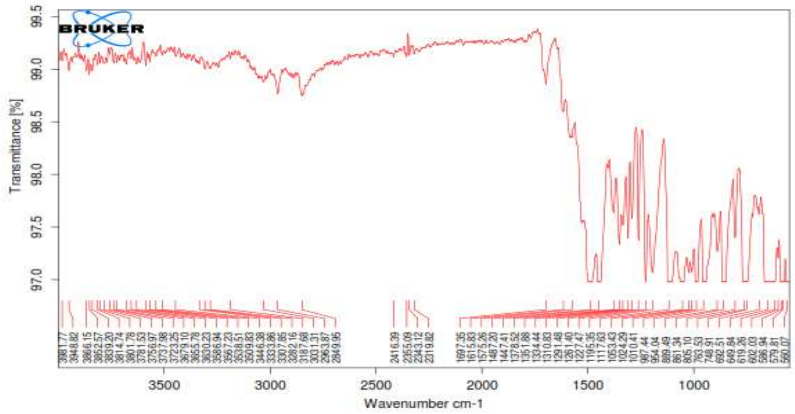

Fig 10: FTIR Peak of pure drug Diacerein

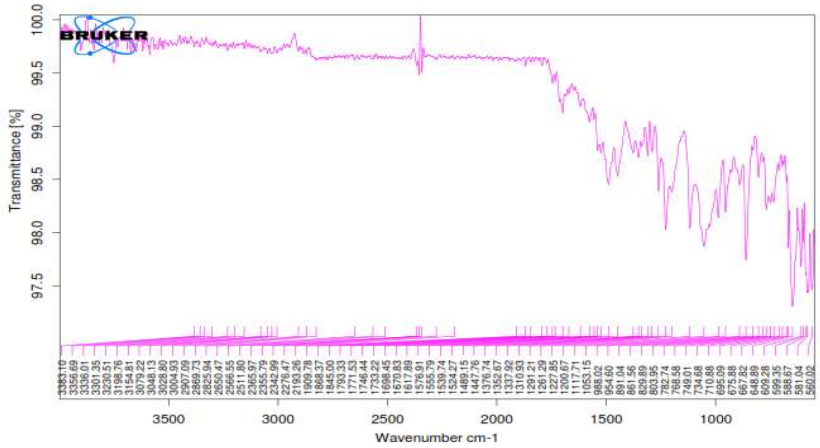

Fig 11: FTIR Peak of Optimised formulation

CONCLUSION

The present research was carried out to develop mucoadhesive bilayer buccal tablets of Diacerein using various polymers. The preparation process was simple, reliable and inexpensive. All the prepared tablet formulations were found to be good without capping and chipping. The mucoadhesive buccal tablets of Diacerein could be prepared using Cashew nut tree gum, Xanthan gum and Karaya gum polymers by using direct compression method. The prepared mucoadhesive buccal tablets subjected to infrared spectrum study suggested that there was no drug -polymer interaction. All the prepared tablets were in acceptable range of weight variation, hardness, thickness, friability and drug content as per pharmacopeial specification. The surface pH of prepared buccal tablets was in the range of salivary pH, suggested that prepared tablets could be used without risk of mucosal irritation. The *in-vitro* release of Diacerein was extended for 8 h. Formulations F4 batch shows good *in vitro* drug release 99.59%. From the results of present investigation it can be concluded that Diacerein can certainly be administered through the oral mucosa and Xanthan gum is suitable for development of buccoadhesive system.

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