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FORMULATION AND *INVITRO* EVALUATION OF BUCCAL PATCHES OF CLONIDINE USING BIODEGRADABLE NATURAL POLYMERS

Banda Raju[1], Padmini Iriventi[*] , Koteswari Poluri

[1]Department of Pharmaceutics, Smt. Sarojini Ramulamma College Of Pharmacy, Palamuru University, Seshadrinagar, Mahabubnagar, Telangana-509001

Abstract:

Mucoadhesive buccal patches of Clonidine were prepared using different polymers like HPMCK4M, Xanthan Gum and Guar gum in various proportion and combinations by solvent casting method.The patches were evaluated for their physical characteristics like thickness, folding endurance, water uptake, bioadhesive strength, drug content uniformity, surface pH, Mechanical strength, Scanning electron microscopy (SEM), In-vitro release study, Invitro residence time study and Kinetic study.

The results obtained showed no physical-chemical incompatibility between the drug and the polymers. F6 formulation has been selected as the best formulation among all the other formulations. The in-vitro drug diffusion studies from the formulation were found to be sustained release. All the evaluation parameters obtained from the best formulation were found to be satisfactory. The data obtained from the in-vitro release studies were fitted to various kinetic models like zero order, first order, Higuchi model and peppas model. From the kinetic data it was found that drug release follows zero order release kinetics model release by diffusion technique from the polymer.

Keywords: *Clonidine, HPMCK4M, Xanthan Gum, Guar gum and Mucoadhesive buccal patch.*

Corresponding author:

Dr. Padmini Iriventi *

Department of Pharmaceutics,
Smt. Sarojini Ramulamma College Of Pharmacy ,
Seshadrinagar, Mahabubnagar,
Telangana 509001.
Email Id- Iriventi-p.iriventi12@gmail.com

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INTRODUCTION:

Oral route has been the commonly adopted and most convenient route for drug delivery. Oral route of administration has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes, ease of administration as well as traditional belief that by oral administration the drug is well absorbed as the food stuffs that are ingested daily. Pharmaceutical products designed for oral delivery are mostly the immediate release types which are designed for immediate release of drug for rapid absorption. The term drug delivery covers a very broad range of techniques used to get therapeutic agents in to human body.[1-2] The limitations of the most obvious and trusted drug delivery techniques those of the ingested tablet and of the intravenous/ intramuscular/ subcutaneous injections have been recognized for some time. The former delivers drug in to the blood only through the hepatic system and hence the amount in the blood stream may be much lower than the amount formulated into the tablet. Further more liver damage is the unfortunate side effect of many soluble tableted drug.[3]

To overcome some of these limitations, other modes of drug delivery in to the body were investigated. Those are

1. Trans Dermal Drug Delivery System (through the intact skin)
2. Trans Mucosal Drug Delivery System (through the intact mucosa of the mouth, intestine, rectum, vagina or nose)
3. Trans Ocular Drug Delivery System (through the eye)
4. Trans Alveolar Drug Delivery System (inhalation through the lung tissue).
5. Implantable Drug Delivery System (through the subcutaneous and deeper implants, deliver into surrounding tissue)
6. Injectables (I.M or Subcutaneous) Of the above modes, Transdermal, Transmucosal, Injectables and Subcutaneous Implants have been found varying degree of commercial acceptance.[4]

TRANSMUCOSAL DRUG DELIVEY SYSTEM [5]

Delivery of drugs through the absorptive mucosa in various easily accessible body cavities, like the Buccal, ocular, nasal, rectal, and vaginal mucosae, has the advantage of bypassing the hepatic-gastrointestinal first pass elimination associated with oral administration. Further more, because of the dual biophysical and biochemical nature of these mucosal membranes, drugs with hydrophilic and/or hydrophobic characteristics can be readily absorbed.

Different types of transmucosal drug delivery systems are

- Buccal Drug Delivery System.
- Ocular Drug Delivery System.
- Vaginal Drug Delivery System.
- Rectal Drug Delivery System.
- Nasal Drug Delivery System.
- Gastro Intestinal Drug Delivery System.
-

BUCCAL DRUG DELIVERY SYSTEM [6]

The mucosa of the mouth is very different from the rest of the gastrointestinal tract and morphologically is more similar to skin. Although the permeability of skin is widely regarded as poor, it is not generally appreciated that the oral mucosa lacks the good permeability demonstrated by the intestine. These differences within the gastrointestinal tract can largely be attributed to the organization of the epithelia, which serve very different functions. A simple, single-layered epithelium lines the stomach, small intestine, and colon, which provides for a Minimal transport distance for absorbents. In contrast, a stratified or multilayered epithelium covers the oral cavity and esophagus and, in common with skin, is composed of layers with varying states of differentiation or maturation evident on progression from the basal cell layer to the surface. Drugs have been applied to the oral mucosa for topical applications for many years. However, recently there has been interest in exploiting the oral cavity as a portal for delivering drugs to the systemic circulation. Notwithstanding the relatively poor permeability characteristics of the epithelium, a number of advantages are offered by this route of administration. Foremost among these are the avoidance of first-pass metabolism, ease of access to the delivery site, and the opportunity of sustained drug delivery predominantly via the buccal tissues. Delivery can also be terminated relatively easily if required. The robustness of the epithelium necessary to withstand mastication also serves the drug delivery process well as fast cellular recovery follows local stress and damage. Indeed the two most challenging issues to be addressed in the oral mucosal delivery of drugs are undoubtedly permeability enhancement and dosage form retention at the site of application. The continuous secretion of saliva and its subsequent swallowing can lead to substantial drug depletion from the dosage form and hence low bioavailability.[7]

Advantages [8]

- ✓ The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein and braciocephalic vein into the systemic

circulation. Following buccal administration, the drug gains direct entry into the systemic circulation thereby bypassing the first pass effect.

- ✓ It is richly vascularized and more accessible for administration and removal of dosage forms.
- ✓ No hepatic first-pass effect.
- ✓ No pre-systemic metabolism in the gastrointestinal tract.
- ✓ Ease of administration
- ✓ High patient accessibility.
- ✓ An expanse of smooth muscle and relatively immobile mucosa, suitable for administration of retentive dosage forms.
- ✓ Bypass exposure of the drugs to the gastrointestinal fluids.
- ✓ More rapid cellular recovery and achievement of a localized site on smooth surface of buccal mucosa.
- ✓ Low enzyme activity, suitability for drugs/ excipients that mildly and reversibly damages or irritates the mucosa.
- ✓ The oral mucosa is routinely exposed to a multitude of different foreign compounds. So it has evolved a robust membrane that is less prone to irreversible damage by drug, dosage form or additives used therein.
- ✓ Non-invasive method of drug administration.
- ✓ Facility to include permeation enhancer or enzyme inhibitor or pH modifier in the formulation.

Disadvantages [9-10]

- ✓ Low permeability of buccal membrane specifically when compared to the sublingual membrane.
- ✓ Small surface area (170 cm2).
- ✓ Saliva (0.5–2 L/day) is continuously secreted into the oral cavity diluting drugs at the site of absorption resulting in low drug concentrations at the surface of the absorbing membrane.
- ✓ Inconvenience of patient when eating or drinking.

Limitations in buccal absorption [11-14]

- ➢ The area of absorptive membrane is relatively smaller.
- ➢ Drugs, which are unstable at buccal pH cannot be administered by this route.
- ➢ Only drugs with a small dose requirement can be administered.
- ➢ Only those drugs, which are absorbed by passive diffusion, can be administered by this route. Eating and drinking may become restricted.
- ➢ There is an ever present possibility of the patient swallowing the tablet.
- ➢ Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by this swelling and hydration of the buccoadhesive polymers.

MATERIALS

Clonidine from Provided by SURA LABS, Dilsukhnagar, Hyderabad.Karaya Gum from Merck Specialities Pvt Ltd, Xanthan Gum from Merck Specialities Pvt Ltd, Guar gum from Merck Specialities Pvt Ltd, Methanol from Merck Specialities Pvt Ltd, Propylene glycol from Merck Specialities Pvt Ltd, Dimethyl sulfoxide from Merck Specialities Pvt Ltd

METHODOLOGY

Preparation of reagents:

Preparation of 0.2M NaOH Solution

Dissolved 4g of Sodium hydroxide pellets in to 1000mL of Purified water and mixed.

Preparation of pH 6.8 Phosphate buffer

Dissolved 6.805 g of Potassium dihydrogen phosphate in to 800mL of purified water and mixed added 112mL of 0.2M NaOH solution and mixed. Diluted to volume 1000mL with purified water and mixed. Than adjusted the pH of this solution to 6.8 with 0.2M NaOH solution.

PREFORMULATION STUDIES:

Preformulation testing first step in development of dosage forms of a drug. It is defined as an investigation of physical chemical properties of drug substance alone and when combined with excipients. The overall concept of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms.

The goals of the Preformulation studies are:

• To establish the necessary physicochemical properties of a new drug substance.

• To determine its kinetic release profile.

• To establish its compatibility with different excipients.

Hence, Preformulation studies on the obtained sample of drug include physical tests and compatibility studies.

A. Identification tests:

- ➢ **IR spectroscopy:**
  The formulations were subjected to FTIR studies to find out the possible interaction between the drug and the excipients during the time of preparation. FT IR analysis of the pure drug and optimized formulation were carried out using an FT IR spectrophotometer (Bruker FT-IR - GERMANY).
- ➢ **Solubility analysis**: Solubility analysis was done to select a suitable solvent system to dissolve the

drug and to test its solubility in the dissolution medium, which was to be used.

- **Melting point determination**: Melting point of drug sample was determined by capillary tube method.

B. Calibration curve.

A. A.UV scan:

A 100mg of Clonidine was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH-7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). Take 10 ml solution from stock II and volume make up to 100 ml with buffer to get 10 µg/ml. 10 µg/ml solution was scanned from 200-400nm.

B. Construction of calibration curve:

A 100mg of Clonidine was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH-7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). It was further diluted with phosphate buffer pH – 7.4 to get solutions in concentration range of 5,10,15,20 and 25 µg /ml. The absorbance of these solutions was determined spectrophotometrically at 270 nm.

PREPARATION OF BUCCAL PATCHES:

Patches containing Clonidine and Karaya Gum, Xanthan Gum and Guar gum different proportions was prepared by the **solvent casting method**. The drug was dissolved in 10ml of methanol and the polymers were dissolved in separate container with 20ml of distilled water under continuous stirring for 4 hours. After stirring, mix the drug and polymer solution. Propylene glycol was added into the solution as a plasticizer under constant stirring. The viscous solution was left over night to ensure a clear, bubble free solution. The solution was poured into a glass petridish and allowed to dry at 40°c temperature till a flexible patch was formed. Dried patch was removed carefully, checked any imperfections or air bubbles and cut into pieces of $1mm^2$ area. The patches were packed in aluminum foil and stored in desiccators to maintain the integrity and elasticity of the patches. Table no. shows the composition of different buccal patches.

Table no1: composition of buccal patches of Clonidine.

INGREDIENTS	FORMULATIONS								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clonidine (mg)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Karaya Gum	10	20	30	-	-	-	-	-	-
Xanthan Gum	-	-	-	10	20	30	-	-	-
Guar gum	-	-	-	-	-	-	10	20	30
Methanol (mL)	10	10	10	10	10	10	10	10	10
Propylene glycol (mL)	5	5	5	5	5	5	5	5	5
Dimethyl sulfoxide (mL)	5	5	5	5	5	5	5	5	5

RESULTS AND DISCUSSION:

Initially the drug was tested by UV to know their significant absorption maximum which can be used for the diffusion study of the drug.

Analysis of drug:

A. UV scan:

The lambda max of Clonidine was found to be 270 nm.

B. construction of calibration curve:

Table 2: Standard graph of Clonidine

Concentration (µg/ml)	Absorbance (at 270nm)
0	0
5	0.128
10	0.234
15	0.362
20	0.475
25	0.592

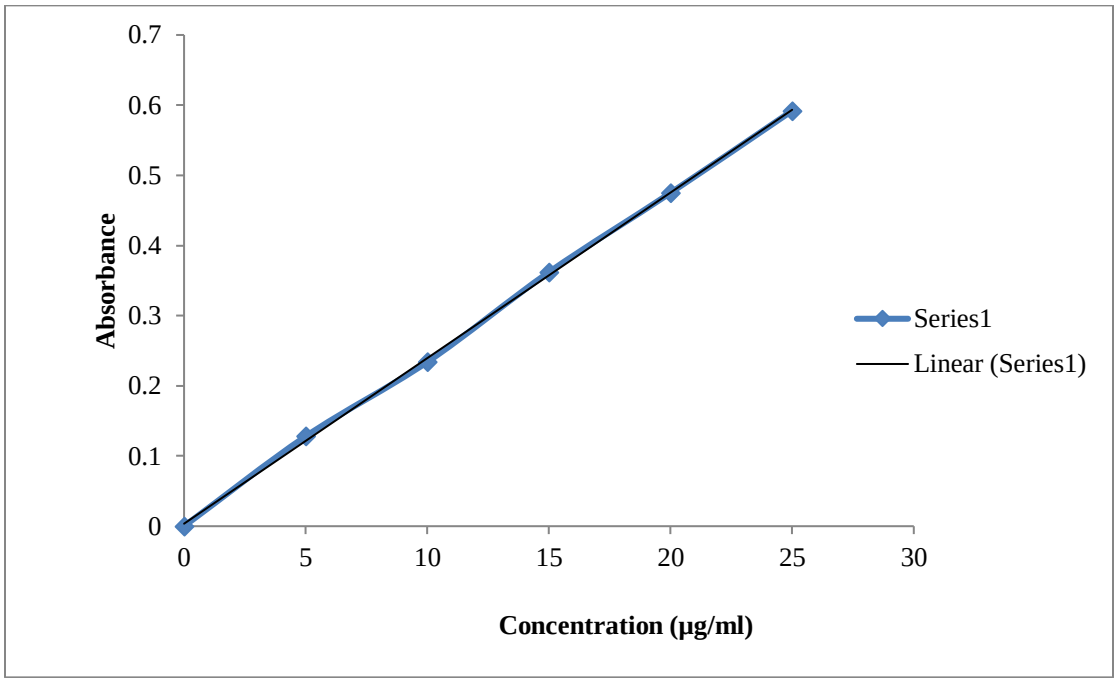

Figure 1: Standard calibration curve of Clonidine

Preformulation parameters of powder blend

EVALUATION PARAMETERS:

Table 3: Physical parameters

Formulation code	Thickness (mm) ±S.D (n=3)	Folding endurance ±S.D (n=3)	Mechanical strength ±S.D (n=3) (kg/mm^2)	Wateruptake ±S.D (n=3)
F1	0.23± 0.001	302± 3.14	5.28± 0.07	2.26± 0.35
F2	0.24± 0.008	304± 2.64	6.04± 0.05	2.14± 0.11
F3	0.23± 0.012	312± 1.30	7.94± 0.09	2.10± 0.10
F4	0.22± 0.005	313± 0.11	5.64± 0.12	2.28± 0.24
F5	0.23± 0.001	316± 2.67	6.86± 0.13	1.99± 0.095
F6	**0.26± 0.005**	**320± 0.34**	**12.84± 0.07**	**2.93± 0.15**
F7	0.23± 0.011	312± 1.12	7.23± 0.32	2.01± 0.35
F8	0.24± 0.002	315± 1.64	9.45± 0.05	2.10± 0.24
F9	0.25± 0.018	316± 3.39	10.14± 0.04	2.41± 0.10

Performance parameters:

Evaluation of Performance parameters of different mucoadhesive buccal patches of Clonidine

Formulation code	Table 4: Performance parameters (Bioadhesive)		
	Bioadhesive strength(gms) ±S.D (n=3)	Force of adhesion(N) ±S.D(n=3)	Bond strength ±S.D (n=3) (kg/mm2)
F1	141.2± 2.9	1.10± 0.01	424.6± 5.34
F2	147.0± 2.2	1.24± 0.05	434.1± 3.65
F3	152.1± 0.5	1.32± 0.02	487.9± 5.23
F4	167.0± 0.6	1.52± 0.01	525.3± 1.86
F5	178.2± 1.2	1.65± 0.02	535.8± 4.33
F6	183.1± 3.0	1.72± 0.01	542.2± 6.98
F7	125.0± 2.2	1.22± 0.06	416.7± 5.32
F8	138.4± 1.1	1.37± 0.04	435.5± 6.90
F9	149.2± 1.4	1.46± 0.02	454.4± 3.23

Table 5: Evaluation of Performance parameters of different mucoadhesive buccal patches of Clonidine

Formulation code	Performance parameters(Bio adhesive)		
	Drug content %	Surface P^H	*Invitro* residence time (min) (kg/mm^2)
F1	75± 0.01	6.2± 0.5	310±10
F2	81± 0.26	6.1± 0.3	321±5
F3	76± 0.02	6.3± 0.5	330± 15
F4	82± 0.05	6.5± 0.4	350± 5
F5	86± 0.20	6.4± 0.5	380±10
F6	95± 0.06	6.2± 0.5	411±10
F7	69± 0.14	6.5± 0.3	300± 10
F8	81± 0.09	6.4± 0.4	311± 15
F9	88± 0.06	6.3± 0.3	380± 5

***In Vitro* Drug Release Studies**

Table6: *In vitro* dissolution data for formulation F1-F9

TIME (H)	% of Drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	21.05	16.92	14.02	27.92	18.92	15.05	18.47	14.15	10.28
2	30.49	24.63	20.63	41.05	25.26	22.82	28.03	23.06	19.46
3	42.36	37.52	27.82	52.16	36.05	28.51	36.43	31.52	26.52
4	53.92	48.14	39.61	70.34	44.10	36.39	44.56	40.37	30.47
5	67.68	57.66	47.56	75.27	59.98	41.71	53.27	48.46	36.61
6	78.92	64.04	51.92	83.98	67.92	48.09	60.84	56.08	42.07
7	89.53	73.56	57.67	87.09	72.63	54.25	68.34	63.31	50.36
8	99.14	84.12	62.02	94.39	78.09	68.15	79.25	71.49	56.13
9		95.28	68.57	97.47	84.27	79.90	90.38	80.30	61.23
10		97.64	77.92		87.99	88.56	98.04	87.21	68.31

11			84.09		95.05	94.05		92.55	75.43
12			95.67			99.38		97.12	81.37

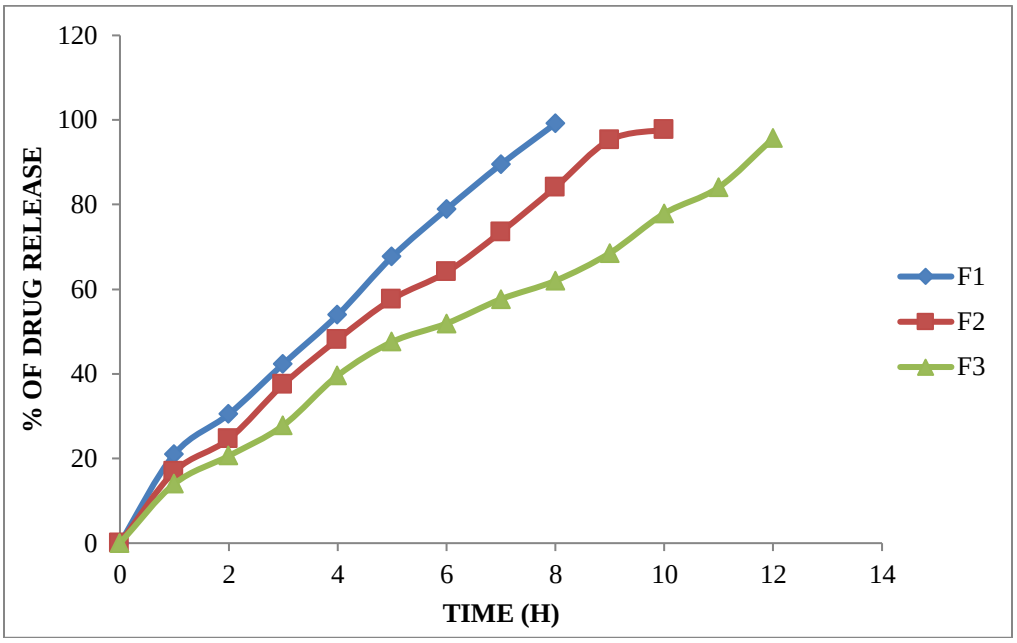

Fig 2: *In vitro* dissolution data for formulation F1-F3

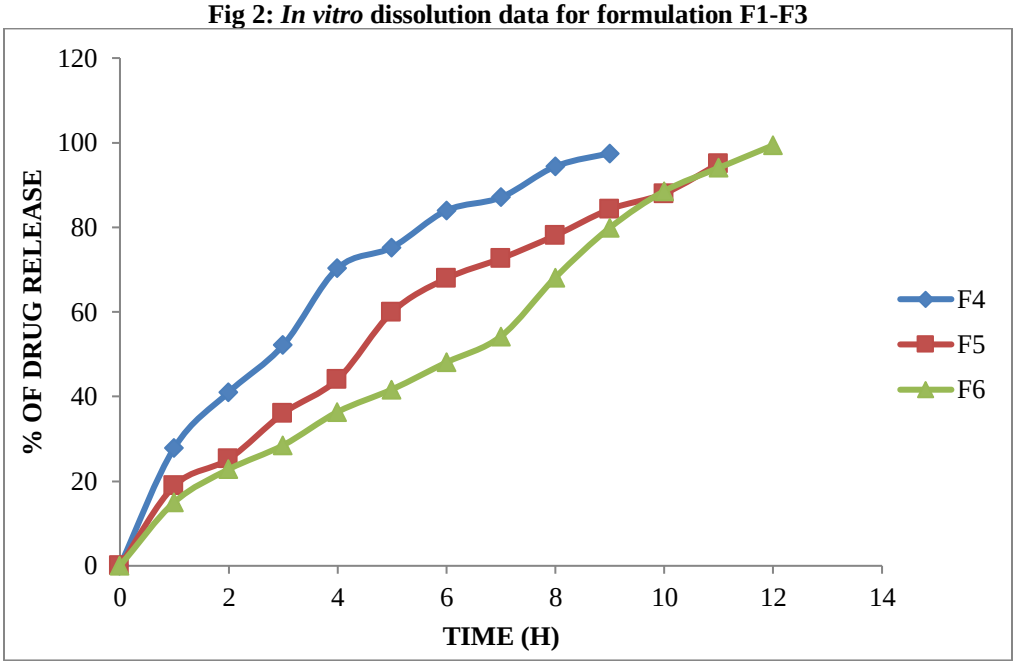

Fig3: *In vitro* dissolution data for formulations F4-F6

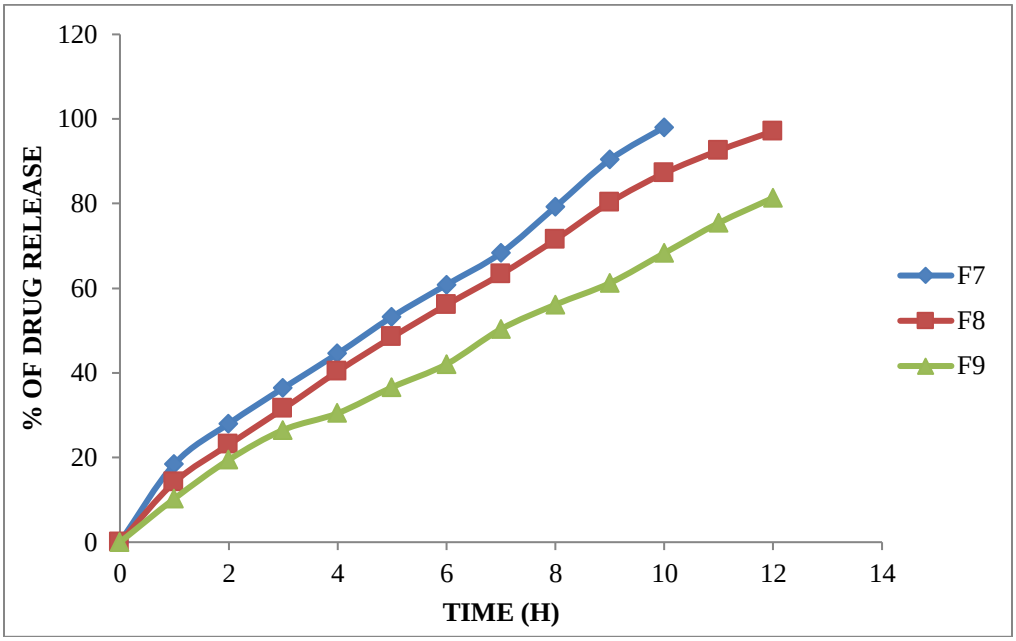

Fig: 4 *In vitro* dissolution data for formulations F7-F9

Table 7:Kinetic models for Clonidine

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
15.05	1	1.000	1.178	0.000	1.929	15.050	0.0664	-0.822	84.95	4.642	4.396	0.246
22.82	2	1.414	1.358	0.301	1.888	11.410	0.0438	-0.642	77.18	4.642	4.258	0.384
28.51	3	1.732	1.455	0.477	1.854	9.503	0.0351	-0.545	71.49	4.642	4.150	0.491
36.39	4	2.000	1.561	0.602	1.804	9.098	0.0275	-0.439	63.61	4.642	3.992	0.650
41.71	5	2.236	1.620	0.699	1.766	8.342	0.0240	-0.380	58.29	4.642	3.877	0.764
48.09	6	2.449	1.682	0.778	1.715	8.015	0.0208	-0.318	51.91	4.642	3.730	0.911
54.25	7	2.646	1.734	0.845	1.660	7.750	0.0184	-0.266	45.75	4.642	3.577	1.065
68.15	8	2.828	1.833	0.903	1.503	8.519	0.0147	-0.167	31.85	4.642	3.170	1.472
79.9	9	3.000	1.903	0.954	1.303	8.878	0.0125	-0.097	20.1	4.642	2.719	1.923
88.56	10	3.162	1.947	1.000	1.058	8.856	0.0113	-0.053	11.44	4.642	2.253	2.388
94.05	11	3.317	1.973	1.041	0.775	8.550	0.0106	-0.027	5.95	4.642	1.812	2.830
99.38	12	3.464	1.997	1.079	-0.208	8.282	0.0101	-0.003	0.62	4.642	0.853	3.789

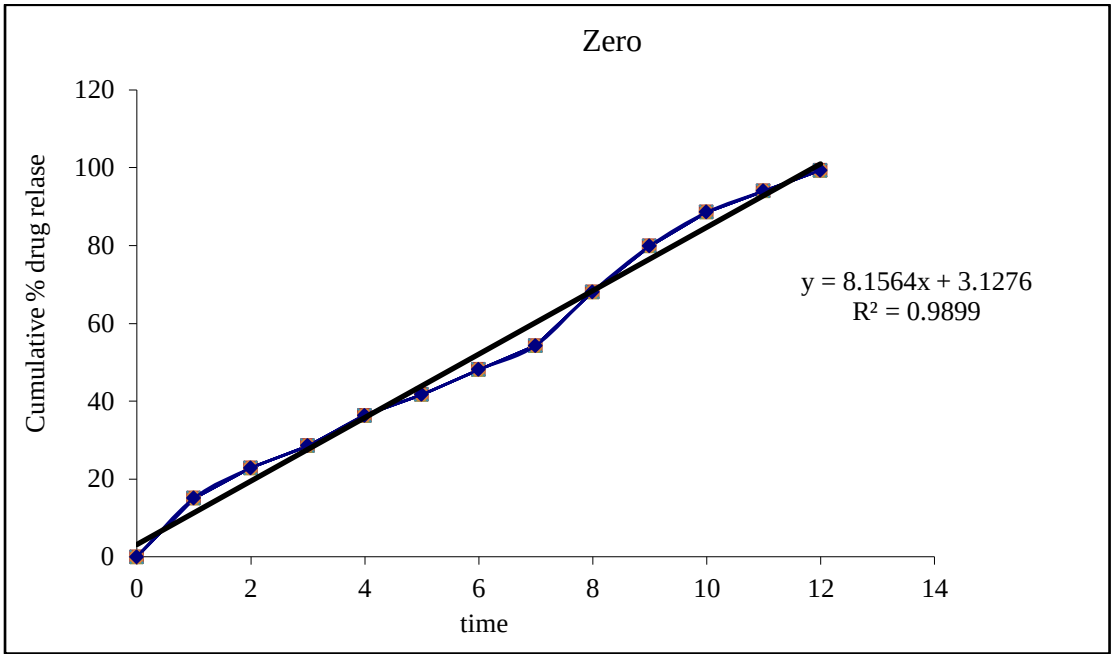

Figure: 5 Graph of Zero order kinetics

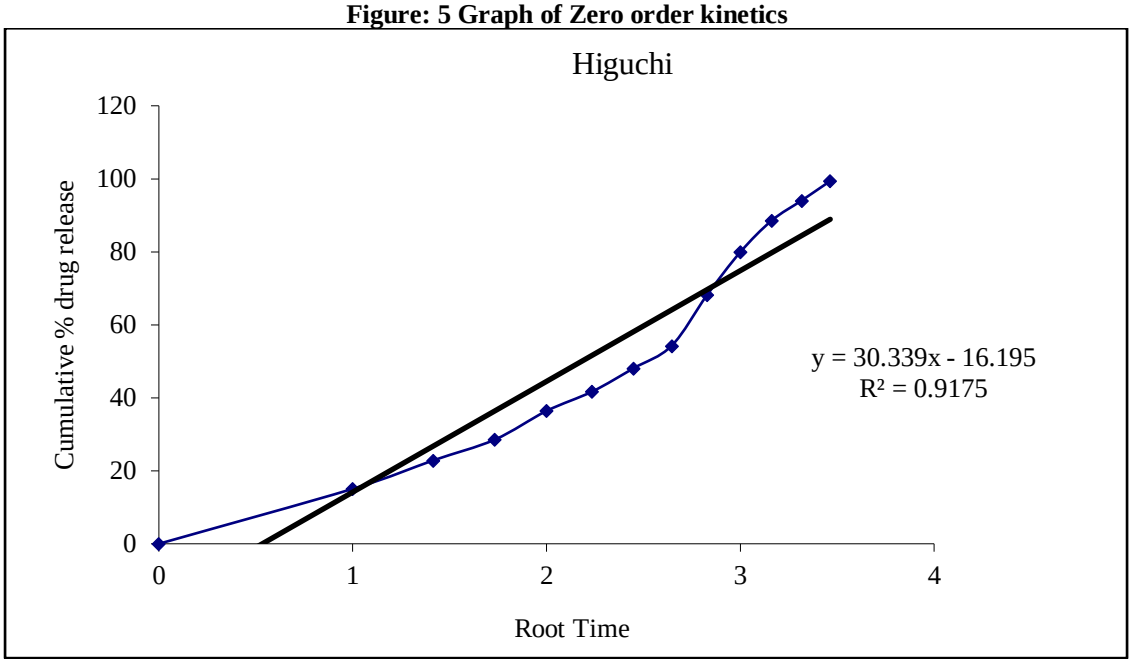

Figure: 6 Graph of Higuchi release kinetics

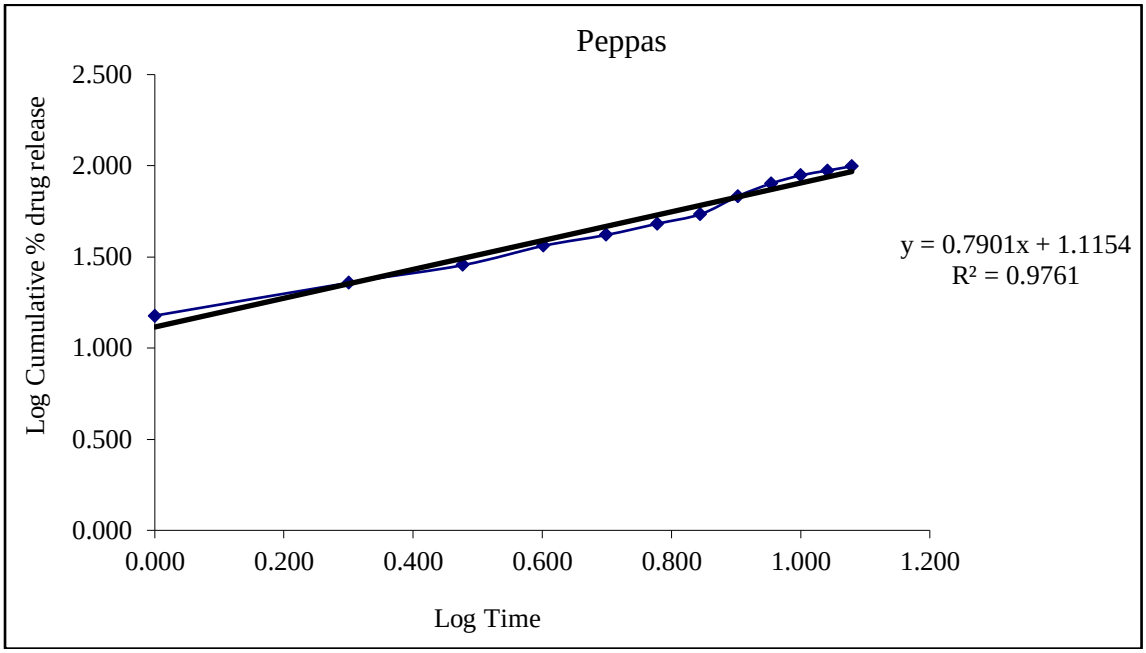

Figure : 7 Graph of peppas release kinetics

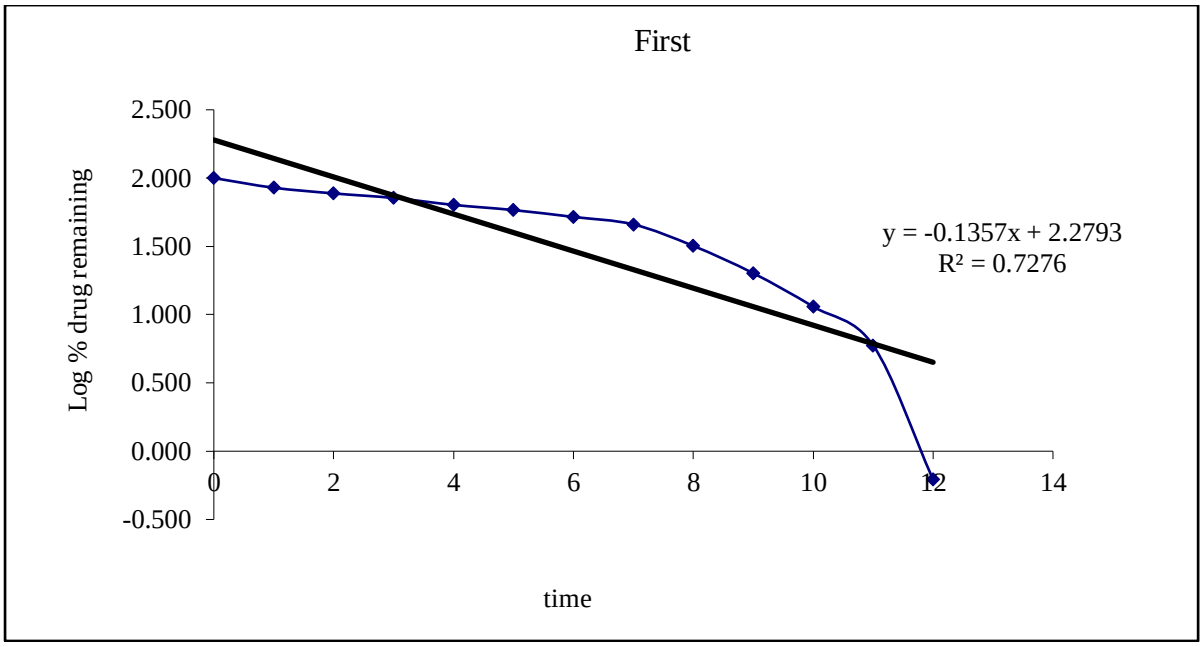

Figure: 8 Graph of First order release kinetics

Drug – Excipient compatibility studies
Fourier Transform-Infrared Spectroscopy:

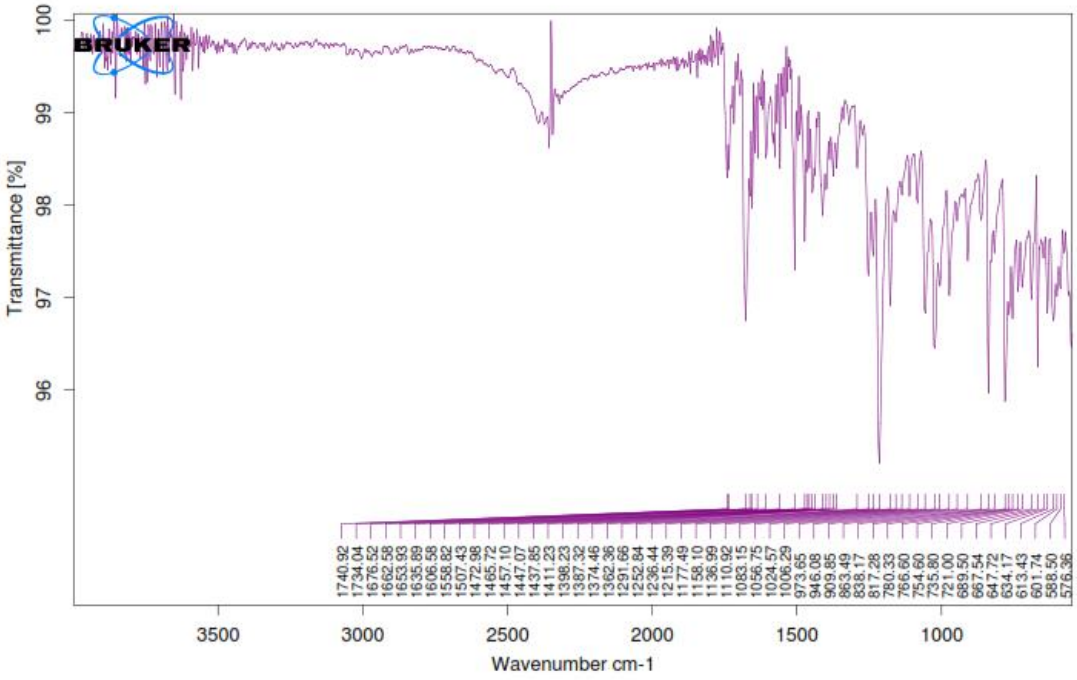

Figure 9: FTIR Spectrum of pure drug

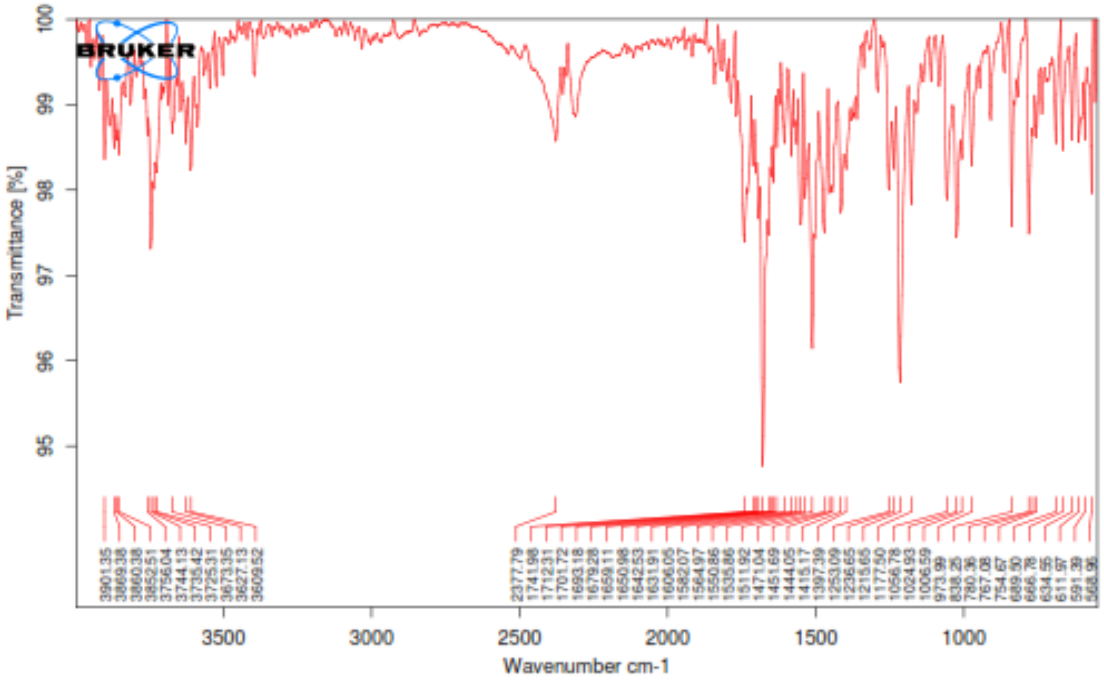

Fig 10 FTIR Spectrum of optimised formulation

SCANNING ELECTRON MICROSCOPY (SEM)

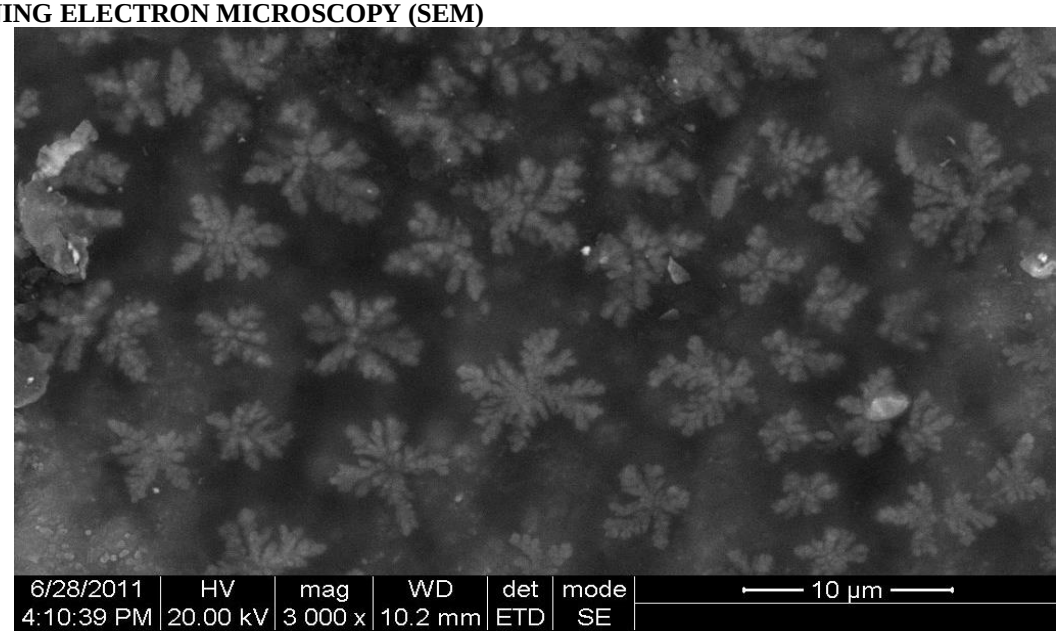

Fig 11: SEM optimized formulation

CONCLUSION:

In the present study, an attempt has been done to develop a novel mucoadhesive drug delivery system in the form of the buccal patches for the release of Clonidine in a bidirectional manner, to maintain constant therapeutic levels of the drug for long time.

Buccal formulations of Clonidine in the form of mucoadhesive patches were developed to a satisfactory level in term of drug release, bioadhesive strength, content uniformity, percentage water uptake, surface PH, thickness and mechanical strength.

Although all buccal patches exhibited satisfactory results, best results were obtained with optimized formulation F6 containing Karaya Gum, Xanthan Gum and Guar gum in 1:1, 1:2 and 1:3 ratios. *Invitro* dissolution studies of the optimized formulation showed that the percentage cumulative drug release about the release of Clonidine from the patches in the present work appeared to occur due to diffusion and erosion mechanism. The release pattern was found to be non-Fickian.

The above study concluded that the possibility of the making of mucoadhesive drug delivery system for Clonidine which will be more efficacious and acceptable than conventional drug delivery of Clonidine and also having satisfactory controlled release profile which may provide an increased therapeutic efficacy.

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