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PREPARATION AND CHARACTERIZATION OF NICARIDIPINE BUCCAL MUCOADHESIVE TABLETS

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Abstract:

Hypertension is a medical condition where the blood pressure is chronically elevated is one of the commonly found diseases throughout the world. Buccal route of drug delivery have significant attention to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Such routes haveexpanded important notice due to their presystemic metabolism or instability in the acidic environment associated with the oral administration. Along with the variety of buccal layer mucosae of the oral cavity has convenient and easily effective site for the delivery of therapeutic agents. Nicardipine belongs to the drug class known as calcium channel blockers. It relaxes and dilates the blood vessels thereby allowing blood to flow more freely throughout the body. The buccal route has long been advocated as possible route of delivery of drugs having poor oral bioavailability because of high first pass metabolism or degradation in the gastrointestinal tract. The buccal mucosa reaching the heart directly via the internal jugular vein as this route is well vascularised with venous blood draining. Although, the drug fluxes via this route are less than that obtained with sublingual mucosa due to permeability barrier, the relative immobility of buccal musculature, as compared to that of sublingual route, makes this site ideally suited for delivery of drugs. The aim of the present research work is to develop buccal tablets of Nicardipine hydrochloride to reduce dosage frequency; obtain optimized and controlled therapy, better patient compliance.

Keywords: *Nicardipine; Buccal tablet; Mucoadhesive; Drug Release; HPMC; Carbopol 934, SCMC*

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INTRODUCTION:

The buccal region is an attractive site for target-specific delivery of the active(s) on the mucosa for local and/or systemic effect by absorbing through the mucosal membrane barrier covering the oral cavity [1]. Buccal administration exhibits better patient adherence in contrast to other non-oral drug-delivery routes. This route is excellent for potent drugs especially targeted for acute conditions with rapid clinical response due to direct access to the jugular vein and for extended therapeutic effect [2]. Hydrophilic, acid and enzyme susceptible proteins and peptides that cannot be delivered via oral route because of poor absorption can be alternatively administered through the buccal route. Traditionally buccal dosage forms frequently fail to maintain desired drug concentration level either on the targeted mucosal site and/or in the systemic circulation [3]. The key formulation challenges are salivary renovation cycle and mechanical stress due to masticatory effect during eating and drinking. This can shift the drug aside from the site of absorption hence decreasing the contact time and change in distribution kinetics of the drug. To sustain the therapeutic effect, it is essential to extend the intimate association between active(s) and the membrane barrier of buccal tissue. To address these issues, buccal delivery system should be designed in such a manner to remain at the absorption site for desired duration of time, enhance the drug permeation across the mucosa to systemic circulation or into submucosal epithelial layers unaffected by the impact of salivary flow, pH, electrolytes, and mucosal enzymes [4]. The components in the buccal dosage forms are mainly classified as mucoadhesive polymers, penetration enhancers and enzyme inhibitors**.** Polymer hydration and swelling owing to diffusion of water and ensuing mucin dehydration are the main driving factor for mucoadhesion. Swelling should promote flexibility of the polymer chain and interpenetration between mucin chains thus reinforcing the mucoadhesive strength. The extent of spreadability and ability to form different types of intermolecular bonds at various hydration stages determines the characteristic of polymer to be used for buccal formulation. Various mucoadhesive polymers have been investigated for prolonging the retention time of dosage forms or actives at targeted sites of oral mucosa [5]. The most frequently used polymers in buccal dosage forms include poly(acrylic acid) and its copolymers such as acrylic acid polyethylene glycol (PEG) monomethyl ether copolymer, polyvinyl alcohol (PVA), chitosan, sodium alginate, gelatin, carrageenan, hyaluronic acid, cellulose derivatives such as sodium carboxymethyl cellulose (NaCMC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), eudragit RS 100. Positively charged, biocompatible and biodegradable natural polymer, chitosan has been widely exploited as mucoadhesive polymer because of its electrostatic interaction with the negatively charged O-linked oligosaccharide chain of mucin [6]. Buccal tablets have been the most commonly investigated dosage forms for buccal drug delivery. Several bioadhesive buccal tablet formulations have been developed by direct compression method in recent years either for local or systemic drug delivery. They are designed to release the drug either unidirectionally by targeting buccal mucosa or multi- directionally into the saliva. Alternatively, the dosage form can contain an impermeable backing layer to ensure that drug is delivered unidirectionally [7]. Disadvantages of buccal tablets may be patient acceptability (mouth feel, taste and irritation) and the nonubiquitous distribution of drug within saliva for local therapy. It is important to point out the possible problems those children and the elderly may experience by the use of adhesive tablets such as possible discomfort provoked by the material applied to the mucosa and the possibility of the separation of dosage form the mucosa, swallowing, and then adherence to the wall of the esophagus [8]. A typical bioadhesive formulation of this type consists of a bioadhesive polymer (such as polyacrylic acids or a cellulose derivative), alone or in combination, incorporated into a matrix containing the active agent and excipients, and perhaps a second impermeable layer to allow unidirectional drug delivery. Nicardipine is a potent calcium channel blockader with marked vasodilator action. It has antihypertensive properties and is effective in the treatment of angina and coronary spasms without showing cardiodepressant effects. It has also been used in the treatment of asthma and enhances the action of specific antineoplastic agents.

MATERIAL AND METHODS:

Nicardipine was received as a gift sample from Intas Pharm. Pvt. Ltd., Indore, India. The UV Spectroscopy of drug sample was done by serial dilution which was scanned between the wavelengths of 400-200 nm using UV spectrophotometer (UV-1601, Shimadzu, Kyoto, Japan) to determine the wavelength of maximum absorption. The calibration Curve for drug in phosphate buffer pH 6.8 (Simulated Salivary Fluid) to stock arrangement adjustment bend norms (2, 4, 6, 8, & 10 µg/ml) were readied utilizing phosphate cushion pH 6.8. The absorbance of aliquates was estimated for all adjustment bend benchmarks at 307 nm &grap was plotted between fixations versus absorbance [9].

Preformulation study: A various parameter i.e. particle size, flow properties, solubility studies, melting point, partition coefficient and drug excipients incompatibility study.

Formulation of buccal mucoadhesive tablets: Mucoadhesive tablets were prepared by adopting a previously established method with slight modification. Direct compression technique was applied for the tablet compression, using varying proportions of different grades of polymer. All the powders in pure form were accurately weighed. Nicardipine (NIC) was then mixed with Carbopol 934. The remaining polymers Hydroxypropyl methylcellulose (HPMC) or Sodium carboxymethylcellulose (SCMC) were mixed with talc in a separate pouch. These two mixtures were then mixed for 5 min after passing through a #40 mesh sieve. Micro crystalline cellulose (MCC 200) was mixed in a separate pouch for 2 min. Then it was mixed with the previous mixture for 5 min. Finally, magnesium stearate was added and the resultant mixtures were mixed and the blend was then compressed into tablets having an average weight of 200 mg, using a ten-station tablet punch. Twelve batches were prepared and coded from NMT1 to NMT8 [10].

Evaluation of buccal mucoadhesive tablets of nicardipine: Physical parameters of buccal mucoadhesive nicardipine tablets were performed for isolation of quality of the preparation. The various parameters i.e. Appearance, thickness, weight variation, hardness, friability, drug content, mucoadhesive strength, swelling Index, in-vitro drug release study

Appearance: The prepared buccal mucoadhesive nicardipine tablets were white yellowish color, circular shape in nature.
Thickness: Randomly selected three tablets were determined with vernier calipers. Calculate the mean thickness of the tablets.

Weight variation: Randomly selected in each formulation of twenty tablets, weighed individual tablets separately. Calculate the average mass of the tablets.

Hardness: Hardness of tablet was measured by Monsanto tester and expressed in Kg/cm2. Randomly three tablets were selected in every formulation, measure the hardness by placing each tablet in obliquely among the two plungers by applying force till the tablet divide into 2 parts and reading was noted.

Friability: This test performed to assess the capacity of the tablet to with stand wear and tear in transportation, packing. Twenty tablets are weighed and put in the plastic chamber and pivot for 4 minutes. In this revolution the tablet falls in the distance of 6 inches. The tablets are removed from the chamber and weighed.

Drug content: Randomly selected 20 tablets in every formulation. Tablets taken into motor triturate until to get fine powder. 10 mg of nicardipine fine powder taken in 100ml volumetric flask & make up final volume with pH 6.8 phosphate buffer and subjected for filtration. Each sample measured for drug content at max 357 nm in UV-Visible spectrometer.

Disintegration test A 1000 mL beaker was filled with 900 mL of distilled water and was maintained at a temperature of 37 + 0.5 ºC. Six tablets were placed in each of the cylindrical tubes of the basket. To avoid floating of the tablets, discs were used. The time taken to break the tablets into small particles was recorded. The limit for buccal tablets is 4 hours.

Surface pH study: The surface pH must be closed to the salivary pH, so that it would not irritate the buccal mucosa. The salivary pH has the range of 6.5 to 7.5. The tablets were allowed to swell for 2 hours in 1 mL of distilled water. The surface pH of the tablet was then measured using a digital pH meter. The pH electrode was placed near the surface of the tablet and was allowed to equilibrate for 1 minute before reading the measurement.

Swelling Index: The swelling study was performed on petri dishes containing 1% agar gel. Four tablets were weighed and placed in a petri dish. The petri dishes contained 4 tablets, and each was placed in an incubator at 37 ºC + 1 ºC. After 1, 2, 3 upto 5 hours, excess water on the surface was carefully removed using the filter paper without pressing. The tablets were reweighed and the swelling index was calculated using the formula:

$$\text{Swelling Index} = \frac{Wi \times Wf * 100}{Wi}$$

Wi Where Wi is the initial weight and Wf is the final weight of the tablet. Appropriate swelling property of buccal formulations is needed for proper adhesion

In vitro* drug release studies:In vitro* drug release studies were carried out using USP II (rotating paddle) dissolution apparatus with minor modifications. The dissolution medium consisted of 200 ml of phosphate buffer pH 6.8 with 2.5% polysorbate 80. The release study was performed at 37°C ± 0.5°C, with a rotation speed of 25 rpm. The backing layer of the buccal tablet was attached to the glass disk with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Samples of 5 ml were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.2-µm Whatman filter paper and analyzed after appropriate dilution by UV spectrophotometer (Shimadzu, 1800) at 307 nm. The drug was quantified by UV spectrophotometry (1601 Shimadzu). All the measurements were made in triplicate and expressed as mean ± RSD. The steady-state flux was calculated from the slope of the linear region ofthe cumulative amount of nicardipine hydrochloride permeated versus time plot. The absorbance of aliquates was estimated for all adjustment bend benchmarks at 307 nm [11].

RESULT AND DISCUSSION:

The UV Spectroscopy of drug Nicardipine was done and λmax of drug was found to be 307 nm (Figure 1). The standard curve of drug concentration from 2-10 µg/ml, shown the linearity plot was appeared in Figure 2. Preformulation is characterized as an examination of physicochemical properties of medication substance, independently and in blend with excipients. Before beginning the manufacturing procedure of any formulation, chosen active ingredient and polymers were subjected for assessment like description, loss on drying and organoleptic properties. The obtained results were satisfactory in all preformulation studies. The unadulterated active ingredient and different excipients were stuffed in shut vials and subjected to quickened air conditions for four weeks. At that point the physical observation was done and adjusted that the active ingredient and blends does not demonstrate any adjustment in their physical properties.

Nicardipine (crystalline form) is a yellow powder soluble in methanol and practically insoluble in water. Solubility of nicardipine was determined in several reagents/buffers covering entire pH range of GI tract. Results obtained in solubility study inferred that drug is practically insoluble in water but its solubility marginally increases in acidic pH. Above pH 5 its solubility again decreases. Thus it can be inferred that nicardipine is practically insoluble over the entire pH range of GIT.i.e. 1-8. The FTIR spectrum of nicardipine as shown in Figure 3 exhibits a weak absorption band at 3387 cm-1 due to the presence of secondary amine functionality. The presence of aromatic system is evident from the characteristic absorption bands at 3063 cm-1 due to aromatic C–H stretch and at 1525-1489 cm-1 due to the skeletal vibrations involving C-C stretching within the aromatic ring. The spectrum demonstrates the CH3 aliphatic stretch at 2949 cm-1 . Prominent C=O stretch at 1691 cm-1 indicates that the ester functionality is associated with a conjugated system. Characteristic peaks at 1220 cm-1 and 1114 cm-1 correspond to the C-C=O-C stretching of saturated ester. The NO2 vibrations at 1550 and 1350 cm–1 are too extensive and overlap with the aromatic vibrations. A weak shoulder at 777 cm-1 can be assigned to the C-N stretching vibration of aromatic nitro group. The IR spectra of drug and its polymer mixtures were identical and characteristic absorption peaks of drug remained unchanged in polymer admixture which indicates there is no prominent chemical reaction between drug and polymer mixture.

The prepared buccal mucoadhesive was evaluated with various parametrs. The tablet thickness and tablet diameter opf all the tablets are within the acceptable range for tablet thickness with values ranging from 4.71 mm to 4.80 mm. Tablet diameter of the tablets showed values ranging from 8.01 mm to 8.08 mm, which fall within the acceptable range. The specification of tablet weight with 200 mg is ±5% difference. The tablet weights should be 205 mg to 195 mg. The tablet hardness shows that all tablets are within the range. The results show acceptable resistance of the tablet to shipping during storage and transport. All the tablets fall within the in-house hardness range of 4.8 kg to 5.5 kg. The percent friability should not be more than 0.8% for new formulations. All tablets are within range; therefore, the tablet is resistant to breaking due to storage and transportation. The drug content varied between 97.67 to 103.03% which reflects good uniformity in drug content among different batches. All the tablets disintegrated within 60 sec. The surface pH of the tablet should be close to the salivary pH so that the tablet will not irritate the buccal mucosa. The salivary pH is 6.50 to 7.50. Since the surface pH of the buccal tablet is within the limits of salivary pH, it shows that the tablet will not irritate the buccal mucosa. The percent swelling of all formulations were 55.90% and 54.03%, respectively. The swelling property of all the batches was performed by evaluating the swelling index at different time intervals (1, 2, 4, and 8 h). All the formulations showed an appreciable increase in swelling index, proportional to the time increased, and achieving maximum swelling effect at 8 h. The tablets did not show any significant change in their morphological shape and form, throughout the study. The highest swelling was shown by the batch NMT8 containing CP and SCMC i.e. 450.19% whereas the lowest swelling behavior was shown by the batch NMT1 (112.23%) containing HPMC and CP. To achieve the desired characters of the mucoadhesive tablet, the proper combination of all the polymers is crucial. Among all 8 different batches, NMT5–NMT8 exhibited rapid drug release. Due to this reason, these batches could not meet the sustained release criteria. Also, they had a relatively higher swelling index than the normal. Thus, further modification and study of these batches is necessary to achieve desired characters. The in vitro dissolution study of formulated batches of mucoadhesive tablets was carried out. The in vitro drug release studies revealed that the release of drug depends upon the nature and proportion of polymers used. Moreover, this study also suggested that HPMC can play a significant role to regulate the swelling behavior, bioadhesion force, and drug release rate of the tablet. Although it has moderately swelling property, it enables steady entry and entrapment of liquid in the polymeric network, which is very significant to achieve sustained release of the drug. Thus many researchers prefer the combination of HPMC/CP mixture as a bioadhesive material.

SUMMARY AND CONCLUSION:

The study was conducted to formulate and evaluate mucoadhesive buccal tablets of nicardipine with a sustained release property, to achieve patient compliance for the management of different types of pain. Among all 8 different batches, NMT1 showed sustained and effective drug release, swelling index as well as mucoadhesive strengths. Its physicochemical properties also complied with the pharmacopoeial standards. The results also demonstrate that CP has a major role to increase the mucoadhesive strength. The swelling behavior of the formulation can be optimized by changing the proportion of CP and SCMC. However higher concentration of SCMC can result in abrupt release of the drugs. Therefore HPMC can play a significant role to check the swelling behavior and drug release rate. However, extensive research in suitable polymers and drug candidates is indispensable. Moreover, the formulation of an nicardipine mucoadhesive tablet can be an effective alternative route to prevent the first-pass effect and to improve the bioavailability of aceclofenac through the mucosal membrane. It can also enhance patient compliance by fascinating extended release of the drug.

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REFERENCES:

1. Gilhotra, R.M.; Ikram, M.; Srivastava, S.; Gilhotra, N. A clinical perspective on mucoadhesive buccal drug delivery systems. J. Biomed. Res. 2014, 28, 81–97.
2. Baus RA, Jouzdani F, Dünnhaupt S, Atyabi F, Schnürch A, “Mucoadhesive hydrogels for buccal drug delivery: In vitro-in vivo correlation study,” European Journal of Pharmaceutics and Biopharmaceutics, 2019, 142, 498-505.
3. Kottke D, Bjoern B. Burckhardt, Tanja C. Knaab, Jörg Breitkreutz, Björn Fischer, Development and evaluation of a composite dosage form containing desmopressin acetate for buccal administration, International Journal of Pharmaceutics: X, 3, 2021, 100082.
4. Patel V R, Agrawal Y K. 2011. Nanosuspension: An approach to enhance solubility of drugs. J Adv Pharm Technol Res. 2(2), 81-7.
5. Wertz, P.W. Roles of lipids in the permeability barriers of skin and oral mucosa. Int. J. Mol. Sci. 2021, 22, 5229
6. Xu J, Strandman S, Zhu J, Barralet J, Cerruti M, “Genipin-crosslinked catechol-chitosan mucoadhesive hydrogels for buccal drug delivery,” Biomaterials, 2015, 37, 395-404.
7. Andrews, G.P.; Laverty, T.P.; Jones, D.S. Mucoadhesive polymeric platforms for controlled drug delivery. Eur. J. Pharm. Biopharm. 2009, 71, 505–518.
8. Jin H, Ngo HV, Park C, Lee BJ. Mucoadhesive buccal tablet of leuprolide and its fatty acid conjugate: Design, in vitro evaluation and formulation strategies. Int J Pharm. 2023, 25;639:122963.
9. Duchene D, Touchard F and Peppas N A. Pharmaceutical and medical aspects of Bioadhesive system for drug administration. Drug Dev. Ind. Pharm.; 14, 283-381, 1998.
10. Macedo, A.S.; Castro, P.M.; Roque, L.; Thomé, N.G.; Reis, C.P.; Pintado, M.E.; Fonte, P. Novel and revisited approaches in nanoparticle systems for buccal drug delivery. J. Control Release 2020, 320, 125–141.
11. Gu J M, Robinson J R and Leung S. binding of acrylic polymers to mucin/epithelial surfaces; Structure property-relationship. Crit. Rev. Ther. Drug Car. Sys.; 5, 21-67, 1998.
12. Russo E, Selmin F, Baldassari S, Gennari CGM, Caviglioli G, Cilurzo F, Minghetti P, Parodi B, “A focus on mucoadhesive polymers and their application in buccal dosage forms,” Journal of Drug Delivery Science and Technology, 2016, 32, B, 113-125.

Table 1: Composition of various batches of mucoadhesive buccal tablets

Ingredients	NMT1 (mg)	NMT2 (mg)	NMT3 (mg)	NMT4 (mg)	NMT5 (mg)	NMT6 (mg)	NMT7 (mg)	NMT8 (mg)
NIC	10	10	10	10	10	10	10	10
Carbopol 934	60	65	70	75	60	65	70	75
HPMC	60	55	50	45	-	-	-	-
SCMC	-	-	-	-	60	55	50	45
Magnesium stearate	10	10	10	10	10	10	10	10
MCC 200	50	50	50	50	50	50	50	50
Talc	10	10	10	10	10	10	10	10
Total weight	200	200	200	200	200	200	200	200

Table 2: Different quality control evaluation parameters of the buccal mucoadhesive granules of different batches

Formulation code	Angle of repose (θ) Mean ± SD (n=3)	Bulk density (g/cc) Mean (n=3)	Tapped density (g/cc) Mean (n=3)	Carr's index (%)	Hausner's ratio
NMT1	27.02 ± 0.21	0.541	0.617	12.32	1.14
NMT2	28.47 ± 0.62	0.509	0.597	14.74	1.17
NMT3	23.11 ± 0.42	0.583	0.654	10.86	1.12
NMT4	26.36 ± 0.09	0.546	0.628	13.06	1.15
NMT5	23.05 ± 0.37	0.861	0.947	9.08	1.1
NMT6	25.54 ± 0.26	0.772	0.869	11.16	1.13
NMT7	26.68 ± 0.32	0.781	0.876	10.84	1.12
NMT8	23.33 ± 0.17	0.954	1.046	8.79	1.1

Table 3: Different quality control evaluation parameters of the buccal mucoadhesive tablets of different batches

Formulation Code	Hardness (kg/cm2) Mean ± SD (n=3)	Thickness (mm) Mean ± SD (n=3)	Average weight (mg) Mean ± SD (n=10)	Friability (%)	Drug content (%) Mean ± SD (n=3)
NMT1	5.87 ± 0.16	3.03 ± 0.16	206.8 ± 1.2	0.11	99.37 ± 0.82
NMT2	5.71 ± 0.14	3.14 ± 0.14	201.7 ± 1.2	0.18	97.55± 0.84
NMT3	5.81 ± 0.13	3.23 ± 0.13	207.6 ± 1.3	0.16	99.83 ± 1.13
NMT4	7.01 ± 0.17	3.21 ± 0.09	208.4 ± 0.8	0.13	98.24 ± 0.87
NMT5	6.57 ± 0.08	3.11 ± 0.08	202.8 ± 1.0	0.18	101.13 ± 0.66
NMT6	6.02 ± 0.09	3.08 ± 0.17	206.1 ± 0.9	0.13	102.50 ± 0.72
NMT7	6.72 ± 0.09	3.07 ± 0.09	206.9 ± 0.8	0.17	99.45 ± 1.12
NMT8	6.81 ± 0.15	3.10 ± 0.15	209.6 ± 1.1	0.19	99.31 ± 0.76

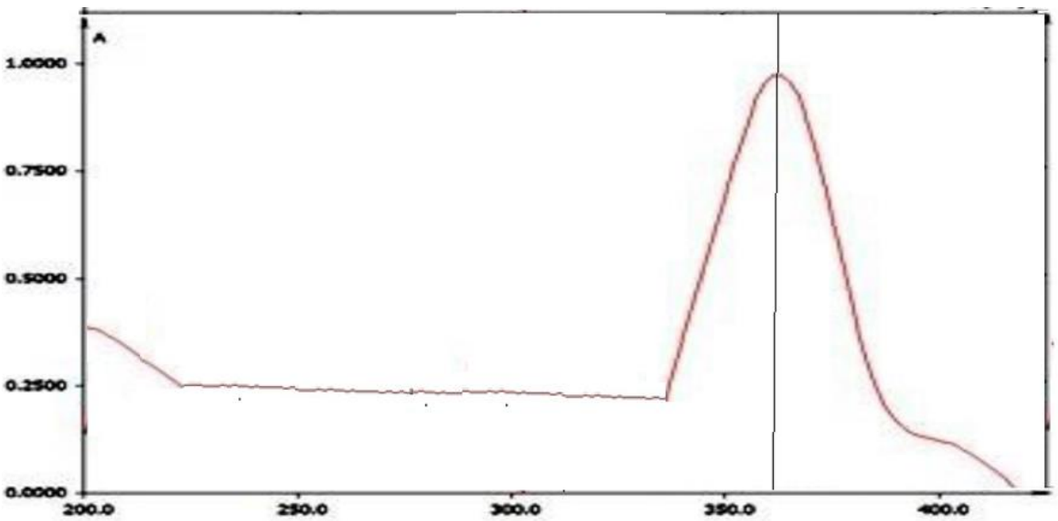

Figure 1: Determination of maximm wavelength (λmax) of nicardipine by Using phosphate buffer pH 6.8

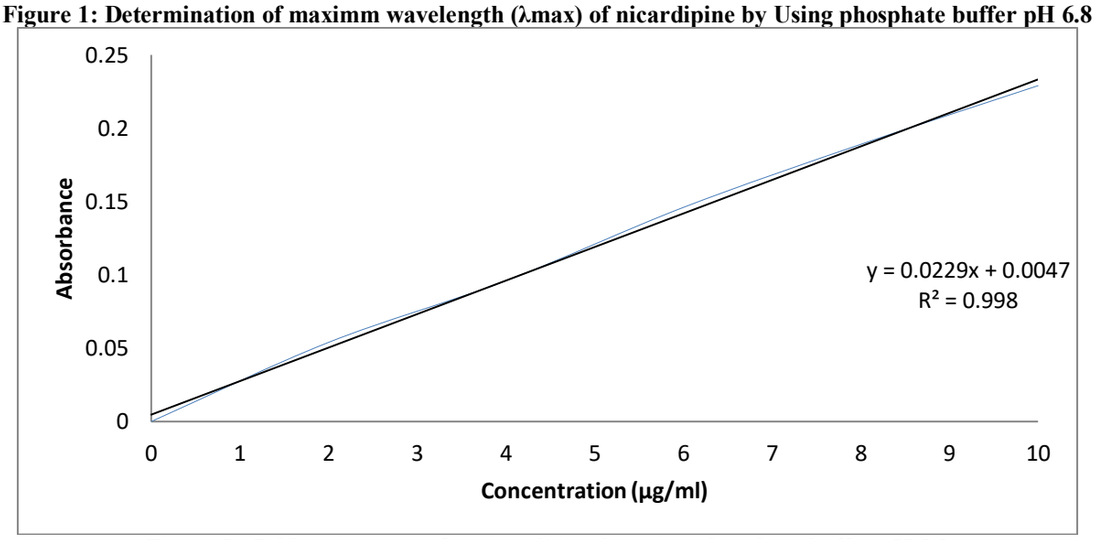

Figure 2: Calibration curve for nicardipine by using phosphate buffer pH 6.8

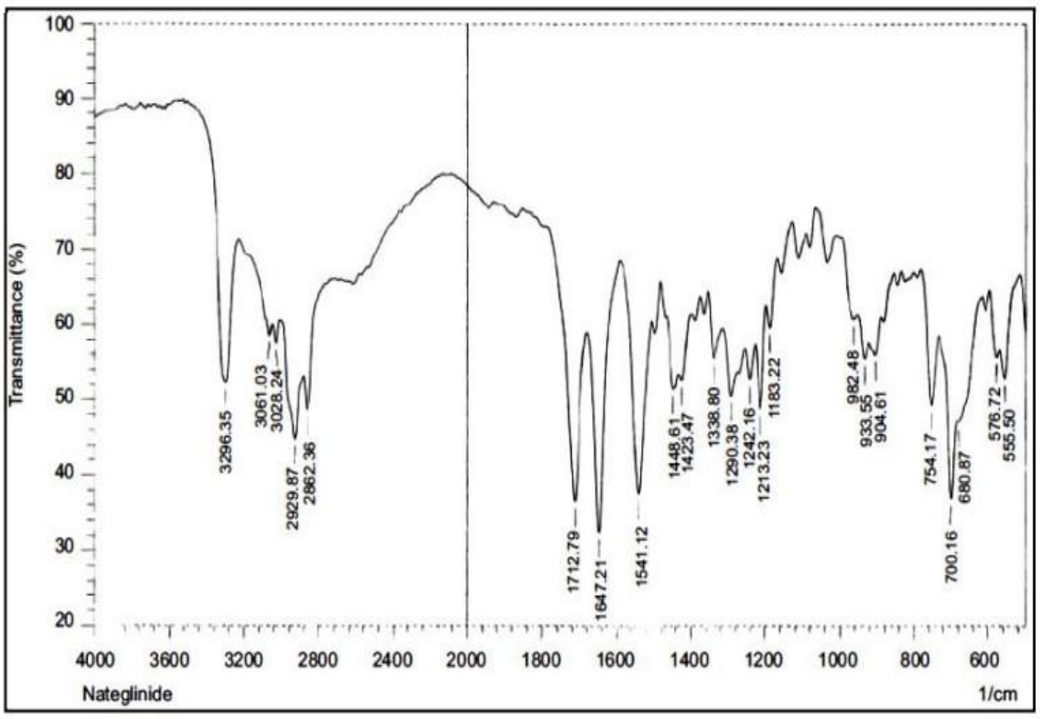

Figure 3: FTIR study of nicardipine and excipients

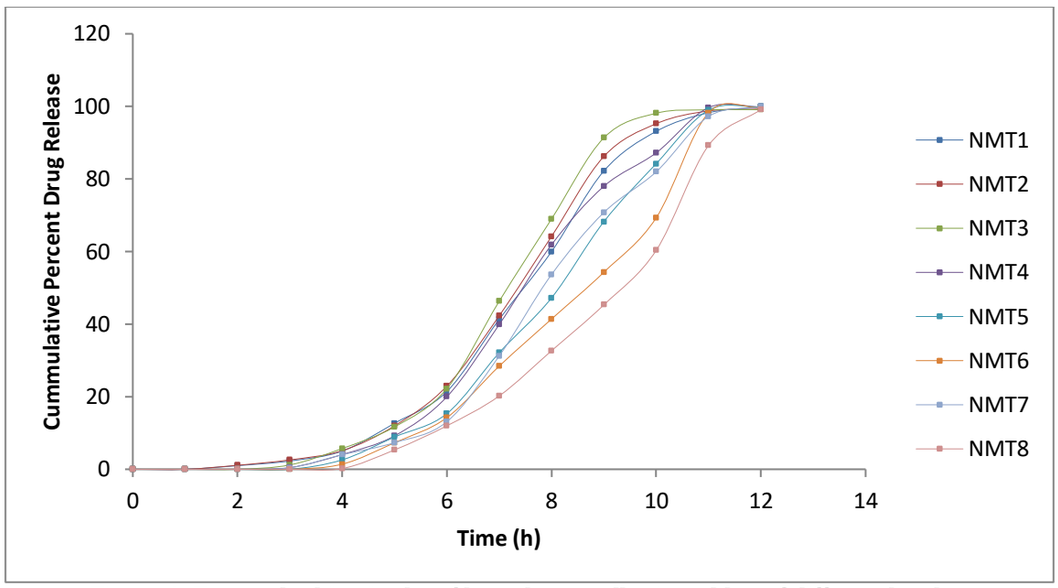

Figure 4: Zero-order kinetic plot of buccal mucoadhesive tablets of different batches