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Design and in vitro Evaluation of Mucoadhesive Buccal Tablets of Perindopril Prepared by Sintering Technique

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Abstract: The aim of the present study was to prepare and evaluate a mucoadhesive buccal tablet containing antihypertensive drug i.e. Perindopril to avoid the first pass metabolism and to improve its bioavailability with reduction in dose and also dose related side effects. The half life of Perindopril is approximately 0.8 to 1 hrs. The tablets were prepared by direct compression method containing polymer Polyethylene oxide and carnauba wax. The prepared tablets were sintered at various temperatures like 60^0 C and 70^0C for 1.5 hr and 3 hr**.** The sintered tablets were tested for weight variation, hardness, surface pH, drug Content Uniformity, swelling index, bioadhesive strength sand *in-vitro* drug dissolution study. FTIR studies showed no evidence on interactions between drug, polymers, and excipients. The *in-vitro* release of Perindopril was performed under sink conditions (Phosphate buffer PH 6.8, 37±0.5 ºC, rpm 50) using USP-XXIV dissolution apparatus. The sintering times and the sintering temperature markedly affected the drug release properties of Perindopril buccal tablets. It is notable that the release rate of Perindopril from buccal tablets was inversely related to the time of sintering and the sintering temperature. This is may be due to increase in extent and firmness of sintering which compacts the mass further, so that the drug release is affected. The best *in-vitro* drug release profile was achieved with the formulation F4 A (sintered at 60^0c for 1.5 hr.) which contain the drug, polyethylene oxide and carnauba wax in the ratio of 1:15:10.The surface pH, bioadhesive strength and swelling index of formulation F4 A was found to be 6.27, 34.8 gm and 179.31 (after 12 hr). The tablets (formulation F4 A) containing 4 mg of Perindopril exhibited 8 hrs sustained drug release (98 %) with desired therapeutic concentration. The drug release followed diffusive mechanism with first order release kinetics. The stability studies showed that optimized formulation was considered to be highly stable.

Key words: Buccal tablet, Swelling Index, Bioadhesive Strength and Surface pH.

Introduction and Experimental

Buccal mucosa[1] is a potential site for the delivery of drugs to the systemic circulation . A drug administered through the buccal mucosa enters directly systemic circulation, thereby minimizing the first pass hepatic metabolism and adverse gastrointestinal effect[2]. Buccal region of the oral cavity is an attractive target for administration of the drug of choice[3]. Buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally to prevent

accidental swallowing [4-7]. Therefore adhesive mucosal dosage forms were suggested for oral delivery [8]. Buccal mucosa makes a more appropriate choice of site if prolonged drug delivery is desired because buccal site is less permeable than the sublingual site.

In addition, there is excellent acceptability and the drug can be applied, localized and may be removed easily at any time during the treatment period [9]. Hence buccoadhesive drug delivery systems have been developed basically to increase the retention of drug in the oral cavity.

Adhesion to specific sites such as oral and nasal cavities increases bioavailability by virtue of optimum contact with adhesive surface which increases absorption of drug and prolongs gastric residence [10].

Exploration of the sintering concept in the pharmaceutical sciences is relatively recent, and presently, research interests relating to this process have been growing. In powder metallurgy, sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in compact, by the application of heat[11]. The conventional sintering technique involves the heating of compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure.

The concept of sintering was applied in the investigation of the effect of heating on the mechanical properties of pharmaceutical powders. The formation of solid bonds within a powder bed during tablet compression was also studied in terms of sintering. The changes in the hardness and disintegration time of tablets stored at elevated temperatures were attributed due to sintering.

Perindopril Eribumine [12-14] is an angiotensin converting enzyme inhibitor and is used in the treatment of hypertension and congestive cardiac failure. The bioavailability of Perindopril following oral administration is very low. Perindopril is absorbed rapidly on oral administration. When administered orally, frequent dosing is needed due to its short biological half-life (0.8 to 1hr). Secondly drug undergoes high hepatic first pass metabolism. (Thus bioavailability is reduced to 20%.) reducing the bioavailability & 20%.

In the present work, an attempt was made to formulate Mucoadhesive buccal tablets of Perindopril using sintering technique in order to avoid extensive first pass metabolism, degradation in the stomach and to prolong the duration of action.

Materials and Methods

Perindopril Erbumine, Polyethylene Oxide and Carnauba Wax were obtained as gift samples from Glenmark Pvt. Ltd., Mumbai. Spray dried lactose, Mannitol, Magnesium Stearate and Talc were procured from Lobachem Pvt Ltd Mumbai. All the reagents used for the study were of analytical grade.

Compatibility Studies

Drug-polymer-excipient compatibility studies:

This can be confirmed by carrying out by infrared light absorption scanning spectroscopy (IR) studies. Infra red spectra of pure drug and mixture of formulations were recorded by dispersion of drug and mixture of formulations in suitable solvent (KBr) using Fourier Transform Infrared Spectrophotometer (FTIR). A base line correction was made using dried potassium bromide and then the spectra of the dried mixture of drug, formulation mixture and potassium bromide and then the spectra of the dried mixture of drug, formulation mixture and potassium bromide were recorded on FTIR at NIST, Rourkela, Orissa.
The data are shown in Figs.1 to 3.

Formulation of Mucoadhesive Buccal Tablets of Perindopril

The prescribed quantity of drug, polymers and excipients (Table-1) were mixed homogeneously in a glass mortar for 15 min. The mixture was then compressed into tablets (150 mg.wt.) using an 8 mm, biconcave punch in a single-stroke using 8-station rotary machine (The Rimek Mini Press-1). The prepared tablets were sintered at two different temperatures like 60 ^{0}C and 70 ^{0}C for 1.5 hr and 3 hr. The temperature of oven was maintained at 60±1 or 70±1 ^{0}C. The tablets were prepared with different compositions and six formulations are shown in Table no. 1 .

Evaluation of Physicochemical Parameters of Tablets

Hardness

The hardness of three randomly selected tablets from each formulation (F1 to F6) was determined by placing each tablet diagonally between the two plungers of tablet hardness tester and applying pressure until the tablet broke down into two parts completely and the reading on the scale was noted down in Kg/cm^2. The results are presented in Tables.2 and 3.

Determination of drug content

Ten randomly selected tablets from each formulation (F1 to F6) were finely powdered and powder equivalent to 8 mg of Perindopril was accurately weighed and transferred to 100 ml volumetric flasks containing 50 ml of phosphate buffer (pH 6.8). The flasks were shaken thoroughly to get uniform solution/suspension. The volume was made up to the mark with the above phosphate buffer pH 6.8 and filtered. One ml of the filtrate after suitable

dilution was subjected for the estimation of Perindopril content at 216 nm using a double beam UV-visible spectrophotometer. Estimations were done in triplicate and their average values were presented in Tables no.4.

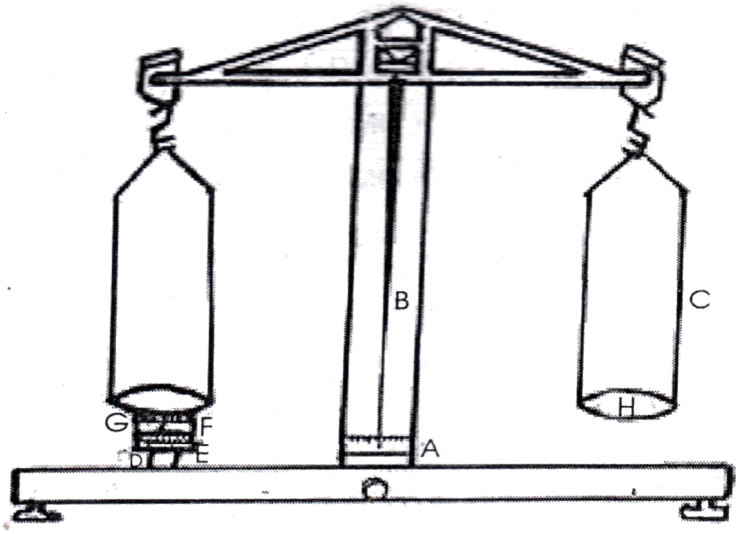
Microenvironment pH

The microenvironment pH (surface pH) of the buccal tablets was determined in order to investigate the possibility of any side effects *in-vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was decided to keep the surface pH as close to neutral as possible. The method adopted by Bottenberg *et al* [15] was used to the determination of the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 5 ml of distilled water (pH 6.5 ± 0.05) for 2 hr at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablets and allowing it to equilibrate for I min. The results are presented in Table.5.

Bioadhesion Studies [1]

The two sides of balance were balanced with a 5 g weight on the right hand side pan. Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues, washed with distilled water and then with phosphate buffer pH 6.8 at 37 ^{0}C

A piece of buccal mucosa was tied with the mucosal side upwards using thread over the protrusion in in the Teflon block. The block was then lowered into the the glass beaker which was then filled with phosphate buffer pH6.8 kept at 37 ± 1 ^{0}C to keep mucosal membrane moist. this was then below the left hand set up of the balance. The tablet to be tested for mucoadhesive strength was then stuck with the little moisture, onto the cylinder (E) hanging on the left hand side. The balance beam was raised. The 5 gm wt. on the right pan was removed. This lowered the Teflon cylinder along with the tablet over the mucosa, with a force of 5 gm.. The balance was kept in this position for 3minutes and then the weights were increased gradually on right pan, till the tablet separated from the mucosal surface. The excess weight on pan i.e. total weight minus 5gm, is the force required to separate the tablet from the mucosa. The results are presented in the table. 6 .



A. Scale
B. Pointer
C. Pan
D. Protrusion for tying mucosal tissue
E. Sheep buccal mucosa
F. Mucoadhesive tablet
G. Double layered adhesive tape
H. Weight

Assembly for measurement of adhesive force

Swelling studies

Five Buccal tablets were individually weighed (W_1) and placed separately in each petri dishe with 5 ml of phosphate buffer (pH 6.8). At time intervals of 1, 2, 4 8 and 12hr. the tablet was removed from each Petri dish and excess surface water from the tablet was wiped out carefully with filter paper. Each swollen tablet was reweighed (W2) and the swelling index (SI) was calculated using the following formula [16,17]

Swelling Index = [(W2-W1)/ W1] ×100

The results are shown in Table. 7.

***In-Vitro* dissolution studies** [8,18]

The *In-vitro* dissolution study was conducted as per the United States Pharmacopoeia (USP) XXIV. The rotating paddle method was used to study the drug release from the tablets. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). The release was performed at $37^0C \pm 0.5^0C$, at a rotational speed of 50 rpm. Five ml samples were withdrawn at predetermined time intervals (1 to 8 hr) and the volume was replaced with fresh medium. The samples were filtered through Whatman filter paper No. 40 and analyzed for Perindopril after appropriate dilution by UV spectrophotometer at 216 nm. The percent drug release was calculated using the calibration curve of the drug in phosphate buffer pH 6.8.

Drug release kinetics

To examine the release mechanism of Perindopril from the prepared buccoadhesive tablets, the results were analyzed according to the following equation.

$$\frac{M_t}{M_\infty} = k.t^n$$

Where M_t / M_∞ is the fractional drug released at time *t*, *k* is a kinetic constant incorporating structural and geometrical characteristics of the drug/polymer system [device], and *n* is the diffusional exponent that characterizes the mechanism of drug release. It is known that for non-swelling tablets, drug release can generally be expressed by the Fickian diffusion mechanism, for which $n = 0.5$, whereas for most erodible matrices, a zero-order release rate kinetics is followed, for which $n = 1$. For non-Fickian release, the *n* value falls between 0.5 and 1.0 [$0.5 < n < 1.0$]; whereas in the case of super case II transport, $n > 1$.

Data of the *in-vitro* release was fit into different equations and kinetic models to explain the release kinetics of Perindopril from buccal tablets. The kinetic models used were zero-order equation (eq. 1), first-order equation (eq. 2), matrix equation (eq. 3), Krosmeyer-Peppas equation (eq. 4), and Hixon-Crowell equation (eq. 5).

$Q_t = K_0 t$ ---------- (1)

$Q_t = Q_0 (1 - e^{-k1} t)$ ---------- (2)

$Q_t = K_H . t^{1/2}$ ---------- (3)

$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t$ ---------- (4)

$Q_t / Q_\infty = K_k t^n$ ---------- (5)

Where,

Q_t ------- Is the amount of drug release in time t

Q_0 ------- Is the initial amount of the drug

F ------- Is the fraction of drug release in time t

n ------- Exponent value

And K_0, K_1, K_H, K_{HC}, and K_k are release rate constants for Zero-order, First-order, Higuchi, Hixon-Crowell, and Koresmeyer-Peppas model respectively.

Zero order represents an ideal release profile in order to achieve the pharmacological prolonged action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets with low soluble drugs. First order is applicable to study of hydrolysis Kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices. Matrix (Higuchi Matrix) is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water-soluble drug. Hixson-Crowell Equation applies to pharmaceutical dosage forms such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time. When this model is used, it is assumed that the release rate is limited by the drug particles dissolution rate and not by the diffusion that might occur through the polymeric matrix. Korsmeyer- Peppas Equation is widely used; when the release mechanism is not well known or when more than one type of release phenomena could be involved. Data of the *in-vitro* release was fit into different equations and kinetic models to explain the release kinetics of Perindopril from buccal tablets. The data are presented in Table.8.

Stability study

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product, which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. Formulations were selected for stability on the basis of the In-vitro drug release profile. The formulations were subjected to accelerated stability studies as per ICH (The International

Conference of Harmonization) guidelines i.e. 25^0C/60% RH and 40^0C/75% RH in air tight high density ethylene bottles for 2 months in thermostated ovens. The samples were taken out at 0, 30, 40, 50 and 60 days. Tablets were evaluated for the different physicochemical parameters i.e. content uniformity, weight variation, bioadhesive strength, surface pH, swelling study, and percentage of drug release.

Result and Discussion

Compatibility studies

The infrared spectra of pure drug Perindopril and mixture of polymer and excipients were studied by FTIR spectroscopy using suitable solvent KBR. The datas are presented in the Figs.1 to 3. The results indicate that there was no chemical incompatibility between drug –polymer, polymer–polymer and polymer – excipients.

Evaluation of Physiochemical Parameters

Hardness

The hardness of unsintered and sintered tablets were presented in Tables 2 and 3 respectively. The hardness was found to be increased with increased in sintering time and sintering temperature.

Content uniformity

The tablets from all the formulations (F1 to F6) were subjected to drug content evaluation. The results are shown in Table no. 4 .

The maximum percentage of drug content from all the formulations was found to be 101.00 and minimum was found to be 95%. Hence it is concluded that all the formulations are falling with in the pharmacopeial limits.

Micro environment pH

The surface pH (microenvironment pH) of all the formulations (F1 to F6) was determined by using combined glass electrode and results are presented in Table no. 5.

The maximum and minimum surface pH value from the formulations were found to be 6.50 and 5.93 respectively. The acceptable pH of saliva is in the range of 5 to 7. So these formulations may not produce any irritation to the buccal mucosa.

Bioadhesive strength

. The bioadhesive strength of tablets were found to be function of the polymer concentration. The bioadhesive strength of tablets was found to be increased with increase in the concentration of mucoadhesive polymer (PEO). Formulation F_6 showed the highest bioadhesive strength while F_1 showed lowest bioadhesive strength. The results are presented in Table 6 and fig no.4.

Swelling studies:

The swelling studies were conducted and the results are presented in Table 7 and Fig no.5. The formulations were hydrated generally by keeping the tablets in contact with water for 1 to 12hrs.. The swelling indices of tablets are considered to be function of the polymer concentration. In all the formulations 50 % to 100 % of thydration tablets was observed within the first hour itself. The fastest hydration rate, (100%) was observed with the formulation F_6 within the first hour. High rate of water uptake may be due to quick hydration of polyethylene oxide (PEO). It is also observed that the tablets was increased with increase in the concentration of PEO in tablets.

In- vitro dissolution studies

The dissolution profile of the all formulations of unsintered tablets is shown in Figure no. 6. It was observed from the figure that mere incorporation of polyethylene oxide and carnauba wax into the formulations did not rretard the release. Complete drug release (100%) was observed to all the formulations of unsintered tablets. Hence the sintering technique was adopted during manufacturing of tablets to control the drug release.

To retard the release of the drug, the earlier prepared tablets were sintered at temperatures of 60 ^{0}C and 70 ^{0}C for 1.5hr and 3.0hr in an oven.

[The *in-vitro* drug release profile of Perindopril buccal tablets containing polyethylene oxide (PEO) and carnauba wax showed] The percentage drug release for formulation F1 was 23.7 % and 17.67 % (sintered at 60^0c and 70^0c for 1.5 hr respectively) and 19.82 % and 13.66 % (sintered at 60^0c and 70^0c for 3 hr respectively) during first hour. Also at the end of 8 hr, percentage drug release was found to be 63.88 % and 49.82 % (sintered at 60^0c and 70^0c for 1.5 hr respectively) and 55.84 % and 41.78 %(sintered at 60^0c and 70^0c for 3 hr respectively). On physical examination of tablets during dissolution study, it was found that tablets were initially swelled and were non erodible over the period of time.

The *in-vitro* drug release profile of Perindopril buccal tablets containing polyethylene oxide (PEO) and carnauba wax showed percentage drug release for formulation F2 were 25.71 % and 21.69 % (sintered at 60^0c and 70^0c for 1.5 hr respectively) and 23.71 % and 17.67 % (sintered at 60^0c and 70^0c for 3 hr respectively) during first hour. Also at the end of 8 hr, percentage drug release was found to be 69.91 % and 57.85 % (sintered at 60^0c and 70^0c for 1.5 hr respectively) and 63.88 % and 47.81 %(sintered at 60^0c and 70^0c for 3 hr respectively). On physical examination of tablets during dissolution study it was

found that tablets were initially swelled and were non erodible over the period of time.

The *in-vitro* drug release profile of Perindopril buccal tablets containing polyethylene oxide (PEO) and carnauba wax showed percentage drug release for formulation F3 were 31.35 % and 25.70 % (sintered at 60^0c and 70^0c for 1.5 hr respectively) and 27.72 and 23.7 (sintered at 60^0c and 70^0c for 3 hr respectively) during first hour. Also at the end of 8 hr, percentage drug release was found to be 85.97 % and 70.91 % (sintered at 60^0c and 70^0c for 1.5 hr respectively) and 75.93 % and 63.88 %(sintered at 60^0c and 70^0c for 3 hr respectively). On physical examination of tablets during dissolution study it was found that tablets were initially swelled and were non erodible over the period of time.

The *in-vitro* drug release profile of Perindopril buccal tablets containing polyethylene oxide (PEO) and carnauba wax showed percentage drug release for formulation F4 were 37.75 % and 29.73 % (sintered at 60^0c and 70^0c for 1.5 hr respectively) and 31.34 % and 25.73 % (sintered at 60^0c and 70^0c for 3 hr respectively) during first hour. Also at the end of 8 hr, percentage drug release was found to be 98% and 83.97 % (sintered at 60^0c and 70^0c for 1.5 hr respectively) and 90 % and 75.94 % (sintered at 60^0c and 70^0c for 3 hr respectively). On physical examination of tablets during dissolution study it was found that tablets were initially swelled and were non erodible over the period of time.

The *in-vitro* drug release profile of Perindopril buccal tablets containing polyethylene oxide (PEO) and carnauba wax showed percentage drug release for formulation F5 were 29.34 % and 24.71 % (sintered at 60^0c and 70^0c for 1.5 hr respectively) and 26.72 % and 22.7 % (sintered at 60^0c and 70^0c for 3 hr respectively) during first hour. Also at the end of 8 hr, percentage drug release was found to be 85.98 % and 71.91 % (sintered at 60^0c and 70^0c for 1.5 hr respectively) and 77.94 % and 66.89 %(sintered at 60^0c and 70^0c for 3 hr respectively). On physical examination of tablets during dissolution study it was found that tablets were initially swelled and were non erodible over the period of time.

The *in-vitro* drug release profile of Perindopril buccal tablets containing polyethylene oxide (PEO) and carnauba wax showed percentage drug release for formulation F6 were 29.73 % and 23.72 % (sintered at 60^0c and 70^0c for 1.5 hr respectively) and 25.71 % and 21.69 % (sintered at 60^0c and 70^0c for 3 hr respectively) during first hour. Also at the end of 8 hr, percentage drug release was found to be 75.93 % and 65.89 % (sintered at 60^0c and 70^0c for 1.5 hr respectively) and 69.91 % and 59.86 %(sintered at 60^0c and 70^0c for 3 hr respectively). On physical examination of tablets during dissolution study it was found that tablets were initially swelled and were non erodible over the period of time.

The sintering time and temperature markedly affected the drug (Perindropril) release properties of buccal tablets. It was observed that the release rate of Perindopril from buccal tablets was inversely related to the time or temp. of sintering. This may be due to the increase in the extent and firmness of sintering which compacts the mass further so that the drug release is affected. Also, the cumulative percent of Perindopril released was decreased as the sintering time and temperature were increased for all formulations. Increasing the temperature or time of exposure to a particular temperature often decreased the release rate. This is probably due to the fusion of polymer granules or formation of welded bonds between the polymer particles.

The release of Perindopril from buccal tablets was varied according to the ratio of polyethylene oxide (PEO) and carnauba wax. The carnauba wax concentration did play a significant role in the release of the drug. At higher concentrations of carnauba wax, release rates were decreased.. An increase in the polymer concentration increases the viscosity of the gel as well as the formation of gel layer resulting with longer diffusional path. This could cause a decrease in the effective diffusion co-efficient of drug and therefore reduction in drug release rate. Furthermore, the dissolution pattern of Perindopril from buccal tablets revealed that the drug release was increased as the polyethylene oxide (PEO) was decreased. Among the six formulations F_4 showed the highest drug release. Tablets from formulation F_4 which were made by sintering at 60^0 C for 1.5hr showed drug release of nearly 98% at 8hours.

At the end of 8hr, the shape of the tablets was not distorted, suggesting that the drug release is controlled by diffusion. The surface of the sintered tablets after dissolution was porous in appearance where as the tablets before dissolution was quite smooth. The appearance of the porous structure may be due to the release of dispersed Perindopril and other additives from sintered tablets.

Drug release kinetics:

The *in vitro* drug release data of all the buccal tablet formulations was subjected to goodness of fit test by linear regression analysis according to zero order equation, Higuchi's and Korsmeyer-Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table no.8.

The values of regression co-relation co-efficient (R^2) were evaluated for all the formulations (F1 A to F6 D) whose values were close to 1. Among regression co-relation co-efficient (R^2) values of

Higuchi equation, Krosmeyer-peppas equation and Hixon-Crowell equation; R^2 values of Higuchi equation were found to be higher. Similarly among zero-order equation and first-order equation; R^2 values of first-order equation were found to be higher. Hence the drug release followed diffusive mechanism with first order release kinetics.

Stability studies

The stability studies were conducted on the selected formulation F_4 (Sintered at 60^0 c for 1.5hr) as per the ICH guidelines. The stability studies were done at the intervals of 0,30,40,50 and 60days. The parameters studied were percentage drug content. surface pH, bioadhesive strength, swelling index and percentage of drug release. The results are shown in Table. No.9.

From the results it was concluded that there were no significant changes in any values. Hence this formulation was considered to be highly stable.

TABLE- 1 Composition of different formulations. (mg/tablet)

Formulation code / **Ingredients**	**F 1**	**F 2**	**F 3**	**F 4**	**F 5**	**F 6**
Drug	4	4	4	4	4	4
Poly ethylene oxide (PEO)	30	40	50	60	70	80
Carnauba wax	70	60	50	40	30	20
Spray dried lactose	32	32	32	32	32	32
Manitol	9	9	9	9	9	9
Magnesium stearate	3	3	3	3	3	3
Talc	2	2	2	2	2	2
Total	150	150	150	150	150	150

TABLE-2: Hardness of unsintered Perindopril buccal tablets (kg/cm^2)

FORMULATION CODE	HARDNESS (Avg.± S.D)
F1	2.5±0.23
F2	3.0±0.23
F3	3.0±0.00
F4	3.0±0.23
F5	3.5±0.23
F6	3.5±0.00

All the values are expressed as mean±S.D, n=10.

TABLE-3 Hardness of sintered Perindopril buccal tablets (kg/cm^2)

SINTERING TEMPERATURE	**SINTERING TIME (hr)**	**FORMULATION CODE**					
		F1	**F2**	**F3**	**F4**	**F5**	**F6**
60°C	1.5	3.5 ±0.23	3.5 ±0.0	3.5 ±0.23	3.5 ±0.23	4.0 ±0.23	4.0 ±0.23
	3	4.0 ±0.23	4.0 ±0.23	4.0 ±0.23	4.0 ±0.23	4.0 ±0.23	4.5 ±0.0
70°C	1.5	4.0 ±0.23	4.0 ±0.23	4.0 ±0.23	4.5 ±0.0	4.5 ±0.23	4.5 ±0.0
	3	4.5 ±0.23	4.5 ±0.23	4.5 ±0.23	4.5 ±0.23	5.0 ±0.23	5.0 ±0.23

All the values are expressed as mean±S.D, n=3

TABLE-4 Percentage of drug content in buccal tablets

SINTERING TEMPERATURE	SINTERING TIME (hr)	FORMULATION CODE					
		F1	F2	F3	F4	F5	F6
60°C	1.5	97.00	98.78	99.00	101.00	98.5	98.00
	3	95.5	99.25	98.5	99.5	96.25	96
70°C	1.5	96.25	97.75	97.00	98.25	95	97.5
	3	95.75	95	98	96.75	95	95.75

TABLE-5 : Surface pH of Perindopril buccal tablets

SINTERING TEMPERATURE	SINTERING TIME (hr)	FORMULATION CODE					
		F1	F2	F3	F4	F5	F6
60°C	1.5	5.93	6.32	6.33	6.27	6.42	6.12
	3	6.09	6.41	6.43	5.98	6.38	6.24
70°C	1.5	6.34	6.50	6.19	6.39	6.20	6.38
	3	6.28	6.27	6.46	6.16	6.18	6.22

TABLE-6 : Bioadhesive strength of Perindopril buccal tablets (in gm)

SINTERING TEMPERATURE	SINTERING TIME (hr)	FORMULATION CODE					
		F1	F2	F3	F4	F5	F6
60°C	1.5	20.7	24.8	30.2	34.8	39.9	45.4
	3	20.5	24.7	30.0	34.8	39.7	45.2
70°C	1.5	20.5	24.5	29.8	34.7	39.6	45.0
	3	20.3	24.3	29.7	34.5	39.7	44.9

TABLE-7 : Percentage swelling index of Perindopril buccal tablets

	1hr	2hr	4hr	8hr	12hr
F1	56.54	63.26	72.37	109.78	145.34
F2	64.79	74.80	85.38	118.32	160.78
F3	73.08	83.24	98.32	130.64	170.05
F4	83.52	92.47	112.23	125.28	179.31
F5	94.02	110.34	128.09	138.72	190.28
F6	106.31	122.74	141.79	165.08	204.76

TABLE- 8: Drug Release Kinetic Studies on perindopril from Buccal Tablets

FORMULATIONS	ZERO ORDER (R^2)	FIRST ORDER (R^2)	Higuchi (R^2)	Hixon Crowell (R^2)	Koresmeyer Peppas (R^2)
F1 A	0.9171	0.9804	0.9968	0.9587	0.9940
F1 B	0.8971	0.9596	0.9980	0.9418	0.9959
F1 C	0.8996	0.9514	0.9965	0.9362	0.9951
F1 D	0.8655	0.9094	0.9832	0.8956	0.9657
F2 A	0.8859	0.9687	0.9971	0.9506	0.9961
F2 B	0.8869	0.9645	0.9972	0.9433	0.9950
F2 C	0.8799	0.9504	0.9958	0.9301	0.9927
F2 D	0.8886	0.9246	0.9969	0.9265	0.9964
F3 A	0.9035	0.9928	0.9992	0.9815	0.9983
F3 B	0.9151	0.9908	0.9986	0.9753	0.9972
F3 C	0.9044	0.9819	0.9989	0.9632	0.9981
F3 D	0.9087	0.0764	0.9991	0.9589	0.9973
F4 A	0.8875	0.9174	0.9970	0.9815	0.9958
F4 B	0.9247	0.9814	0.9994	0.9896	0.9993
F4 C	0.9256	0.9909	0.9991	0.9856	0.9974
F4 D	0.9327	0.9945	0.9981	0.9840	0.9979
F5 A	0.8827	0.9951	0.9941	0.9745	0.9924
F5 B	0.9058	0.9911	0.9978	0.9726	0.9975
F5 C	0.9182	0.9890	0.9991	0.9730	0.9990
F5 D	0.9089	0.9792	0.9991	0.9615	0.9989
F6 A	0.8947	0.9854	0.9983	0.9650	0.9986
F6 B	0.8997	0.9793	0.9984	0.9539	0.9981
F6 C	0.9021	0.9757	0.9991	0.9566	0.9989
F6 D	0.9046	0.9692	0.9990	0.9156	0.9982

A: - Sintered at 60^0 for 1.5 hr; **B: -** Sintered at 60^0 for 3 hr; **C: -** Sintered at 70^0 for 1.5 hr;
D: - Sintered at 70^0 for 3 hr.

TABLE- 9 Stability study of Formulation F4 A

Parameters	Time (Days)				
	0	**30**	**40**	**50**	**60**
	25 ± 2^0 C 60 ± 5% RH	**25 ± 2^0 C 60 ± 5%RH**	**40 ± 2^0 C 75 ± 5% RH**	**25 ± 2^0 C 60 ± 5% RH**	**40 ± 2^0 C 75 ± 5% RH**
Drug Content (%)	99.80	99.25	99.48	99.28	98.48
Surface pH	6.27	6.22	5.80	6.05	5.98
Bioadhesive Strength (gm)	34.5	35.2	35.5	35.8	34.0
Swelling Index (after 12 hr)	179.54	180.2	180.5	181.1	179.87
% Drug release	98	96	96	98	96

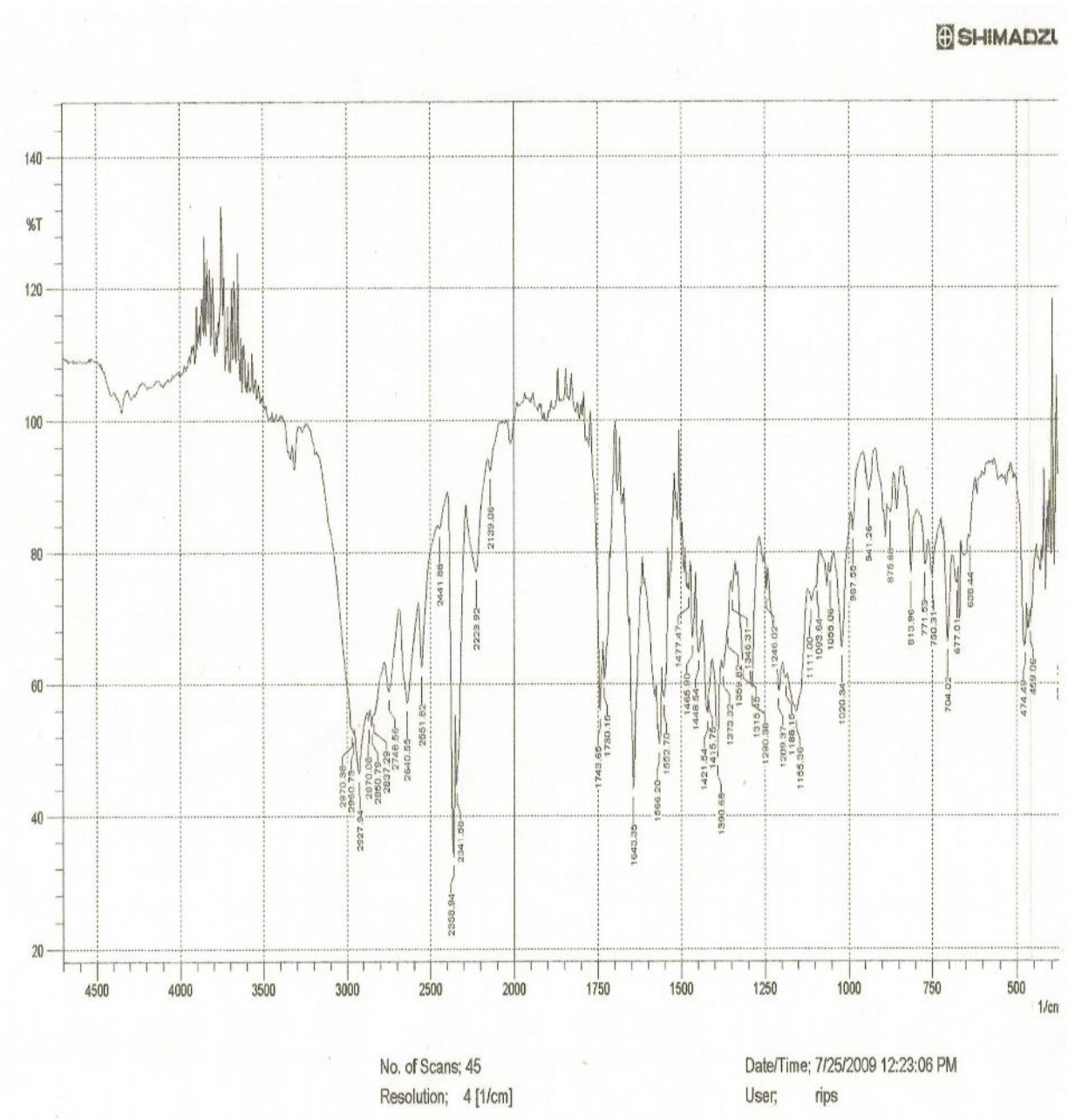


FIG 1. FTIR spectrum of drug (Perindopril Erbumine)

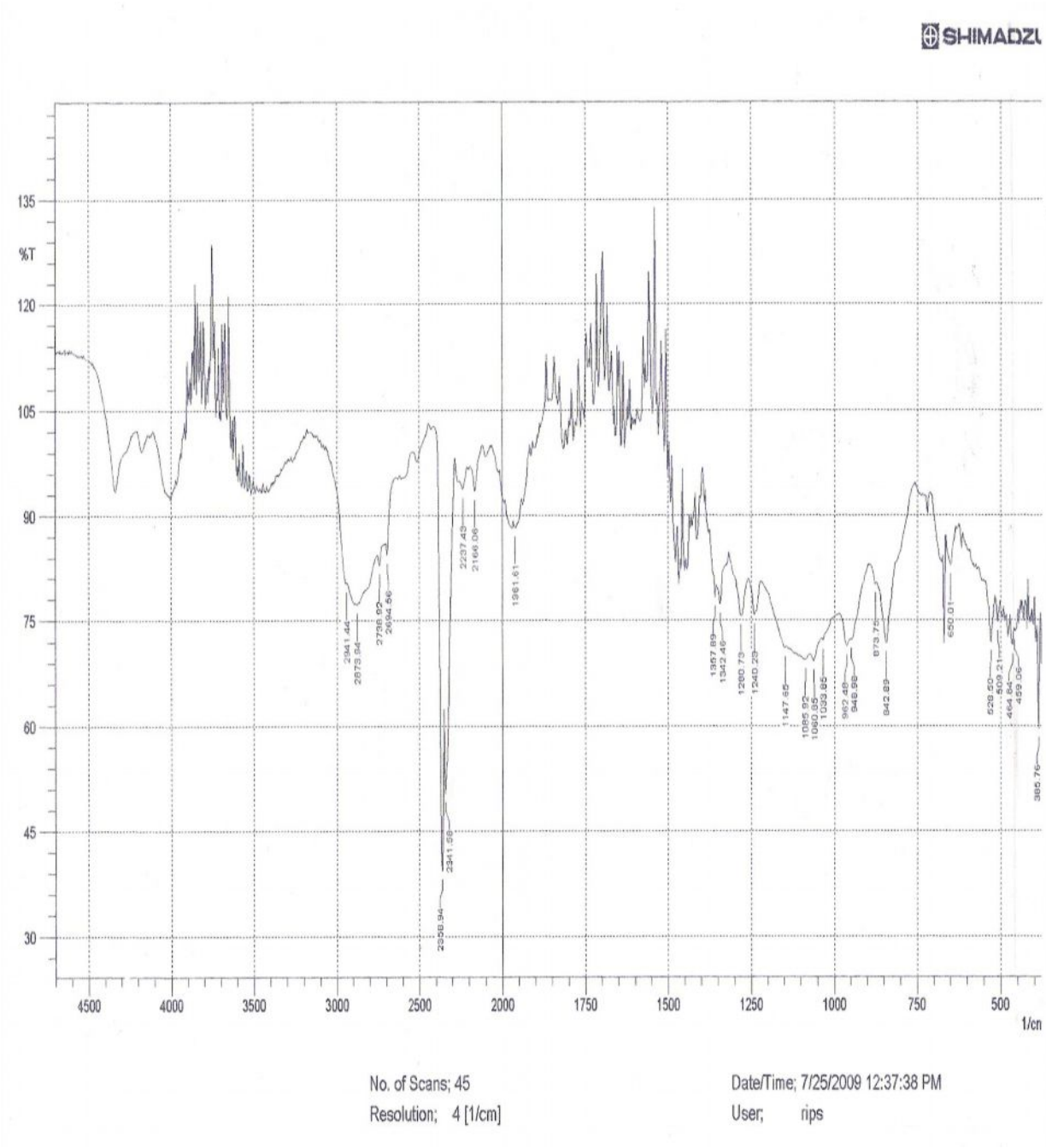


FIG 2. FTIR spectrum of mixture of drug and polyethylene oxide (PEO)

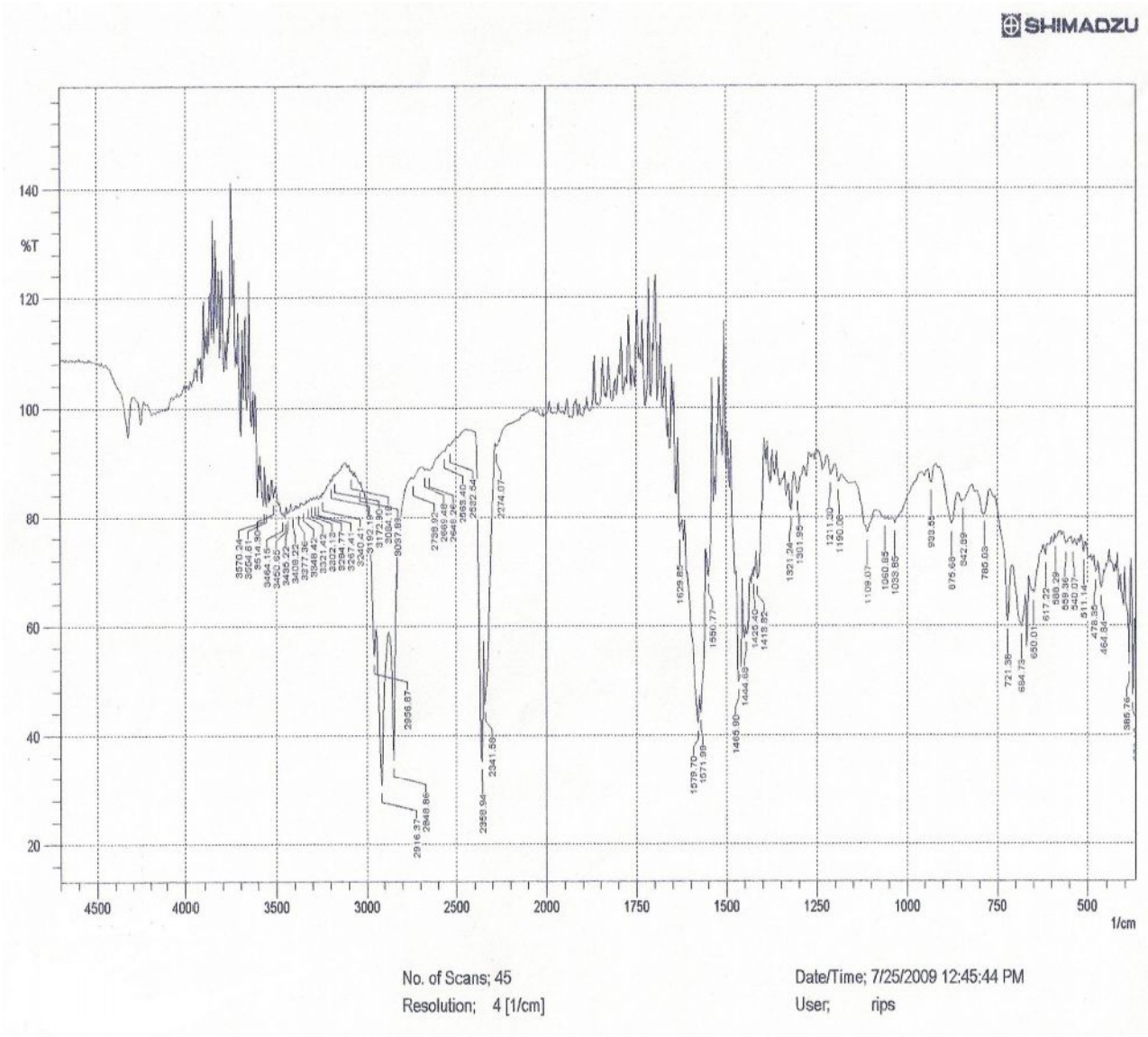


FIG 3. FTIR spectrum of mixture of drug, polyethylene oxide, carnauba wax, spray dried lactose, mannitol, magnesium stearate, Talc.

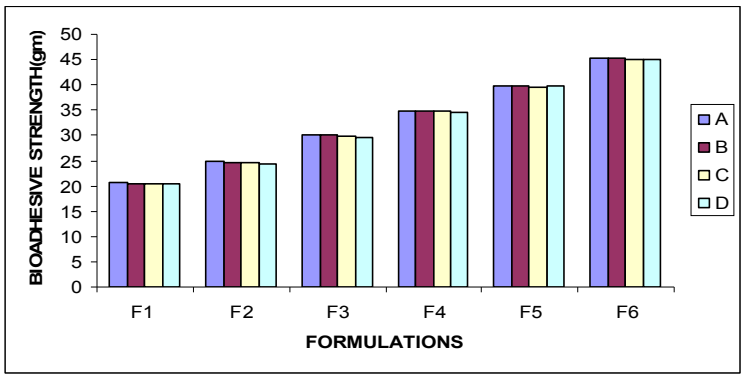


FIG 4. Bioadhesive strength of of six formulations of perindopril buccal tablets
A: - Sintered at 60^0 for 1.5 hr. **B: -** Sintered at 60^0 for 3 hr. **C: -** Sintered at 70^0 for 1.5hr.
D: - Sintered at 70^0 for 3 hr.

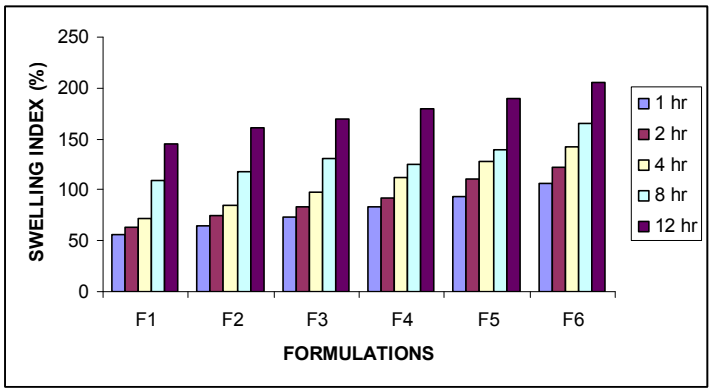


FIG 5. Swelling index profile of different formulations of perindopril buccal tablets

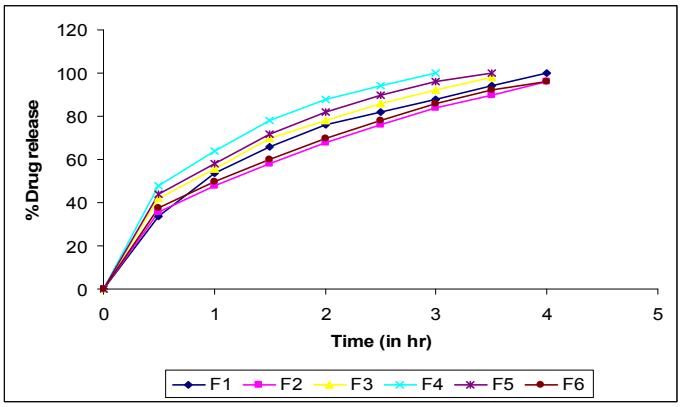


FIG 6. Dissolution profiles of various formulations of unsintered tablets.

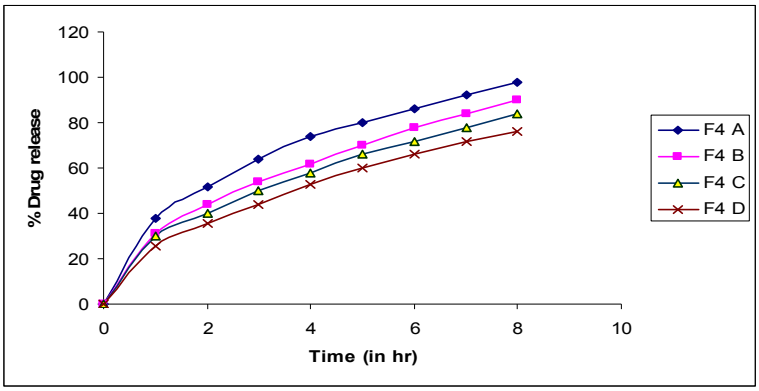


FIG 7. Dissolution profiles of Perindopril from formulation F4
A: - Sintered at 60^0 for 1.5 hr. **B: -** Sintered at 60^0 for 3 hr. **C: -** Sintered at 70^0 for 1.5hr.
D: - Sintered at 70^0 for 3 hr.

Conclusion

Among the different strategies employed for the design of controlled release dosage forms, sintering technique was found to be good for the preparation of mucoadhesive buccal tablets for the controlled release of Perindopril.

The best *in-vitro* drug release profile was achieved with the formulation F4 A (sintered at 60^0c for 1.5 hr.) which contains the drug, polyethylene oxide and carnauba wax in the ratio of 1:15:10. The tablets (formulation F4 A) containing 4 mg of Perindopril exhibited 8 hrs sustained drug release with desired therapeutic concentration.

So mucoadhesive buccal tablets of Perindopril prepared by sintering technique may be good approach to bypass the extensive hepatic first pass metabolism, to improve the bioavailability and to prolong the duration of action.

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