DESIGN AND *IN VIVO* EVALUATION OF CARVEDILOL BUCCAL MUCOADHESIVE PATCHES

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ABSTRACT
The buccal region offers an attractive route of administration for systemic drug delivery. Carvedilol (dose, 3.125-25 mg) is β-adrenergic antagonist. Its oral bioavailability is 25-35% because of first pass metabolism. Buccal absorption studies of a carvedilol solution in human volunteers showed 32.86% drug absorption. FTIR and UV spectroscopic methods revealed that there was no interaction between carvedilol and polymers. Carvedilol patches were prepared using HPMC, carbopol 934, eudragit RS 100, and ethylcellulose. The patches were evaluated for their thickness uniformity, folding endurance, weight uniformity, content uniformity, swelling behaviour, tensile strength, and surface pH. *In vitro* release studies were conducted for carvedilol-loaded patches in phosphate buffer (pH, 6.6) solution. Patches exhibited drug release in the range of 86.26 to 98.32% in 90 min. Data of *in vitro* release from patches were fit to different equations and kinetic models to explain release profiles. Kinetic models used were zero and first-order equations, Hixon-Crowell, Higuchi, and Korsmeyer-Peppas models. *In vivo* drug release studies in rabbits showed 90.85% of drug release from HPMC-carbopol patch while it was 74.63 to 88.02% within 90 min in human volunteers. Good correlation among *in vitro* release and *in vivo* release of carvedilol was observed.

Keywords: Carvedilol; buccal patches; *in vitro* release; *in vivo* release; evaluation.

INTRODUCTION

Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drugs. The mucosa is relatively permeable with a rich blood supply. The oral transmucosal drug delivery bypasses liver and avoids pre-systemic elimination in the GI tract and liver (Edith *et al.,* 1999). These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery. A few drugs, such as buprenorphine (Guo, 1994), propranolol (Coutel, 1992), salbutamol sulphate (Pavankumar *et al.,* 2005), diclofenac sodium (Patil and Rao, 2003), flurbiprofen (Barsuhn *et al.,* 1988), and fexofenadine (Thimmasetty *et al.,* 2007) have been successfully administered via the buccal route.

Carvedilol is a non- selective β-adrenergic blocking agent with α_1-blocking activity. It is widely used to treat essential hypertension and angina pectoris. Though it is rapidly absorbed after oral administration, the bioavailability of carvedilol is 25-35% (Vamshi *et al*., 2007), as it undergoes stereo-selective first pass metabolism and will be eliminated from body through urine (16%) and feces (60%). Carvedilol is a weak base and its p*Ka* value is approximately 7.8, which satisfies the criterion for the selection of the drug. The log PC (partition coefficient) value for carvedilol is about 3.967. It indicates that carvedilol has sufficient lipophilicity to pass through the buccal membranes. The t_{max} of carvedilol is 1.2 h (Mollendorff *et al*., 1987) by peroral route, which is long and variable. The dose of carvedilol is 25 mg twice a day, however, a lower effective dose is reported to be approximately 3.125 mg (Michael, 1998). By observing the above points, it is inferred that carvedilol has a need to formulate into buccal patches and the drug is suitable for it.

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MATERIALS AND METHODS

Materials

Carvedilol was a gift sample (Dr. Reddy's Labs, Hyderabad, India), Carbopol 934 and hydroxypropyl-methylcellulose (47 centipoise) (HPMC) were obtained from Cadila Health Care Ltd., (Ahmedabad, India) ethyl cellulose was obtained from Suvidhinath Laboratories, (Baroda, India) and eudragit RS100 was obtained from Rohm Pharma, (Weiterstadt, Germany). Other chemicals used were of analytical grade and procured from S.D. Fine Chemicals (Mumbai, India).

Concentrations of carvedilol were measured with a UV-VIS spectrometer (UV-1601PC, Shimadzu Corporation, Tokyo, Japan). Interaction between carvedilol and polymers was verified using FTIR and UV-VIS spectrometric methods.

Methods

Preparation of the patches

Buccal patches of carvedilol were prepared by solvent casting technique (Anders and Merkle, 1989) using film forming polymers for the patches mentioned in table 1. HPMC polymer (200 mg) was weighed accurately and

dissolved in 2 ml of ethanol. The beaker containing polymer and ethanol was kept aside for 5 min for swelling of the polymer. Further 3 ml of ethanol was added to the above polymer solution and the dispersion was stirred. Then one drop of (0.0294 g) glycerin was added to the polymer solution. Simultaneously carvedilol (15 mg) was accurately weighed and dissolved in 1 ml of ethanol in another beaker. The drug solution was added to the polymer solution and was mixed thoroughly with the help of a magnetic stirrer. The glass mould of size 5×3 cm^2 was placed over a flat surface. The whole solution was poured into the glass mould. Inverted funnel was placed over the mould to avoid sudden evaporation. The mould containing polymeric solution of drug was kept 12 hours at room temperature for drying. After drying, the films were observed and checked for possible imperfections upon their removal from the moulds. They were covered with wax paper and preserved in desiccator till the evaluation tests were performed. These new films were examined in order to select the film having the best characteristics.

Similarly, patches II to VI were prepared. For preparing patches II and III, eudragit was dissolved in 1 ml acetone and HPMC in 6 ml alcohol and the two polymeric solutions were mixed. For preparing patches IV and V, carbopol 934 was placed in 4 ml of water and stirred for 60 min and HPMC was dissolved in 3 ml of water, the two polymeric solutions were mixed. For preparing patch VI, ethyl cellulose and HPMC were dissolved in alcohol. The moulds containing polymeric solutions of drug were kept aside for 12 h at room temperature for drying of patches II, III, and VI, whereas for patches IV and V, the drying time was 72 hours. Similarly dummy patches were prepared, without adding drug. Formulated patches were subjected to the evaluation tests. Patches with any imperfections, entrapped air, differing in thickness, or weight (or) content uniformity were excluded from further studies.

Table 1: Composition of different buccal mucoadhesive formulations containing carvedilol

Formulations	Patch Code					
	I	II	III	IV	V	VI
Carvedilol, mg	15	15	15	15	15	15
HPMC (47 cps), mg	200	100	150	100	150	150
Eudragit-RS 100, mg	-	100	50	-	-	-
Carbopol - 934, mg	-	-	-	100	50	-
Ethyl cellulose, mg	-	-	-	-	-	50
Glycerin (1 drop), g	0.0294	0.0294	0.0294	0.0294	0.0294	0.0294
Ethanol, ml	7	6	6	-	-	7
Acetone, ml	-	1	1	-	-	-
Tween 80, g	-	0.0315	0.0315	-	-	-
Water, ml	-	-	-	7	7	-

HPMC = Hydroxy propyl methyl cellulose

Table 2: Characteristics of buccal mucoadhesive patches containing carvedilol

PC	TN (mm)	WU (mg)	Swelling		TS (kg)		CU	FE
			% weight increase after 30 min	% area increase after 60 min	Dummy patches	Drug loaded patches		
I	0.170	19.53	690.98	41.00	5.440	8.887	87.41	> 300
II	0.146	15.46	533.53	29.00	2.898	5.074	84.28	> 300
III	0.152	13.36	618.01	32.20	3.273	5.334	85.11	> 300
IV	0.212	27.40	697.33	47.66	2.194	4.215	91.05	> 300
V	0.172	28.90	700.75	45.00	2.019	3.714	89.47	> 300
VI	0.156	20.16	554.92	33.16	3.772	5.908	83.69	> 300

PC is patch code (I, II, III, IV, V and VI are formulations). TN, WU, TS, CU, and FE are thickness, weight uniformity, tensile strength, content uniformity and folding endurance, respectively. Each value is an average of five determinations.

Evaluation of the patches

Thickness uniformity of the patches

The thickness of each patch was measured using screw gauge at five different positions of the patch and the average was calculated.

Folding endurance

Folding endurance of the patches was determined (Khanna *et al.,* 1997) by repeatedly folding one patch at the same place till it broke or folded upto 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on five patches.

Uniformity of weight of the patches

Patches sizes of 1x1 cm^2 were cut. The weights of five patches were taken and the weight variation was calculated.

Drug content uniformity of the patches

The patches were tested for the content uniformity. A patch of size 1×1 cm^2 was cut and placed in a beaker. Ten ml of a 0.1 N hydrochloric acid solution was added. The contents were stirred in a cyclo-mixer to dissolve the film. The contents were transferred to a volumetric flask (10 ml). The absorbance of the solution was measured against the corresponding blank solution at 241 nm.

Swelling studies of the patches

Weight and area increase due to swelling were measured (Gua and Cooklock, 1995).

Weight increase due to swelling: A drug-loaded patch of 1x1 cm^2 was weighed on a preweighed cover slip. It was kept in a petridish and 50 ml of phosphate buffer, pH 6.6 was added. After every five min, the cover slip was removed and weighed upto 30 min. The difference in the weights gives the weight increase due to absorption of water and swelling of patch.

Area increase due to swelling: A drug loaded patch size of 1x1 cm^2 was cut and placed in a petridish. A graph paper was placed beneath the petridish, to measure the increase in the area. Fifty ml of phosphate buffer, pH 6.6, was poured into the petridish. An increase in the length and breadth of the patch was noted at five min intervals for 60 min and the area was calculated. The percent swelling, %S, was calculated using the following equation:

$$\%S = \frac{X_t - X_o}{X_o} \times 100$$

where X_t is the weight or area of the swollen patch after time t and X_o is the original patch weight or area at zero time.

Tensile strength of the patches

Tensile strength of the patch was determined with Digital Tensile Tester (DY-20, Adamulthomargy, France 1986). The sensitivity range of the machine is 1 to 10 Newtons. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test patch of size (5×3 cm^2) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the patch was taken directly from the dial reading in Newtons, which was converted into kilograms.

Surface pH

Buccal patches were left to swell for 1 h on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 6.6 under stirring and then poured the solution into the petridish allowed to stand till gelling at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patch (Noha *et al.,* 2003).

Viscosity

Aqueous solutions containing both polymer and plasticizer were prepared in the same concentration as that of patches. A model LVDV-E Brookefield viscometer attached to the helipath spindle number 18 and small sample adaptor was used. The viscosity was measured at 20 rpm at room temperature. The recorded values were the mean of five determinations (Noha *et al.,* 2003).

In vitro release studies of carvedilol patches in phosphate buffer (pH 6.6)

A patch of 1x1 cm^2 size was cut and attached to a glass slide with a few drops of phosphate buffer (pH 6.6). This slide was kept at an angle of 45^o in a 250 ml beaker containing 100 ml of phosphate buffer (pH 6.6) solution. The beaker was kept in circulating water bath in which the temperature was maintained at 37^{o}C. A non-agitated system was selected to eliminate any effect of turbulence on the release rate (Borodkin and Tucker, 1974). Samples were withdrawn periodically after removing the slide from the beaker. The solution was stirred with a glass rod and 5 ml of sample was withdrawn using a graduated pipette, whose tip was attached to a tube with glass wool (as a filter). The slide was quickly reintroduced into the beaker. Five ml of the buffer was replaced immediately and the beaker was kept covered with a petridish to prevent evaporation of the fluid. The samples were taken after every 10 min upto 90 min. and analyzed for drug content at 241 nm. The release studies were conducted for three times and average was determined.

In vivo studies

Buccal absorption test in human volunteers

Buccal absorption test was carried out on three healthy male student volunteers aged between 23 to 25 years (Beckett and Triggs, 1967). Since this test indicates the *prima facei* evidence of buccal absorption of carvedilol,

only three human volunteers (Males) were selected. Before the test, the volunteers were asked to moisten their mouth with a few ml of buffer solution. Twenty five ml of phosphate buffer (pH 6.6) containing 1 mg of the drug was placed in the volunteer's mouth. The volunteers were asked to swirl the solution approximately at 60 swirlings/min. for 5 min. Then the solution was expelled and the mouth was rinsed further. The expelled solutions were combined, suitably diluted, and analyzed at λ_{max} 241 nm using UV-Visible spectrometer.

In vivo patch test in human volunteers

Among 18 male human volunteers selected for this test, 16 were research scholars and 2 were authors. All were of the age between 23 to 35 years. The details of the test and drug were informed to the volunteers and consent was taken from them before the commencement of the work. Permission to carryout this work was obtained from the Institutional Ethics Committee.

A patch of 1 x 1 cm^2 containing 1 mg of carvedilol was cut and fixed on a cellophane paper, which acted as a backing layer so that the drug release will be unidirectional. Before application of the patch, the human volunteers were asked to rinse their mouth thoroughly with water. The patches were applied to the buccal mucosa of human volunteers. After 90 min, the patches were taken out and added to a beaker containing 10 ml of phosphate buffer solution (pH 6.6). The volunteers were directed to rinse their mouth with 10 ml of phosphate buffer solution (pH 6.6). The washing was added to the previous solution. After appropriate dilution, solutions were analyzed for drug content at 241 nm. The results represent the amount of drug remaining unabsorbed.

In vivo patch test in rabbits

In vivo absorption studies were conducted on rabbits, which were procured from the Animal House of J.J. Medical College (Davangere, India). Three male rabbits (Siegel *et al*., 1981) weighing 5.0, 5.5, and 6.0 kg of either sex were used for the release study of the carvedilol. The animals were fasted for overnight with *adlibitum* storing them in individual cages before the experiment was carried out. The approval to carryout the work on animals and human volunteers was given by Institutional Ethics Committee, Bapuji Pharmacy College (Davangere, India).

The rabbits were anesthetized with phenobarbital sodium IP (1 ml containing 200 mg) by intra peritoneal route. Patches of size 1 x 1 cm^2 were cut and fixed on a cellophane paper which acted as a backing layer so that the drug release was made unidirectional and threads tied to it, so that the patches were easily removed from the buccal cavity. After 10 min. of the anaesthetic injection, the patches were placed (separately) in the buccal cavity one at time. After a gap of 2 min. further patches were attached. The patches were taken out at 15, 30, 45, 60, 75, and 90 min for HPMC- Carbopol patch (Patch IV). The process was repeated two more times to validate the result. The patches were dissolved in 10 ml of phosphate buffer, pH 6.6. The drug remained unabsorbed was analyzed at 241 nm.

Ageing

Optimized medicated patches were subjected to stability testing. Patches were placed in a glass beaker lined with aluminium foil and kept in a humidity chamber maintained at 40 $\pm$ 2°C and 75 $\pm$ 5% relative humidity for 1 month. Changes in the appearance and drug content of the stored patches were investigated at the end of every week. The data presented were the mean of three determinations (Gua and Cooklock, 1995).

RESULTS AND DISCUSSION

Drug estimation

Calibration curves of carvedilol in 0.1 N HCl and phosphate buffer (pH 6.6) solutions were obtained at λ_{max} 241 nm with a UV-VIS spectrometer (UV-1601PC, Shimadzu Corporation, Tokyo, Japan). Beer's law obeyed to construct the calibration curve was in the concentration range of 2-10 μg/ml. Analyses were done in triplicate.

Drug-polymer compatibility

IR spectra of carvedilol alone and its combination with polymers are shown in fig. 1. An IR spectrum of pure carvedilol showed the peaks 3345.89 cm^{-1} (N-H, str), 2995.87 cm^{-1} (C-H, str, Sp^2), 2923.56 cm^{-1} (C-H, str, Sp^3), and 1106 cm^{-1} (C-O, str). These peaks can be considered as characteristic peaks of carvedilol and were not affected and prominently observed in IR spectra of carvedilol along with polymers as shown in the fig. 1, indicated no interaction between carvedilol and polymers. Further, the interference was also verified using UV-spectrometric method.

Preparation of the patches

The patches of HPMC (47 cps) were prepared. Further different copolymers like carbopol 934, eudragit RS 100 and ethyl cellulose were added to HPMC. Addition of the plasticizer produced a patch of good strength. Maximum drug (%) was released from HPMC patches in 90 min. Therefore eudragit and ethyl cellulose polymers were added to HPMC by maintaining polymer:drug ratio constant (1:1). By trial methods eudragit 100 mg was found satisfactory. Carbopol 934 was found to possess higher bioadhesion compared to HPMC. By trial methods 100 mg of carbopol 934 was added to HPMC films (patch V) and was considered to be a right candidate. The patches were translucent and visually smooth surfaced.

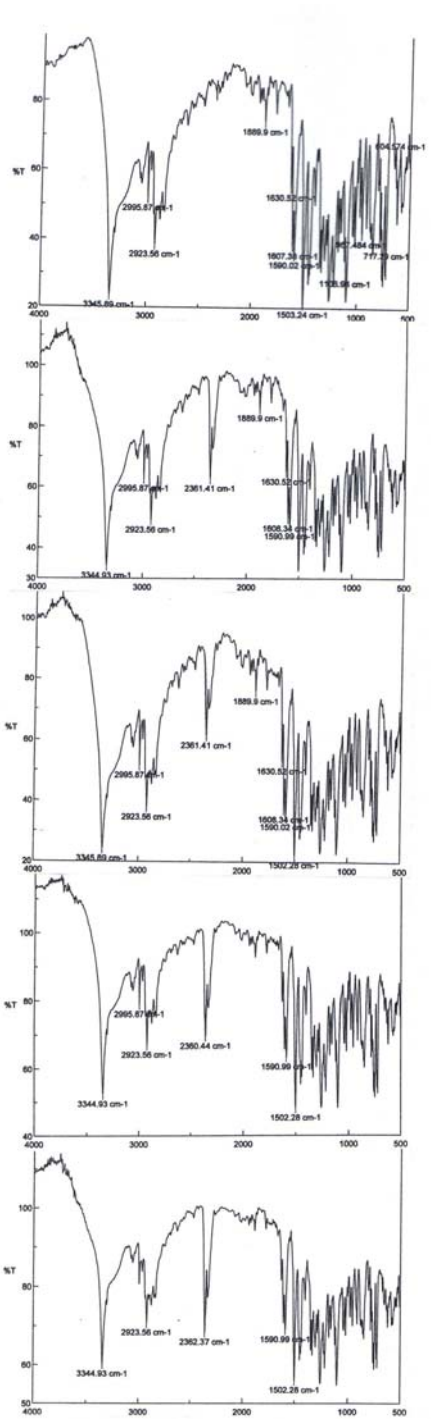

Fig. 1: FTIR of a) carvedilol pure b) carvedilol with hydroxy propyl methylcellulose 47 cps c) carvedilol with eudragit RS 100 d) carvedilol with carbopol 934 e) carvedilol with ethyl cellulose. (from top to bottom)

Evaluation of the patches

Thickness uniformity: All the patches have uniform thickness throughout. Average thickness found was about 0.168 mm.

Folding endurance: Films did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point. Folding endurance did not vary when the comparision was made between plain films and drug-loaded films.

Weight uniformity: Drug loaded patches (1 x 1 cm^2) were tested for uniformity of weight. The patches were found uniform. The average weight of the patch found was about 20.80 mg.

Content uniformity: The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 83.69 to 91.05%. In case of patch VI, the percent recovery was low may be due to ethyl cellulose polymer.

Swelling studies: The swelling of the patches were observed in phosphate buffer solution (pH 6.6) and shown in table 2. Swelling was more pronounced in patches IV and V which contain HPMC and carbopol in a ratio of (1:1) and (1.5:0.5), respectively. Patches II and VI showed less swelling (weight basis), may be due to the presence of Eudragit RS 100 and ethyl cellulose, respectively. These results were in agreement with the increase in area due to swelling.

Tensile strength: The tensile strengths of drug-loaded patches were higher than dummy patches (table 2). This is justified because dissolved carvedilol strengthened the bonding of polymer chains. The tensile strengths of patches were in the order of I > VI > III > II > IV > V. This indicates ethyl cellulose and eudragit produce effective cross-linking. The cross linking is also more with ethyl cellulose and eudragit RS 100 when compared to carbopol 934. Among all the patches studied patch I showed highest tensile strength and patch V showed lowest tensile strength. This must be due to the hydrogen bonding between alcohol groups of drug and polymer. However, patch V in presence of drug showed increased tensile strength.

Surface pH: The surface pH of all formulations was within $\pm$ 0.5 units of the neutral pH and hence no mucosal irritation was expected and ultimately achieve patient compliance.

Viscosity: The viscosities of the solutions were 20.5, 11.1, 9.98, 22.9, 14.5, and 19.8 cps for the solutions of patches I to VI, respectively. Viscosity of the solution of patch IV was high when compared to others, because of the presence of carbopol.

In vitro release: The release data of carvedilol from all the patches are given in fig. 2. A perusal to fig. 2 indicated that the drug release was higher in HPMC (patch I) and HPMC-carbopol combinations (patches IV

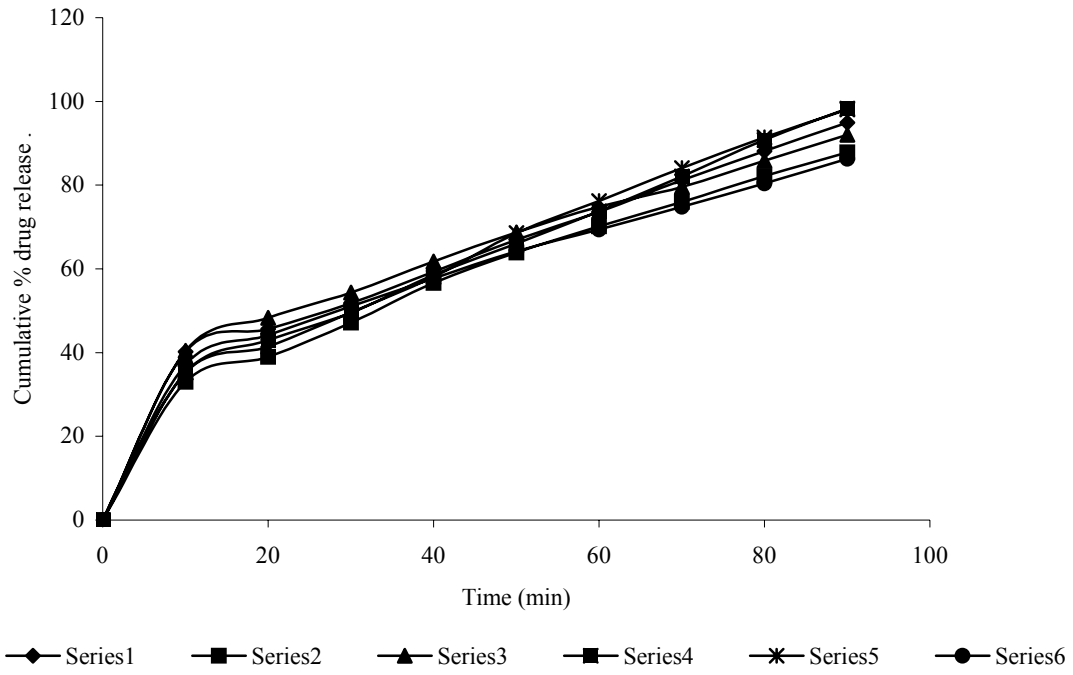

Fig. 2: *In vitro* release of carvedilol from buccal mucoadhesive patches I to VI.

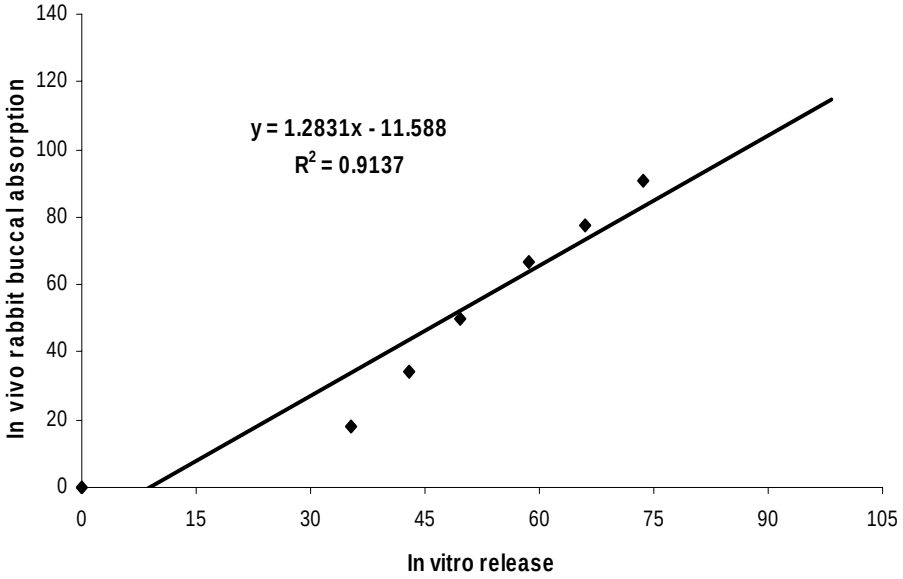

Fig. 3: *In vitro* release vs *in vivo* rabbit buccal absorption of carvedilol from patch IV.

and V). At pH 6.6, carbopol is present in the ionized state and as a result the polymeric network gets loosened comparatively, attributing for the higher drug release (Balamurugan *et al*., 2001). Eudragit retarded the release rate of drug from HPMC patches (patch II and III). An increase in the polymer content was associated with a corresponding decrease in the drug-release rate (Choy *et al.*, 1999). Data of the *in vitro* release were fit into different equations and kinetic models to explain the release kinetics of carvedilol from these buccal patches. The kinetic models used were a zero-order equation, first-order equation, Hixson-Crowell equation, Higuchi release, and Korsmeyer and Peppas models.

The release kinetics of carvedilol followed first order from the patches I to VI except the patches IV and V, which followed zero order. To understand the mechanism of release of carvedilol from the patches the drug release

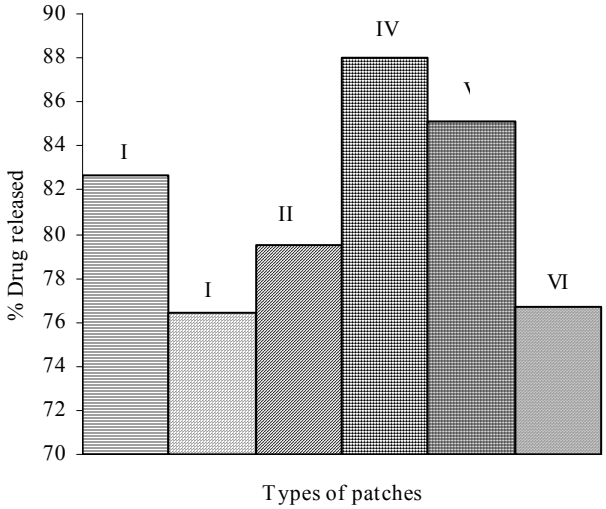

Fig. 4: *In vivo* release of carvedilol from patches I to VI in human volunteers.

data was fit into the Hixon – Crowel and Higuchi's models. The better fit (highest R^2 values) was observed in case of Hixon – Crowel model than Higuchi's model. Hence mechanism of drug release from the carvedilol patches followed is dissolution controlled.

Buccal absorption test in rabbits and humans

a) On human volunteers

i) Buccal absorption test: The buccal absorption test was suggested as an *in vivo* model for passive drug transfer through a lipid membrane. The absorption of drugs increases linearly with the time of contact of the drug solution with the buccal membrane. It was found that a rapid absorption of drug takes place upto 5 min. Buccal absorption test revealed the satisfactory amount (32.86 $\pm$ 2.311 %) of drug absorption. Higher absorption could be possible, with the increased contact time. Absorption of drugs is dependent on the concentration gradient (Michael, 1996) and therefore, it may be possible to increase the amount of absorption by increasing the dose of the drug administered. These results encouraged the designing of buccal adhesive patches of carvedilol.

ii) Patch test on human volunteers: In this test, *in vivo* drug release was estimated than *in vivo* absorption for simplifying the method. Therefore, this test gives an indirect evidence of extent of absorption of drug from the patches. Carvedilol has an intrinsic ability to get absorbed from buccal mucosa, which was evidenced by buccal absorption test. Percentages of drug released in 90 min from ***in vivo*** patch test are given in fig. 4. The study revealed that, the release of carvedilol from the patches was appreciable. The kinetics of *in vivo* drug release from buccal patches in human volunteers (measurement of disappearance) indicated that about 76.45 to 88.02% of the drug was released in 90 min from the patches. During *in vivo* patch test, none of the films had to be removed due to irritation. The films did not cause any discomfort to the volunteers. No side effects like taste alteration, heaviness, dry mouth, or severe salivation were observed. The system claims the potential clinical usefulness in delivering the drug.

b) On rabbits: The *in vivo* release studies were conducted on rabbits for the patch IV, which was selected based on *in vitro* drug release characteristics and stability studies. The method used for this purpose was the measurement of disappearance of the drug from the patches. About 90.85 % of carvedilol was released from HPMC-carbopol patch within 90 min. The release data were processed to understand the kinetic principles (regression analysis). The buccal absorption of carvedilol from rabbit buccal mucosa followed zero order from patch IV.

The concept of *in vitro - in vivo* correlation has been extensively used by pharmaceutical scientists. *In vitro* release studies and their correlation with *in vivo* studies will be helpful to predict therapeutic efficiency of the dosage form. So correlation between *in vitro* release behavior of a drug and its *in vivo* absorption in rabbits is demonstrated experimentally to reproduce therapeutic response. The data of *in vitro* release and *in vivo* rabbit buccal absorption of carvedilol from patches IV were regressed using MS-Excel statistical program to understand *in vitro* and *in vivo* correlation. A good correlation was observed (since R^2 value was 0.9137) for patches IV (fig. 3).

Ageing: Patches that were placed in humidity chamber for ageing studies were withdrawn every week and analysed

for their drug content. Percentage drug present in the patches was determined spectrometrically. Drug content retained in the patches was to the extent of 61.15 to 80.13%. It was found that the drug loss was less though the patches were stored for one month. The patches were also observed for their appearance and texture. These properties did not change in patches IV and V during the period of study. The remaining patches (I to IV) turned little rough probably due to decreased plasticizing property of the patches. Buccal mucoadhesive patches containing carvedilol using carbopol-934 and HPMC polymers showed satisfactory characteristics without being drastically influenced by ageing.

CONCLUSION

Good results were obtained both *in vitro* and *in vivo* conditions for carvedilol films. The buccal release of carvedilol from patches in healthy human beings and rabbits showed a significant improvement. The results can be extrapolated to the human beings as the structure and permeability of buccal membrane of rabbits is similar to that of human beings. Hence the development of bioadhesive buccal formulations for carvedilol may be a promising one as the dose of carvedilol may be decreased and hence side effects may be reduced.

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