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Research Paper

Formulation and Evaluation of Pimozide Buccal Mucoadhesive Patches

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ABSTRACT: Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. Pimozide patches were prepared using HPMC (15 & 47 cPs), carbopol 934, poly vinyl alcohol, and poly vinyl pyrolidone. FTIR and UV spectroscopic methods revealed that there is no interaction between pimozide and polymers. 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 of pimozide-loaded patches in phosphate buffer (pH, 6.6) exhibited drug release in the range of 55.32 % to 97.49 % in 60 min. Data of *in vitro* release from patches were fit in to different equations and kinetic models to explain release kinetics. The models used were zero and first-order equations, Hixon-Crowell, Higuchi and Korsmeyer-Peppas models. *In vivo* absorption of pimozide from all the patches ranged from 47.96 % to 83.42 % in 60 min in human volunteers. *In vivo* studies in rabbits showed 85.97% of drug absorption from HPMC-15 cPs patch in 60 min. Good correlation among *in vitro* release and *in vivo* absorption of pimozide was observed.

KEYWORDS: Pimozide; buccal patches; *in vitro* release; in vivo absorption; evaluation.

Introduction

The buccal mucosa provides a readily accessible route for transmucosal delivery. The oral cavity is being increasingly used for the administration of drugs, which are mainly designed for the contained medicaments through the oral mucosa into the systemic circulation. Buccal mucosa consists of stratified squamous epithelium supported by a connective tissue lamina propia was investigated as a site for drug delivery several decades ago, and the interest in this area for the transmucosal drug administration is still growing. (Narendra et al., 2005) Delivery of drug through buccal mucosa overcomes premature drug degradation within the GI tract, as well as active drug loss due to the first pass metabolism, and inconvenience of parenterals administration. 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. A few drugs, such as metaprolol tartarate (Narendra et al., 2005), ibuprofen (Luana et al., 2004), salbutamol sulphate (Pavankumar et al., 2005), diclofenac sodium (Panigrahi et al., 2005), diltiazem hydrochloride (Semalty et al., 2005), isosorbide dinitrate (Manvi et al., 2006), propranolol hydrochloride (Balamurgan et al., 2001), cetyl pyridinium chloride (Noha et al., 2003), fexofenadine hydrochloride (Thimmasetty et al., 2006) and carvedilol (Madhusudan Rao et al., 2007) have been successfully administered via the buccal route.

Pimozide is a diphenylbutylpiperidine derivative, an antipsychotic agent. It is widely used to treat schizophrenia, chronic psychosis, and Gilles de la Tourette syndrome. Though it is rapidly absorbed after oral administration, the bioavailability of pimozide is 40-50% (Willem et al., 2003) as it undergoes significant first pass metabolism and will be eliminated from body through urine and feces. Pimozide is a weak base and its p*K*a value is approximately 7.32, which satisfies the criterion for the selection of the drug. The log P (partition coefficient) value for pimozide is about 5.3432. It indicates that pimozide has sufficient lipophilicity to pass through the buccal membranes. The t_{max} of pimozide is 4-12 h by peroral route, which is long and variable. The minimum dose of pimozide is 1 mg/day. By observing the above points, it is inferred that pimozide has a need to formulate into buccal patches and the drug is suitable for it.

Materials

Pimozide was a gift sample (Vasudha Pharma Chem Ltd, Hyderabad, India), Carbopol 934 and hydroxypropylmethylcellulose (15 cPs) (HPMC) were obtained from Cadila Health Care Ltd., (Ahmedabad, India). Poly vinyl alcohol (PVA) and poly vinyl pyrolidone

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(PVP) were obtained from S.D. Fine Chemicals Ltd, (Mumbai, India). HPMC (47 cPs) was obtained from Rolex Chemical Industries, (Mumbai, India). Other chemicals used were of analytical grade and procured from S.D. Fine Chemicals (Mumbai, India).

Methods

Drug-Polymer Compatibility

Drug-polymer interaction was observed by IR spectrophotometry. An FTIR study of pure pimozide and physical mixture of pimozide and polymers were performed by KBr dispersion method.

Preparation of patches

Buccal mucoadhesive films were prepared using polymer or polymer blends along with the drug and a suitable solvent. The buccal mucoadhesive films of pimozide were prepared using HPMC 47 cPs and HPMC 15 cps polymers by casting method. HPMC polymer (200 mg) was weighed accurately and placed in 3 ml of ethanol. The contents in the beaker were stirred on magnetic stirrer for 15 minutes for swelling of polymer. Further 3 ml of ethanol was added to the above polymer solution and stirred the dispersion. Then 3 drops (0.0882g) of glycerin were added to the polymer solution. Pimozide (7.5 mg) was weighed and dissolved in 3 ml of ethanol and 3 drops of Tween 80 in an another beaker. The drug solution was added to the polymer dispersion. The whole mixture 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 drug-polymer mixture was poured into the glass mould. The mould was kept in hot air oven for 1 hour at 50^oC for drying and sudden evaporation. After this period, an inverted funnel was placed over the mould overnight to remove the remaining solvent. The film was removed from the mould, packed in wax paper, and stored in a desiccator. Similarly film-II was prepared.

For preparing films-III and IV, PVA was dissolved in 6 ml water. For preparing film-V, carbopol 934 was placed in 5 ml of water followed by stirring for 60 min and HPMC was dissolved in 4 ml of ethanol. The two polymeric solutions were mixed. For preparing film IV, PVA and PVP were dissolved in hot water. The remaining procedure was same as explained earlier. Similarly, dummy patches were prepared without adding drug. Table 1 shows the composition of all prepared patches.

Table 1. Composition of different buccal mucoadhesive formulations containing Pimozide.

Contents	Patch				
	I	II	III	IV	V
Pimozide, mg	7.5	7.5	7.5	7.5	7.5
HPMC (47cPs), mg	*	200	*	*	*
HPMC (15cPs), mg	200	*	*	*	150
PVA, mg	*	*	500	450	*
Carbopol – 934, mg	*	*	*	*	50
PVP, mg	*	*	*	150	*
Glycerin, mg	88.2	88.2	88.2	88.2	88.2
Ethanol, ml	7	7	4	4	4
Tween 80, mg	31.5	31.5	31.5	31.5	31.5
Hot water, ml	*	*	6	6	5

***** No ingredient is added

HPMC = Hydroxypropylmethylcellulose,

PVA = Poly vinyl alcohol,

PVP = Poly vinyl pyrolidone.

Evaluation of the patches

Formulated patches were subjected to the preliminary evaluation tests. Patches with any imperfections, entrapped air, or differing in thickness, weight (or) content uniformity were excluded from further studies.

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 (Kevin et al., 2008) by repeatedly folding one patch at the same place till it broke or folded upto 300 times manually, which is 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 all the patches for five times.

Uniformity of weight of the patches

Patches sizes of 1 × 1 cm^2 were cut. The weights of five patches were taken using Shimadzu balance of sensitivity 0.0001 g (Shimadzu, Tokyo, Japan) 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 in to a volumetric flask (10 ml). The absorbance of the solution was measured against the corresponding blank solution at 279 nm using UV-VIS spectrometer (UV-1601, Shimadzu corporation, Tokyo, Japan).

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 1 × 1 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 5 min, the cover slip was removed, wiped with tissue paper, 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 1 × 1 cm^2 was cut and placed in a petridish. A graph paper was placed beneath the petridish, to measure the increase in the area. After determination of the original film weight, the samples were allowed to swell on the surface of agar plate kept in a hot air oven maintained at 37°C. 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_0 is the original patch weight or area at zero time.

Tensile strength of the patches

Tensile strength of the patch was determined with Universal Strength Testing Machine (Hounsfield, Slinfold, Horsham, U.K). The sensitivity of the machine is 1 gram. It consists of two load cell grips. The lower one is fixed and upper one is movable. The test patch of size (4 × 1 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 kg.

Surface pH

Buccal patches were left to swell for 1 hr 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 used for preparation of patches. A Brookefield viscometer (LVDV-Brookfield Engineering Labs. Inc, USA) 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 pimozide patches in phosphate buffer (*pH *6.6)*

A patch of 3 × 2.5 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° in a 250 ml beaker containing 100 ml of phosphate buffer (pH 6.6) solution. The beaker was kept in circulating water bath (Research and Test equipments, Bangalore, India) in which the temperature was maintained at 37°C. A non-agitated system was selected to eliminate any effect of turbulence on the release rate (Borodkin et al., 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 5 min and analyzed for drug content after necessary dilution with phosphate buffer, pH 6.6 at 279 nm. The release studies were conducted for six times and average was determined.

Buccal absorption test

Buccal absorption test was carried out on three healthy male student volunteers aged between 23 to 25 years (Beckett et al., 1967). Since this test indicates the prima facie evidence of buccal absorption of pimozide, only three male human volunteers 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 once again. The expelled solutions were combined, suitably diluted and analyzed at λ_{max} 279 nm using UV-Visible spectrometer.

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 were used for the study. The animals were fasted for overnight and storing them in individual cages before the experiment was carried out.

The rabbits were anesthetized with combination of 1 ml of phenobarbital sodium IP (200 mg) and 0.5 ml of diazepam (100 mg) by intra peritoneal route. Patches of size 1 × 1 cm^2 were cut and fixed on a cellophane paper which acts as a backing layer so that the drug release was made unidirectional and threads tied to it, so that the patches can be easily removed from the buccal cavity. After 10 min of the anaesthetic injection, the patches were placed (separately) in the buccal cavity one at a time. The patches were taken out at 15, 30, 45, and 60 minutes for HPMC-(15cps) patch (PC I). The patches were dissolved in 10 ml of phosphate buffer, pH 6.6. The drug present in the patch represents the drug remains unabsorbed which was then analysed by measuring its absorbance at 279 nm using phosphate buffer, pH 6.6. The process was repeated three times to validate the result.

In vivo studies in human volunteers

Among 18 male human volunteers selected for this test. All were of the age between 23 to 37 years. A patch of 1 × 1 cm^2 containing 0.5 mg of pimozide 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 for 15 min. After 15 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 279 nm. Second, third, and fourth patches were applied for 30, 45, and 60 min respectively. Every time new patches were used. The results represent the amount of drug remaining unabsorbed.

Ageing

Optimized medicated patches were subjected to short term stability testing. Patches were placed in a glass beaker lined with aluminium foil and kept in a humidity chamber maintained at 40 ± 2°C and 75 ± 5% RH for 1 month as per ICH guidelines. Changes in the appearance and drug content of the stored patches were investigated after storage at the end of every week. The data presented were the mean of three determinations. The study was conducted on three patches to validate the results. (Gua et al., 1995).

Results and Discussion

Drug Estimation

Calibration curves of pimozide in 0.1 N HCl and phosphate buffer (pH 6.6) solutions were constructed at λ_{max} 279 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 10 – 60 μg/ml. Analysis was done in triplicate.

Drug-Polymer Compatibility

IR spectra of pimozide alone and its combination with polymers are shown in Figure 1**.** An IR spectrum of pure pimozide shows the peaks 3122.19 cm^{-1}, 2936.09 cm^{-1}, 1505.17 cm^{-1}, and 1154.19 cm^{-1}. These peaks can be considered as characteristic peaks of pimozide and were not affected and prominently observed in IR spectra of pimozide along with polymers as shown in the Figure 1, which indicated that there was no interaction between pimozide and polymers.

Evaluation of Patches

Thickness uniformity: All the patches have uniform thickness throughout. Standard deviation of all the patches ranged from -0.0054 to -0.0365.

Weight uniformity**:** Drug loaded patches (1 × 1 cm^2) were tested for uniformity of weight. The patches were found

uniform. Standard deviation of the patches ranged from -0.2774 to -0.4324.

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 comparison was made between dummy films and drug-loaded films.

Content uniformity: The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 84.05 to 88.48%.

Swelling studies: The swelling of the patches were observed in phosphate buffer solution (pH 6.6) and data are shown in Table 2. Swelling was more pronounced in patch I which contains HPMC (15 cps). Patches IV showed least swelling (weight basis), may be due to the presence of carbopol 934. The order of films for their swelling properties is IV < III < V < II < I.

Tensile strength: The tensile strengths of drug-loaded patches were higher than dummy patches (Table 2). This is justified because dissolved pimozide strengthened the bonding of polymer chains. The tensile strengths of patches were in the order of V < I < II < IV < III. This indicates poly vinyl alcohol produces effective cross-linking. Low swelling and higher viscosity supports this results.

Surface pH: The surface pH of all formulations was the neutral pH and hence no mucosal irritation was expected and ultimately achieved patient compliance.

Viscosity: The viscosities of the solutions were 13.23, 20.4, 82.85, 74.29, and 31.59 cps for the solutions of patches I to V, respectively. Viscosity of the solution of patch III was highest when compared to others, because of the presence of poly vinyl alcohol.

In vitro release: The release data of pimozide from all the patches were given in Figure 2. A perusal to figure 2 indicated that the drug release was highest in HPMC (PC-I) and HPMC-carbopol combinations (PC-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). When compared to PC-III (PVA alone), drug release rate is more from PC-IV (PVA+PVP) may be due to the presence of PVP. Data of the *in vitro* release were fit into different equations and kinetic models to explain the release kinetics of pimozide from these buccal patches. The release kinetics of pimozide followed zero order from all the patches I to V. The better fit (highest R^2 values) was observed in case of Higuchi's model than Hixon–Crowel model except patch I. Hence mechanism of drug release from the pimozide patches II to V followed are diffusion controlled and drug release from patch I followed dissolution controlled.

Buccal absorption test in rabbits and humans

(a) ***On rabbits:*** The *in vivo* release studies were conducted on rabbits for the patch I, 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 85.97 % of pimozide was absorbed from HPMC (15cps) patch within 60 min. The release data were processed to understand the kinetic principles (regression analysis). The buccal absorption of pimozide from rabbit buccal mucosa followed zero order from patch I.

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 pimozide from patch I was regressed using MS-Excel statistical program to understand *in vitro* and *in vivo* correlation. A good correlation was observed (since R^2 value was 0.9965) for patches I (Figure 3).

Table 2: Characteristics of buccal mucoadhesive patches containing pimozide.

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	0.225	13.68	772.09	38.06	3.376	4.163	84.05	> 300
II	0.190	13.30	767.98	58.36	3.750	4.213	88.02	> 300
III	0.283	29.08	361.90	48.02	5.073	5.340	88.48	> 300
IV	0.268	37.60	248.04	65.76	4.756	5.223	86.88	> 300
V	0.308	13.32	685.36	27.50	3.116	3.690	87.74	> 300

PC is patch code (I, II, III, IV, and V 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.

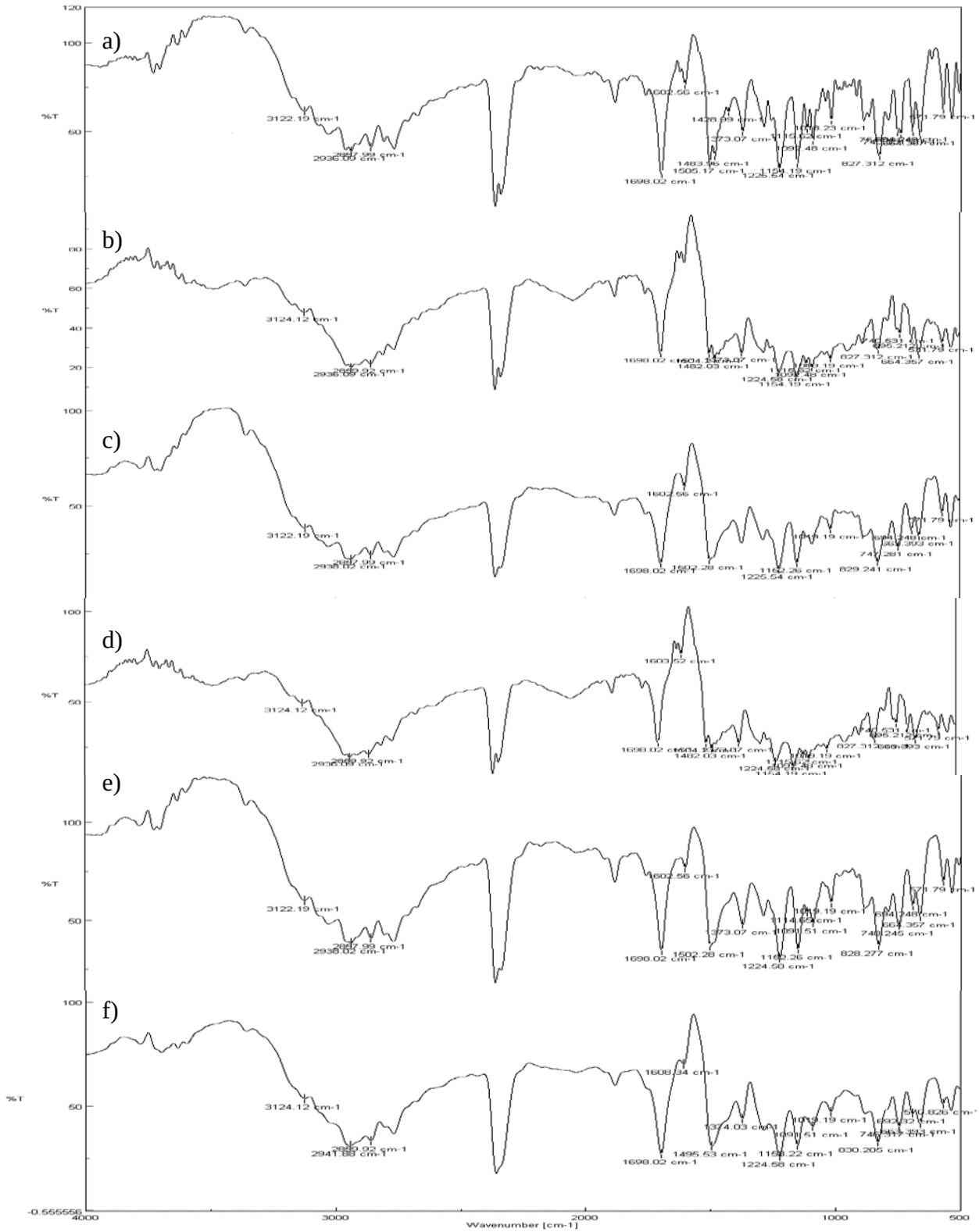

Fig 1. FTIR of a) pimozide pure b) pimozide with hydroxy propyl methylcellulose 15 cps c) pimozide with hydroxy propyl methylcellulose 47 cps d) pimozide with carbopol 934 e) pimozide with PVA f) pimozide with PVP

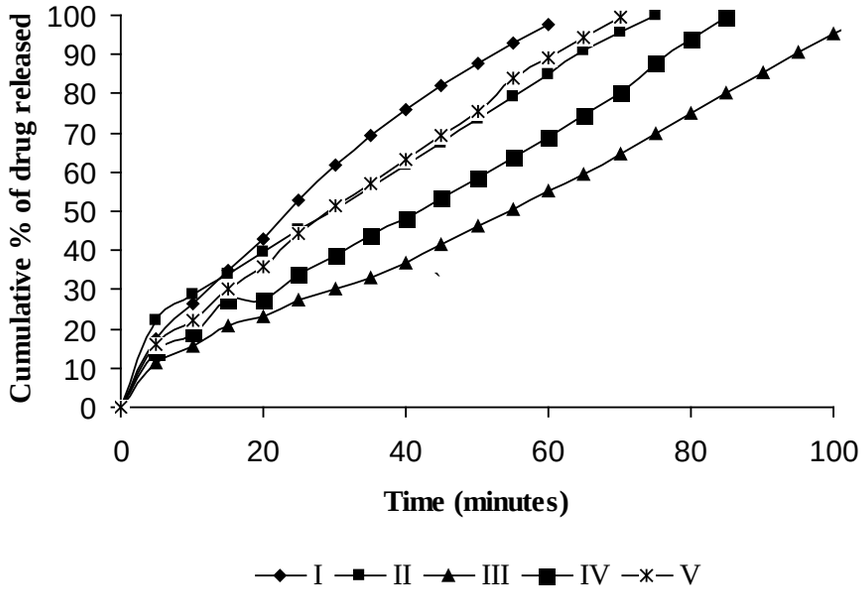

Fig 2. *In vitro* release of pimozide from patches I to V.

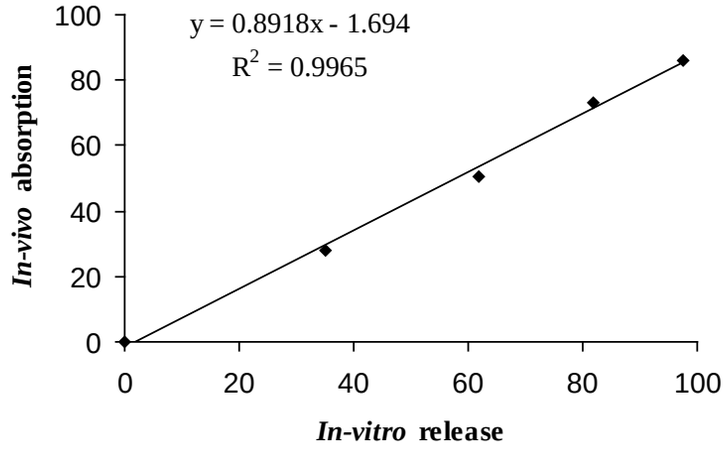

Fig 3. *In vitro* release Vs *in vivo* rabbit buccal absorption of pimozide from patch I.

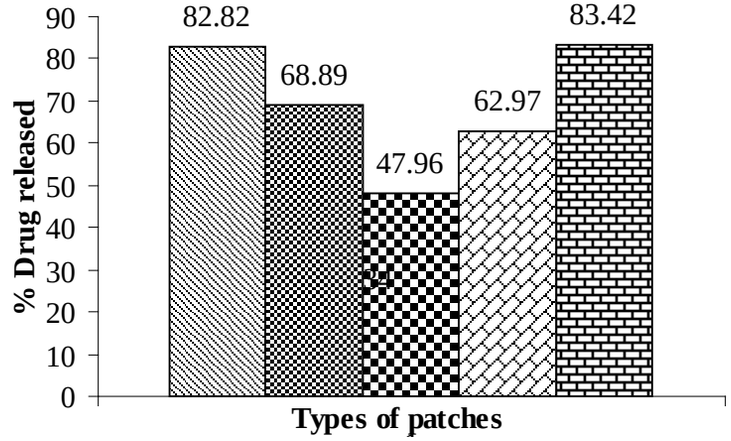

Fig 4. *In vivo* absorption of pimozide from patches I to V in human volunteers.

(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 reveals the satisfactory amount (16.74 $\pm$ 8.3616%) 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 pimozide.

(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. Pimozide has an intrinsic ability to get absorbed from buccal mucosa, which was evidenced by buccal absorption test. Percentages of drug released in 60 min from *in vivo* patch test are given in Figure 4. The study reveals that, the release of pimozide from the patches is appreciable. The kinetics of *in vivo* drug release from buccal patches in human volunteers (measurement of disappearance) indicated that about 47.96 to 83.42 % of the drug was absorbed in 60 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.

Ageing: Patches that were placed in humidity chamber for short time stability studies were withdrawn every week and analysed for their drug content. Percentage drug present in the patches were determined spectrometrically. Decrease in the drug content from the patches ranged from 0.952 to 1.497%. It was found that the drug loss is 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 during the period of study. Buccal mucoadhesive patches containing pimozide using carbopol-934, PVA, PVP, and HPMC polymers showed satisfactory characteristics without being drastically influenced by ageing.

Conclusion

Good results were obtained from *in vitro* and *in vivo* conditions for pimozide films. The buccal release of pimozide 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 pimozide may be a promising one as the dose of pimozide may be decreased and hence side effects may be reduced.

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