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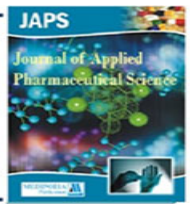

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Design and Evaluation of Tizanidine Buccal Mucoadhesive Patches

Gururaj S. Kulkarni and P.R.Sateesh Babu

ABSTRACT

Mucoadhesive buccal dosage forms are becoming more popular and patient acceptable dosage forms. By this route advantages are many as the dose can be reduced, avoidance of first pass metabolism and liver toxicity, etc. The Tizanidine has first pass metabolism because of this the patient has to take more dose and two to three times in a day. To overcome this problem mucoadhesive patches of tizanidine are prepared and evaluated.

Tizanidine is a non-selective, α-two adrenergic agonist receptor and used as muscle relaxant**.** The oral bioavailability of Tizanidine is 40%, because of first pass metabolism. The polymers used are polyvinyl alcohol and polyvinyl pyrolidine. FTIR and UV spectroscopic methods reveal that there is no interaction between tizanidine and polymers. The patches evaluated for various parameters and results are satisfied. *In vitro* release studies in phosphate buffer (pH, 6.6) exhibited drug release in the range of 71.68 to 97.27% in 90 min. The release of tizanidine from the patches followed first order, Higuchi's model and mechanism diffusion rate limited. *In vivo* buccal absorption studies in rabbits showed 68.85% of drug releases from polyvinyl alcohol patch while it 67.52 to 88.31% within 90 min in human volunteers. Good correlation among *in- vitro* release and *in- vivo* studies observed.

Keywords: Tizanidine, Buccal patches, in vitro release, in vivo release, Evaluation.

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INTRODUCTION

Conventional formulations for local oral delivery are mainly lozenges, mouth paints, oral gels, pastes, and suspensions. Release of drugs from these preparations involves an initial burst of activity, whose level rapidly declines to subtherapeutic concentration (Khanna *et al.*, 1998). 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 (Gua, 1994), propranolol, salbutamol sulphate (Pavankumar *et al.*, 2005), diclofenac sodium (Patil and Rao, 2003), and flurbiprofen (Barsuhn *et al.*, 1988) have been successfully administered via the buccal route. Tizanidine is a skeletal muscle relaxant, and is chemically 5-chloro-N-(4, 5dihydro-1H-imidazol-2yl)-2, 1, 3-benzothiadiazol -4-amine hydrochloride.

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Tizanidine indicated for the treatment of spasticity due to multiple sclerosis and spinal cord injury (Nimje Hemlata *et al.*, 2007). It is widely used as essential muscle relaxant and mild antihypertensive. The oral bioavailability of tizanidine is about 21% mainly due to extensive first-pass metabolism and its mean elimination half-life is approximately 3 h (Granfors *et al.*, 2004). The pK_a of tizanidine is 8.2, which satisfies the criteria for the selection of the drug for buccal patch. The log PC (partition coefficient) of tizanidine is 2.72, which indicates that tizanidine has sufficient lipophilicity to pass through the buccal membranes. The t_{max} of tizanidine is 1 to 4.3 h by peroral route. The dose of tizanidine is 2 to 4 mg twice a day, however, a maximum dose of 36 mg recommended in a day. By observing the above points, it is inferred that tizanidine has a need to formulate into buccal patches.

MATERIALS AND METHODS

Materials

Tizanidine a gift sample (AFD Labs, Bangalore, India), polyvinyl alcohol (PVA) and polyvinyl pyrolidone (PVP), obtained from color corn Pvt ltd Goa. All other chemicals used of analytical grade and procured from S.D. Fine Chemicals (Mumbai, India).

Methods

A) Compatibility study

For determination of drug concentration, Tizanidine measured using UV-VIS spectrometer (UV-1601PC, Shimadzu Corporation, Tokyo, Japan). Interaction between tizanidine and polymers verified using UV-VIS spectrometer and FTIR spectrometer.

A) Preparation of the patches

Buccal patches of tizanidine prepared by solvent casting technique-using film forming polymers for the patches (Table 1) (Anders and Merkle 1989). The FG1 patch prepared as follows. PVA polymer (600 mg) weighed accurately and dissolved in 6 ml of water. The beaker containing polymer and water kept aside for 5 min for swelling of the polymer and the dispersion stirred by using magnetic stirrer. Then one drop of (0.0294 g) glycerin added to the polymer solution. Simultaneously tizanidine (75 mg) accurately weighed and the drug added to the polymer solution mixed thoroughly with the help of a magnetic stirrer. The glass mould of size 5×3 cm^2 placed over a flat surface and the prepared solution poured into the glass mould. The mould containing polymeric solution of drug kept 12 h in a hot air oven at a temperature of 40-45 ^oC for drying. After drying, the films observed and checked for possible imperfections upon their removal from the moulds. They covered with wax paper and preserved in desiccators until the evaluation tests performed. These patches examined in order to select the film having the best characteristics. Similarly, patches FG2, FG3, FPG4, FPG5, and FPG6 prepared. For preparing, patch FG4, propylene glycol used as plasticizer in place of glycerin. For preparing patches FG2 and FPG5, PVP (60mg) used along with PVA. For preparing patches FG3 & FPG6, PVP (300mg) used along with PVA. The formulation code FG indicates that the glycerin used as plasticizer and FPG indicates propylene glycol as plasticizer.

Table. 1: Composition of different mucoadhesive formulations containing Tizanidine.

Formulation patch code	FG1	FG2	FG3	FPG4	FPG5	FPG6
Tizanidine (mg)	75	75	75	75	75	75
PVP (mg)	*	60	300	*	60	300
PVA (mg)	600	600	600	600	600	600
Glycerin (mg)	0.0294	0.0294	0.0294	*	*	*
PG (mg)	*	*	*	0.0289	0.0289	0.0289
Water (ml)	6	6	6	6	6	6

* No ingredient is added, PG = Propylene glycol.

Similarly, dummy patches prepared, by excluding the drug. Formulated patches subjected for evaluation tests. Patches with any imperfections, entrapped air, or differing in thickness, weight (or) content uniformity excluded from further studies. Through out the paper, the term 'patch' used for the entire formulation prepared from the mould and the term 'film' used for the patch of size 1cm^2.

B) Evaluation of the patches

Thickness uniformity of the patches

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

Weight Uniformity of the patches

a film (1 cm2) cut at different places of the patch, the weights of five films taken, and the weight variation calculated.

Swelling studies of the patches

The increase in weight and area due to swelling measured *(Gua JH and Cooklock, 1995).*

Weight increase due to swelling

A drug-loaded film (1 cm^2) weighed on a preweighed cover slip. It kept in a petridish and 50 ml of phosphate buffer, pH 6.6 added. After every five min, the cover slip taken out and weighed upto 60 min. The difference in the weights gives the weight increase due to absorption of water and swelling of film.

Area increase due to swelling

A drug loaded film size of (1 cm^2) placed in a petridish. A graph paper placed beneath the petridish to measure the increase in the area; and about 50 ml of phosphate buffer, pH 6.6, solution poured into the petridish. An increase in the length and breadth of the film noted at five min intervals upto 90 min and the area calculated. The percent swelling, % S 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 film after time t and X_o is the original film weight or area at zero time.

Tensile strength of the patches

Tensile strength of the patch determined with Universal strength testing machine (Baichwal, 1984). The sensitivity of the machine is 1 gm. It consists of two load cell grips. The lower one is fixed and upper one is movable. The test patch of size (5 × 3 cm^2) fixed between these cell grips and force gradually applied till the patch breaks. The tensile strength of the patch taken directly from the dial reading in Newtons, which is converted into kilograms.

Drug content uniformity of the patches

The patches tested for the content uniformity. A film of size (1 cm^2) cut and placed in a beaker and about 100 ml of phosphate buffer, pH 6.6 solution poured to dissolve the patch (Samuelav *et al.,* 1979). The absorbance of the solution measured against the corresponding blank solution by UV spectrometer at 320 nm.

Folding endurance

Folding endurance of the patches determined 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 (Khanna *et al.,* 1997). The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance.

Surface pH

Buccal patches left to swell for 1 hour on the surface of an agar plate prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer, pH 6.6, solution under stirring and then poured the solution into the petridish allowed to stand until gelling at room temperature. The surface pH 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 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 used. The viscosity measured at 20 rpm and at room temperature (Noha *et al*., 2003).

In vitro release studies of tizanidine patches in phosphate buffer, (pH 6.6), solution

A film (1 cm^2) attached to a glass slide with a few drops of phosphate buffer, pH 6.6, solution. This slide kept at an angle of 45^o in a 250 ml beaker containing 100 ml of phosphate buffer, pH 6.6, solution. The beaker kept in circulating water bath in which the temperature maintained at 37 ^oC. A non-agitated system selected to eliminate any effect of turbulence on the release rate (Raghuraman *et al.,* 2001). At predetermined intervals; samples withdrawn, after removal of slide in each interval time from the beaker. The solution stirred with a glass rod and 5 ml of sample withdrawn using a graduated pipette, whose tip attached to a tube with glass wool (as a filter). The slide quickly reintroduced into the beaker. Five ml of the phosphate buffer, pH 6.6, solution replaced immediately and the beaker kept covered with a petridish to prevent evaporation of the fluid. The samples taken after every 10 min upto 90 min. and analyzed for drug content at 320 nm. The release studies conducted for three times and average determined.

In vivo studies

i) Buccal absorption test of tizanidine in human volunteers

Buccal absorption test carried out on three healthy male volunteers aged between 23 to 25 years (Beckett and Triggs, 1667). Since this test indicates the *prima facei* evidence of buccal absorption of tizanidine, only three human volunteers selected. Before the test, the volunteers asked to moisten their mouth with a few ml of buffer solution. Twenty-five ml of phosphate buffer, pH 6.6, solution containing 5 mg of the drug placed in the volunteer's mouth. The volunteers asked to swirl the solution approximately at 60 swirlings/min, for 5 min. Then the solution expelled and the mouth rinsed further. The expelled solutions combined, suitably diluted and analyzed at 320 nm using UV-Vis spectrometer.

ii) In vivo patch test in human volunteers

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

A film (1 cm^2) containing 5 mg of tizanidine 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 asked to rinse their mouth thoroughly with water. The patches applied to the buccal mucosa of human volunteers. After 90 min, the patches taken out and added to a beaker containing 10 ml of phosphate buffer, pH 6.6, solution. The volunteers directed to rinse their mouth with 10 ml of phosphate buffer, pH 6.6, solution. The rinsed solution added to the previous solution. After appropriate dilution, solutions analyzed for drug content at 320 nm. The results represent the amount of drug remaining unabsorbed.

iii) In vivo patch test in rabbits

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

The rabbits anaesthetized with phenobarbital sodium IP (1 ml containing 200 mg) and diazepam 0.5 ml (1 ml containing 100 mg) by intra peritoneal route. Films (1 cm^2) cut and fixed on a cellophane paper which acts as a backing layer so that the drug

release will be unidirectional and threads tied to it, so that the films can be easily removed from the buccal cavity. After 10 min of anesthetic injection, the films placed (separately) in the buccal cavity one at time. After a gap of 2 min, further films attached. The films taken out at 15, 30, 45, and 60 min for PVA film (Patch FG1). The process repeated for two more times. The films dissolved in 10 ml of phosphate buffer, pH 6.6, solution, then diluted suitably and the drug remained unabsorbed analyzed at 320 nm.

Ageing

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

RESULTS AND DISCUSSION

Drug Estimation

Calibration curve of tizanidine in phosphate buffer, pH 6.6, solution obtained at 320 nm using a UV-VIS spectrometer. Beer's law obeyed in the concentration range of 4 – 20 μg/ml. Analyses done in triplicate.

Drug-Polymer Compatibility

The IR spectra of pure tizanidine, pure polymer and in combination of tizanidine with polymers are shown in Figure 1 to Figure 5**.** An IR spectrum of pure tizanidine shows the peaks at 3075.9, 3245.61, and 1644.98 cm $^{-1}$. These peaks can be considered as characteristic peaks of tizanidine and not affected and prominently observed in IR spectra of tizanidine along with polymers as shown in the Figure 1 to Figure 5, which indicates there is no interaction between tizanidine and polymers. Further, the interference also verified using UV- spectrometric method.

Evaluation of patches

Thickness uniformity

All the patches have uniform thickness throughout. Average thickness found 0.222 ± 0.0084 mm (Table 2).

Weight uniformity

Drug loaded films (1 cm^2) tested for uniformity of weight. The patches found uniform. The average weight of the patch found about 42.0 ± 8.75 mg (Table 2).

Swelling studies

The swelling of the patches observed in phosphate buffer, pH 6.6, solution and represented in Table 2**.** Swelling more pronounced in patches FG2 and FPG5, which contain PVA and PVP in a ratio of 1:0.1. Patches FG1 and FPG4 showed less swelling (weight basis) might be due to the absence of PVP. These results in agreement with the increase in area due to swelling.

Tensile strength

The tensile strength of drug-loaded patches higher than dummy patches (Table 2). This is justified because dissolved tizanidine strengthened the bonding of polymer chains. The tensile strength of patches in the order of FPG6 > FG3 > FG2 > FPG5 > FG1 > FPG4, which indicates that as the concentration of PVP increases the tensile strength also increased with effective cross linking.

Content uniformity

The results of content uniformity indicated that the drug uniformly dispersed. Recovery possible to the tune of 88.38 to 92.66%. In case of patch FG1 & FPG4, the percent recovery low which may be due to PVA polymer alone (Table 2).

Surface Ph

The surface pH of all tizanidine patches checked by pH paper on agar plate. The surface pH of all formulations within ± 0.5 units of the neutral pH and hence no mucosal irritation expected and ultimately achieve patient compliance.

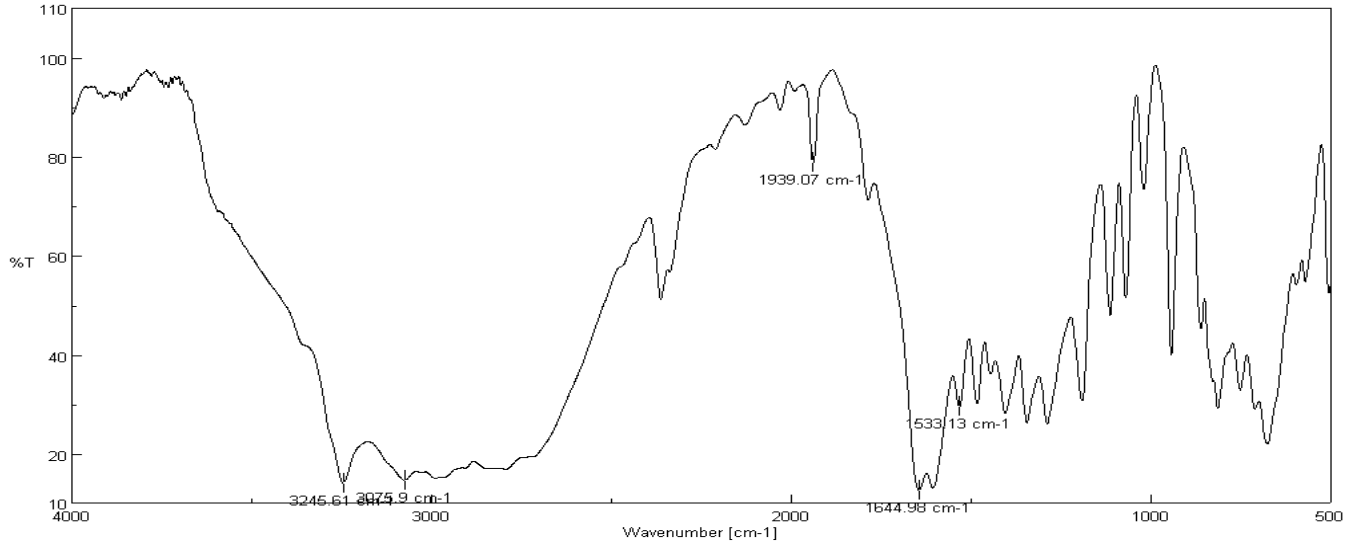

Fig. 1: IR Spectrum of Tizanidine pure.

Table. 2: Characteristics of buccal mucoadhesive patches containing tizanidine.

PC	TN (mm)	WU (mg)	Swelling		TS (kg)		CU	FE
			% weight increase (60 min)	% area increase (90 min)	Dummy patches	Drug loaded patches		
FG1	0.212	34.67	180.37	61.67	4.14	4.84	91.45	> 300
FG2	0.220	38.83	207.62	79.00	4.09	4.82	88.38	> 300
FG3	0.240	52.67	197.46	87.00	4.96	5.63	90.78	> 300
FPG4	0.210	34.33	184.40	60.00	4.18	4.51	92.66	> 300
FPG5	0.222	38.67	203.38	77.00	4.23	4.80	89.71	> 300
FPG6	0.230	52.83	194.30	84.00	5.07	5.68	90.25	> 300

PC is patch code (FG1, FG2, FG3, FPG4, FPG4, FPG5 and FPG6 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

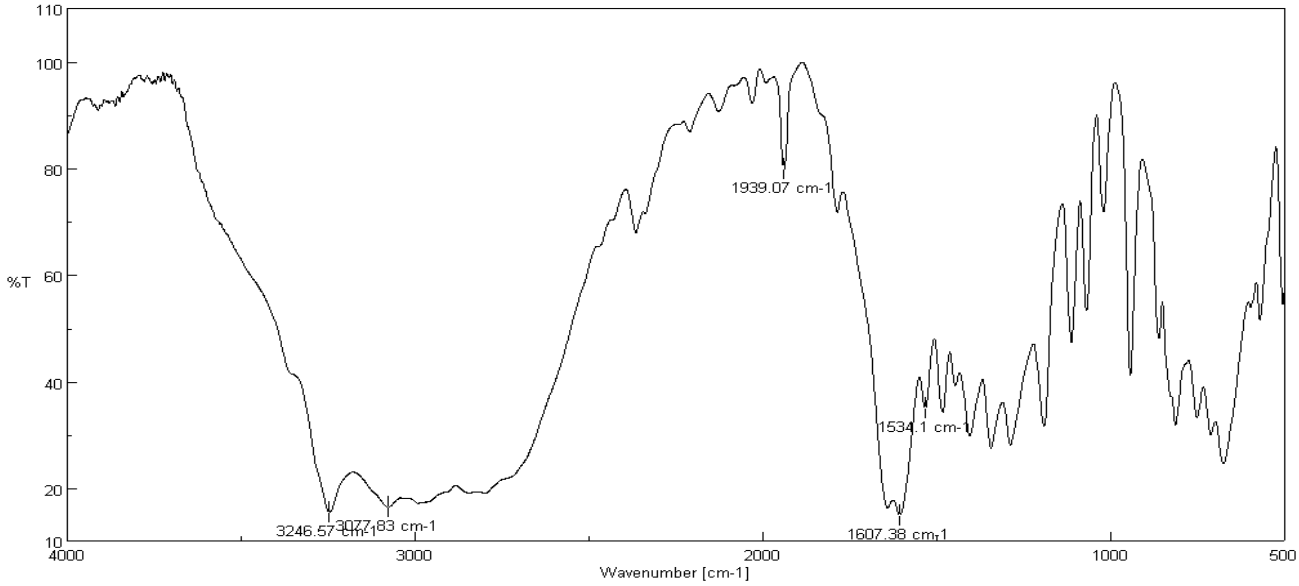

Fig. 2: IR Spectrum of PVA + Tizanidine.

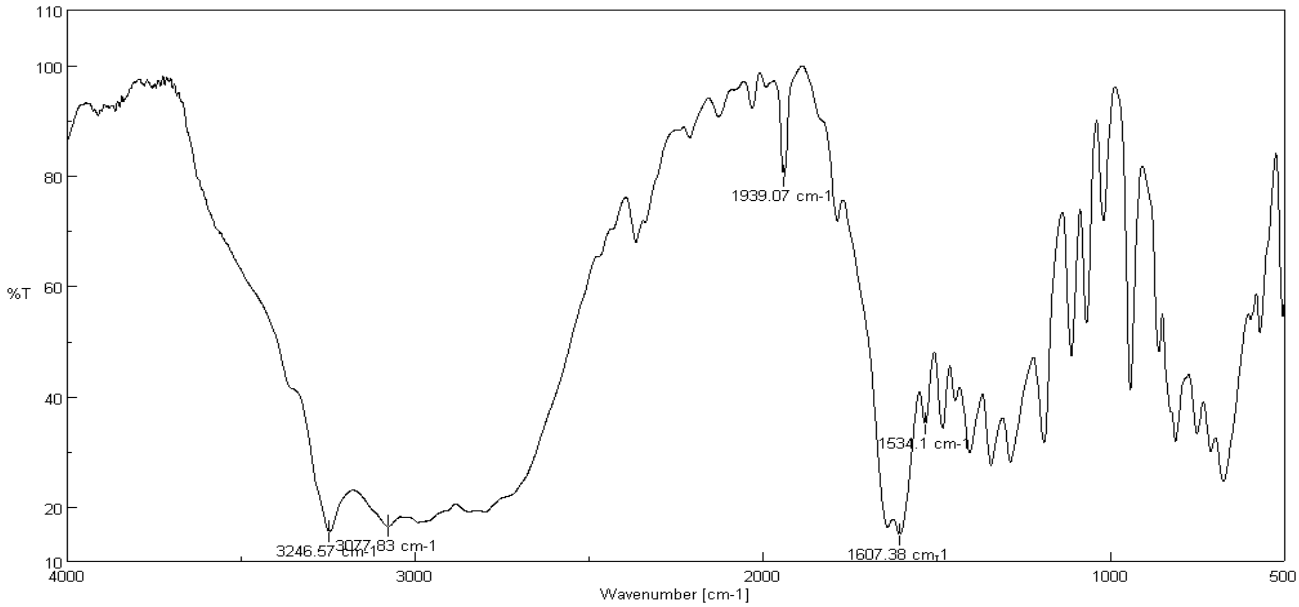

Fig. 3: IR Spectrum of PVP + Tizanidine.

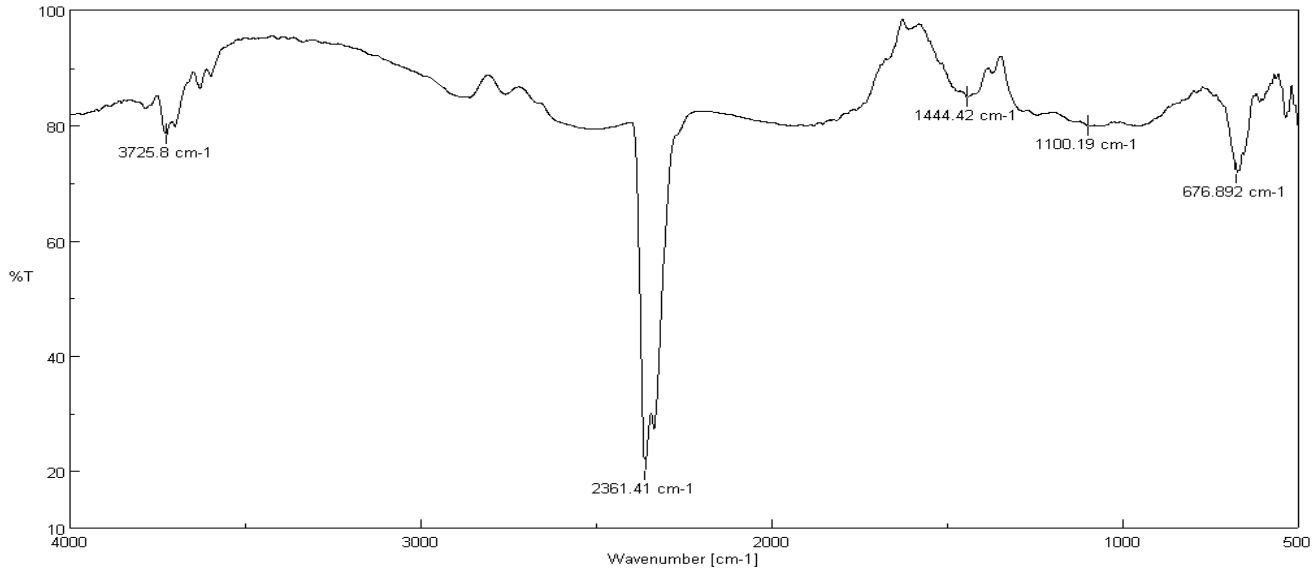

Fig. 4: IR Spectrum of PVA pure.

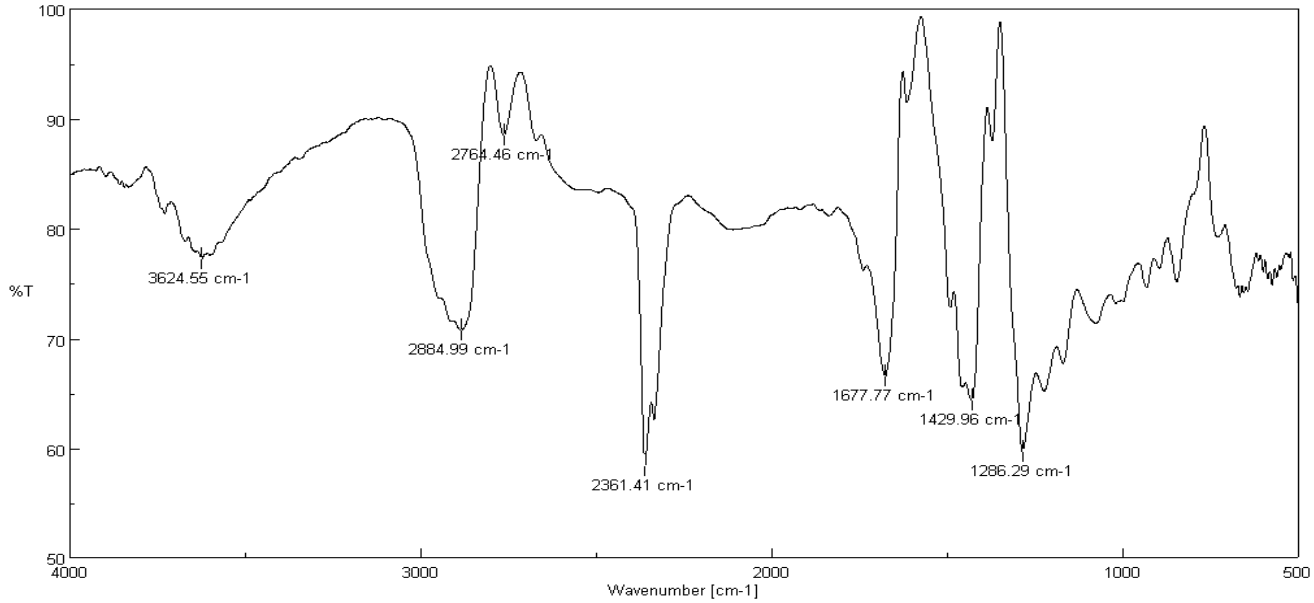

Fig. 5: IR Spectrum of PVP.

Folding endurance

Films did not show any cracks even after folding for more than 300 times. Hence it taken as the end point. Folding endurance did not vary when the comparison made between plain films and drug-loaded films. This study indicates that all formulations had good patch properties (Table 2).

Viscosity

The viscosities of the solutions 85.71, 82.78, 102.72, 82.78, 85.78 and 102.72 cps for the solutions of patches FG1 to FPG6, respectively. Viscosity of the solution of patch FPG3 and FPG6 high when compared to others, because of the presence of PVP in high concentration.

In vitro release

The release data of tizanidine from all the patches given in Figure 6. A perusal to Figure 6 indicated that the release of tizanidine slower in patches FG1 and FPG4, may be due to the single polymer PVA (absence of PVP), in comparison to other patches. The faster release of drug found to be in the patch with high concentration of PVP (FPG6 > FG3 > FPG5 > FG2). Data of the *in vitro* release fit into different equations and kinetic models to explain the release kinetics of tizanidine from these buccal patches. The release kinetics of all tizanidine patches followed first order kinetics. To understand the mechanism of drug release from the patches, the data of drug release fit into the Hixon- Crowell cube root law and Higuchi's models.

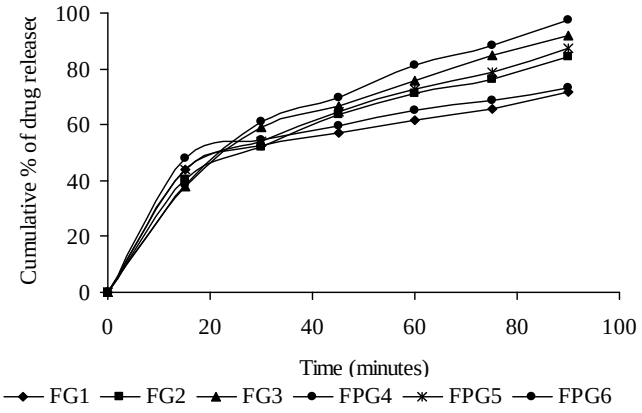

Fig. 6: *in Vitro* Release of Tizanidine from Buccal Mucoadhesive Patches FG1 TO FPG6.

The better fit (highest R^2 values) observed in case of Higuchi's model than Hixon-crowell model. Hence, mechanism of drug release from the tizanidine patches followed is diffusion controlled.

Buccal absorption test in rabbits and humans

a) On human volunteers

i) Buccal absorption test

The buccal absorption test 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 found that a rapid absorption of drug takes place upto 5 min. Buccal absorption test reveals the satisfactory amount (25.54 $\pm$ 0.7580 %) of drug absorption. Higher absorption could be possible, with the increased contact time. Absorption of drugs is dependent on the concentration gradient and therefore, it may be possible to increase the amount of absorption by increasing the dose of the drug administered (Michael *et al.*, 1996). These results encouraged the designing of buccal adhesive patches of tizanidine.

ii) Patch test on human volunteers

In this test, in vivo drug release 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. Tizanidine has an intrinsic ability to get absorbed from buccal mucosa, which evidenced by buccal absorption test. Percentages of drug released in 90 min from in vivo patch test are given in Figure 8. The study reveals that, the release of tizanidine from the patches is appreciable. The kinetics of in vivo drug release from buccal patches in human volunteers (measurement of disappearance) indicated that about 67.52 to 88.31 % of the drug released in 90 min from the patches. During in vivo patch test, none of the patches had to be removed due to irritation. The patches did not cause any discomfort to the volunteers. No side effects like those that taste alteration, heaviness, dry mouth or severe salivation observed. The system claims the potential clinical usefulness in delivering the drug.

(b) On rabbits

The *in vivo* release studies conducted in rabbits for the patch FG1, which selected based on *in vitro* drug release characteristics and stability studies. The method used for this purpose the measurement of disappearance of the drug from the patches. About 68.85 % of tizanidine released from PVA (FG1) patch within 90 min. The release data processed to understand the kinetic principles (regression analysis). The buccal absorption of tizanidine from rabbit buccal mucosa followed first order from patch FG1.

Pharmaceutical scientists have extensively used the concept of *in vitro - in vivo* correlation. *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 demonstrated experimentally to reproduce therapeutic response. The data of *in vitro* release and *in vivo* rabbit buccal absorption of tizanidine from patch FG1 regressed using MS-Excel statistical program to understand *in vitro* and *in vivo* correlation. A good correlation observed (R^2 = 0.9997) for the patch FG1 (Figure. 7).

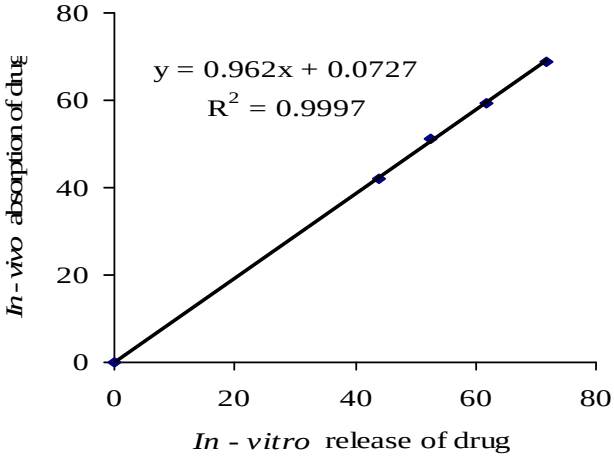

Fig. 7: *In vitro* and *in vivo* Comparison of Tizanidine Buccal Patch of FG1 Formulation.

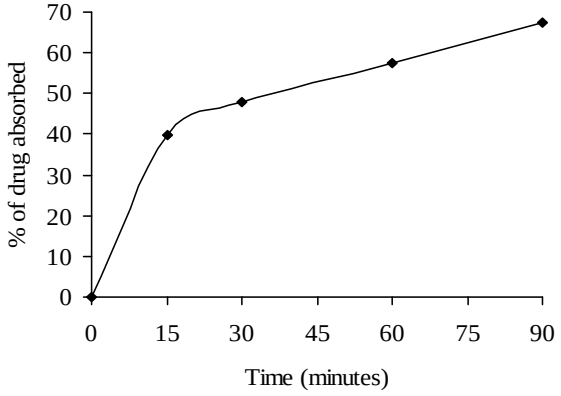

Fig 8: *In-vivo* absorption of tizanidine in human buccal mucosa from patch FG1.

Ageing

The prepared patches subjected to ageing studies. The Patches placed in humidity chamber at 37 $\pm$ 2^{o}C and 75 $\pm$ 5 % RH. The patches withdrawn every week and analysed for their drug content. Percentage drug present in the patches determined spectrometrically. Drug content retained in the patches after 30 days, is to the extent of 85.75 to 88.0%. It found that the drug loss is less though the patches stored for one month. The patches also observed for their appearance and texture. These properties did not change in patches during the period of study.

CONCLUSION

Mucoadhesive patches containing tizanidine using PVA and PVP polymers showed satisfactory mucoadhesive characteristics. Good results obtained for both *in vitro* and *in vivo* studies for tizanidine patches. The buccal release of tizanidine 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 tizanidine may be a promising one as the dose of tizanidine may be decreased and hence side effects may be reduced.

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