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DEVELOPMENT AND CHARACTERIZATION OF BUCCOADHESIVE PATCHES OF PENTAZOCINE

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Buccoadhesive pacthes for the delivery of pentazocine to the buccal mucosa were prepared using polymers like CMC, HPMC K4M and combination of Carbopol 974P and PVA. Patches were evaluated for physical characteristics, in vitro bioadhesion strength, swelling rate of polymers and in vitro drug release characteristics in pH 6.6 phosphate buffer. The formulations showed significant bioadhesive properties and exhibited prolonged and controlled drug release profiles. The type of the polymer and the patch significantly affected the rate and extent of drug release.

Keywords : *Pentazocine; Pentazocine hydrochloride; Buccoadhesive patch; Disperse matrix system; Controlled drug release*

Introduction

Pentazocine (PZ) is used as a potent analgesic in chronic pains as in cancer pain, traumatic pain and post operative pain etc. As for the guidelines of WHO for cancer pain management, analgesics like pentazocine are the drugs of choice (1). Pain prevention in chronic cancer is possible only with time-contingent dosing. Agonist/antagonist opiates, due to their ceiling effects and some associated side effects due to fluctuations in blood level etc. face many problems for administration in conventional dosage forms. These drawbacks can be overcome by designing a suitable rate controlled and prolonged release drug delivery system of PZ. Recently significant interest has been shown in the development of bioadhesive dosage forms for buccal mucosal delivery of drugs (2). This route is easily accessible, has good patient compliance, avoids the first pass metabolism and close contact with the adhesion surface of the oral cavity, increases the absorptions of drugs and results in an enhanced bioavailability.

Shorter elimination half life (3,4 hrs) of PZ, its frequent dosing through conventional formulations, and its low peroral bioavailability due to high first pass metabolism makes it a suitable candidate for incorporation in buccoadhesive dosage forms. Since no report was available in literature on buccoadhesive dosage forms of PZ, an effort has been made by the present authors to design, develop and characterize some buccoadhesive patches of PZ using some selective bioadhesive polymers like hydroxypropyl methylcellulose K4M (HPMC K4M), carbopol 974P CP 974P), carboxymethyl cellulose (high viscosity) (CMC) and polyvinyl alcohol (PVA). Such formulations are expected to perform therapeutically much better because of improved bioavailability of PZ due to avoidance of its first pass metabolism and least side effects due to controlled blood levels with minimum fluctuations as compared to its conventional formulations. This paper describes the development and characterization of a buccoadhesive patch type of dosage form of pentazocine.

Materials

Pentazocine and pentazocine hydrochloride (PZH) (Ranbaxy, India), CP 974P (B.F. Goodrich), CMC (high viscosity) (BDH Poole, UK), PVA Mol wt. 125,000 (Sd. Fine Chem., India), HPMC K4M (Dow Chemicals, France), potassium dihydrogen orthophosphate (Glaxo, India), sodium hydroxide and isopropyl alcohol (E. Merck), Glycrol (Polypharm, India), 3M Transfer Adhesive 3M Foam Tape (3M Pharmaceuticals, USA) and double distilled water were used. All chemicals used were of analytical grade.

Table 1. Formula for the preparation of buccoadhesive patches/disperse matrix systems of pentazocine/pentacocine hydrochloride

S. No	Batch No.	Polymer (s) and their amount (g)	Drug	Plasticizer (Glycerin) Concentration (%w/w of the polymer content)	Drug Loading (g)
1.	A_1	CMC 2	Pentazocine hydrochloride	10	0.4
2.	A_2	CMC 2	Pentazocine	10	0.4
3.	A_2	HPMC K4M 2	Pentazocine	10	0.4
4.	A_3	CP:PVA 0.73:1.47	Pentazocine	10	0.4

Methods

Preparation of buccoadhesive patches

Buccoadhesive patches/disperse matrix systems (DMS) of PZ and PZH were fabricated using CMC, HPMC K4M, CP 974P and PVA in drug: polymer ratio 1:5.

Patches were prepared of two types-one was a translucent patch containing PZH embedded in CMC (Batch A_1) and the others, hereafter called as disperse matrix systems (DMS). DMS were opaque patches containing PZ base dispersed either in CMC (Batch A_2), in HPMC K4M (Batch A_3) or in CP 974P : PVA (1:2) (Batch A_4) (Table 1). Each patch contained glycerol 10% w/w (with respect to polymer weight) used as plasticizer. The glass mould lined inside with release liner, used for casting of patches was fabricated in our laboratory and was of the size 10x10x2 cm^3. The patches were prepared by the following methods.

Patch A_1 : CMC (20 mg per cm^2 area of patch) was dispersed in distilled water by stirring over a magnetic stirrer. The drug PZH (4mg per cm^2 area of the patch) dissolved in distilled water was added to the above polymeric dispersion and stirred until a uniform dispersion was obtained. Glycerol was added and mixed uniformly. The dispersion was deaerated under vacuum, cast in a glass mould and kept in hot air oven at 45±1°C for 24 hours. After drying, patch was removed and wrapped in an aluminium foil and storred in a desiccator.

Patch A_2 : CMC (20 mg/cm^2) was dispersed in distilled water by stirring over a magnetic stirrer. PZ (4 mg/cm^2) dissolved in 12 ml of isopropyl alcohol was added to above polymeric dispersion and stirred until a uniform dispersion was obtained. Glycerol was added and mixed uniformly. Deaeration, casting, drying and storing was done similarly as mentioned for Patch A_1.

Patch A_3: PZ (4mg/cm^2) was dissolved in 12 ml of isopropyl alcohol. A weighed amount of HPMC K4M (20mg/cm^2) was added to the drug solution. Thereafter, measured volume of distilled water was added to it and stirred over the magnetic stirrer until a uniform dispersion was obtained. Glycerol was added and mixed uniformly. Deaeration, casting, drying and storing was done similarly as mentioned for Patch A_1.

Patch A_4: PVA (13.33 mg/cm^2) was dissolved in distilled water by heating at 60°C and stirring over the magnetic stirrer until a uniform solution was obtained. CP 974P (6.67 mg/cm^2) was dissolved separately in distilled water. PZ (4mg/cm^2) dissolved in 12 ml of isopropyl alco-

hol was added to the solution of CP 974P and mixed uniformly. Thereafter, PVA solution was added to this mixture and stirred until a uniform dispersion was obtained. Glycerol was added and mixed uniformly. Deaeration, casting, drying and storing was done similarly as mentioned for Patch A_1.

All the patches were cut into 1 cm^2 surface area using a punching machine. Each unit of the patch was sticked with a backing layer (3M Foam Tape) of 1 cm^2 surface area and thus the assembled buccoadhesive patch was ready for further studies.

Evaluation of buccoadhesive formulation

Thickness uniformity : The thickness of 10 randomly selected unassembled patches /DMS were measured, at different points of each formulation, using screw gauge and average thickness was recorded.

Weight uniformity : The uniformity of weight was determined by weighing 10 randomly sampled unassembled patches/DMS on electronic balance and average weight was recorded.

Drug content uniformity : Randomly selected 10 unassebled patches/DMS were transferred into a 100 ml volumetric flask containing 50 ml of phosphate buffer 6.6 (prepared by homogeneously mixing potassium dihydrogen orthophosphate solution with sodium hydroxide solution) and stirred for 8 hrs on a magnetic stirrer. The volume was made up to 100 ml and after suitable dilution with phosphate buffer, the absorbances were measured in UV spectrophotometer (Shimadzu, Japan) at 278 nm. The concentrations were noted from the standard calibration curve and the average values were calculated.

Swelling index studies : The swelling rate of patch/DMS was evaluated, using (1% w/v) agar gel plate (3) as the simple model of mucosa. 24 units of each assembled buccoadhesive formulation and 6 petridishes with agar gel were used for swelling evaluation. Four preweighed (W_1) pacthes/DMS were placed on agar gel surface in each petridish in such a way that the exposed side of patch/DMS touched the gel surface and backing layer faced uqward (away from the gel surface). The petridishes were kept in an incubator of 37±0.1°C environment. The first petridish was taken out of the incubator at the end of 0.5 hours followed by other petridishes taken out at the end of 1, 2, 3, 4 and 5 hour, respectively. Four swollen patches/DMS from each petridish were removed, weighed (W_2), and swelling indexes were calculated using the formula $[(W_2-W_1)/W_1]$.

In vitro bioadhesion test : Bioadhesion strength of the patches/DMS were examined by the modified procedure of Parodi et al (4) (Fig. 1), using peritoneum of healty albino rats (CF starin) weighing 200-300 g which was removed under sodium pentobarbitone (30 mg/kg) anaesthesia. The peritoneum was washed with saline and was kept in phosphate buffer (pH 6.6) prior to use. A circular piece (surface area 2 cm^2) of peritoneum was cut and glued with cyanoacrylate adhesive on the ground surface of a tissue holder made of plexiglass. Similarly, the patch/DMS was glued to another tissue holder of the same size. Thereafter, the tissue holders with peritoneum and patch/DMS were put in contact with each other with uniform and constant pressure for 5 minutes (preload time) to facilitate adhesion bonding. The tissue holder with peritoneum was allowed to hang on an iron stand with the help of an aluminium wire fastened with the hook provided on the back side of the holder. A preweighed light weight polyprorpylene bottle was attached to the hook on the back side of the formulation holder with aluminium wire. After preload time of 5 minutes, water was added to polypropylene bottle through an i.v. infusion set at a rate of 1 drop/sec till the pacth/DMS detached from the peritoneum. The water collected in the bottle was measured and expressed as weight (gms) required for the detachment.

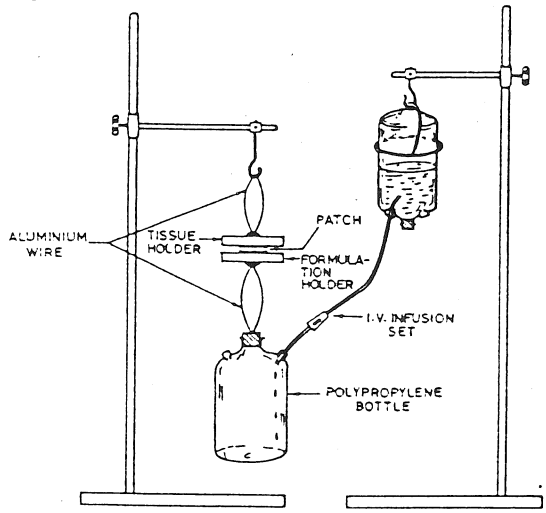

Fig.1. Modified apparatus for *in vitro* bioadhesion Test

In vitro drug release study : All the buccoadhesive patches/DMS were evaluated *in vitro*, in triplicate, using modified Keshary-Chien diffu-

sion cell (Fig.2) in phosphate buffer of pH 6.6. An assembled circular patch/DMS of more than 3.141 cm^2 of surface area was used for evaluation. The 3M transfer adhesive was spread over the rim of the receptor compartment and the exposed surface of pacth/DMS was sticked to it. The surface area of each pacth/DMS thus exposed to receptor fluid for drug release was 3.141 cm^2. The receptor compartment was filled with 17 ml of phosphate buffer (pH 6.6) which served as the elution medium. The whole unit of diffusion cell was placed into a water bath chamber which was finally placed on a magnetic stirrer. The temperature of the bath and thus of the receptor fluid was maintained at 37±0.1°C with the energy controlled hot plate of the magnetic stirrer. The elution medium was stirred with a small star shaped teflon coated magnet at 100 rpm. Samples were collected at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8 and 24 hours. At each sampling time the elution medium was completely withdrawn and immediately replaced with the same volume of prewarmed (37±0.1°C) fresh phosphate buffer. All the collected samples were filtered and analyzed spectrophotometrically at 278 nm. Concentrations were noted from the calibration curve and mean cumulative percent release of drug was calculated.

Table 2. Physical characteristics of prepared patches/disperse matrix systems of pentazocine/pentazocine Hydrochloride

S.No.	Batch No.	Thickness* (mmx10-2)	Weight Uniformity*/cm2 patch/DMS (mg)	Drug Content Uniformity* in 1 cm2 patch/DMS
1.	A_1	18.68±0.12	17.81±0.29	3.95±0.012
2.	A_2	22.90±0.20	38.06±0.96	3.79±0.12
3.	A_3	25.40±0.22	57.70±1.01	4.13±0.18
4.	A_4	22.65±0.15	37.36±1.89	3.90±0.04

*(Mean±SD) n=10

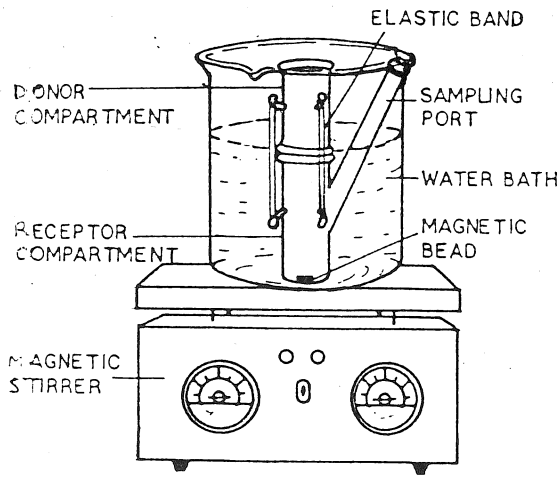

Fig.2. Modified Keshary-Chien diffusion cell used for *in vitro* release study of patches

Results and Discussion

Fabricated patches/DMS were found having smooth and uniform surface with good flexibility. CMC patches were translucent while DMS were opaque. They were evaluated for the following physical characteristics results of which are tabulated in Table 2.

Thickness : The patches/DMS showed uniformity in thickness throughout and the values were found between $18.68x10^{-2}$ –$25.40x10^{-2}$ mm.

Weight uniformity : Weight uniformity results of all the buccoadhesive patches and DMS indicated no significant difference in the weight of individual formulation from the average value and variations were found within the limit.

Drug content uniformity : The results indicated that the contents of PZ/PZH in formulations were within the limit of 100±5%.

Swelling studies : As shown in Table 3 and Fig.3, swelling index of fabricated buccoadhesive patches and DMS exhibited swelling rate in the order of

$A_1 > A_2 > A_3 > A_4$.CMC patches (A_1 and A_2) swelled more than the HPMC K4M and CP 974P : PVA (1:2) patches (A_3 and A_4). Results indicate that formulation A_1 exhibited faster swelling and the maximum swelling index was attained in 2 hours. Thereafter, polymer erosion probably stated in the medium and thus resulted in continuous sharp decline in swelling beyond 2 hours. DMS A_3 and A_4 exhibited significantly lower swelling rates than the A_1 and A_2 and not much difference in swelling rate was observed between A_3 and A_4. Though, DMS containing CP:PVA in 1:2 ratio (Batch A_4) showed higher swelling rate than batch A_3 during one hour, this was attributed to the presence of soluble polymer polyvinyl alcohol in batch A_4. Literature reports have shown that soluble material causes greater increase in the matrix swelling than the less soluble material and

Table 3. Swelling index studies of prepared patches/disperse matrix systems of pentazocine/pentazocine Hydrochloride

S. No.	Time (hrs)	Swelling Index (Mean*±SEM)			
		A_1	A_2	A_3	A_4
1.	0.5	4.42±0.06	5.86±0.12	0.56±0.03	1.84±0.15
2.	1.0	13.10±0.70	8.50±0.14	1.42±0.04	1.94±0.06
3.	1.5	16.30±0.02	10.61±0.08	1.99±0.08	1.90±0.13
4.	2.0	17.99±0.08	13.10±0.21	2.50±0.09	2.13±0.08
5.	3.0	14.31±0.04	16.34±0.07	3.42±0.15	2.45±0.13
6.	4.0	11.51±0.07	13.75±0.04	3.80±0.05	3.20±0.02
7.	5.0	9.60±0.05	11.50±0.03	3.75±0.01	3.70±0.08

*Mean of four readings

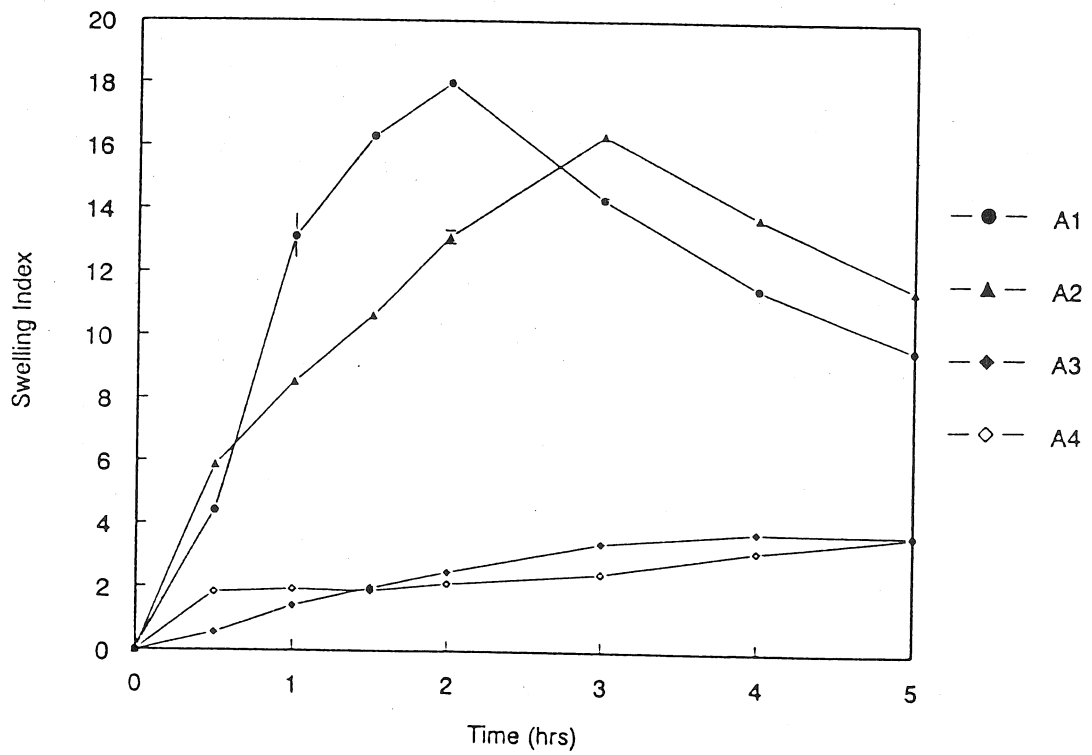

Fig.3. Swelling index studies of patches/disperse matrix systems

exhibits faster release rate (5). Thus, more swelling in batch A_1 was also attributed to the presence of pentazocine as soluble hydrochloride salt in batch A_1 as compared to the presence of insoluble form of pentazocine base in other patches of DMS type.

In vitro bioadhesion study : The bioadhesive strength of different buccoadhesive formulations were investigated to assess the relative difference in the bioadhesive property of various polymers used in the fabrication of formulations. Results are shown in Table 4. The maximum bioadhesive strength was observed with CMC patches (batch A_2 and A_1), and comparatively lower bioadhesive strength was noted with DMS of HPMC K4M (Batch A_3) and CP 974P and PVA combination (Batch A_4).

Table. 4. In-vitro bioadhesion study of prepared patches/disperse matrix systems of pentazocine/pentazocine hydrochloride.

S.No	Batch No	Bioadhesive Strength* (g)
1.	A_1	260±6.0
2.	A_2	290±8.0
3.	A_3	192±6.0
4.	A_4	142±5.0

*(Mean±SEM) n=3

In vitro release study : The *in vitro* release profiles of PZ/PZH from buccoadhesive patches/DMS are shown in Fig. 4. Results indicate that the rate and extent of drug release was significantly affected by the type of polymers and the patch. Buccoadhesive formulations (A_1, A_3 and A_4) exhibited faster though controlled drug release till 8 hours followed by slow and constant drug release till 24 hours. However, DMS A_2, after giving faster drug release till 2 hours which may serve the role of loading dose, provided constantly release slow but controlled drug release profile till 24 hours. The results indicate that the rate and extent of drug release from CMC patch (Batch A_1) was much higher than the patches of DMS type. The cumulative percent release (CPR) of PZH in 24 hours from formulation A_1 was 99.9% as compared to CPR of PZ from DMS containing CMC (Batch A_2) being only 63.2%. The relative difference in the rate and extent of drug release from A_1 and A_2 inspite of the fact that same polymer CMC was used in their fabrication, is attributed to the following facts. Firstly, PZH being more soluble in pH 6.6 phosphate buffer, more solubilized drug molecules easily diffuse out of the swelled polymer in patch A_1, causing initially faster release till 8 hours, followed by decline in release rate beyond 8 hours till 24 hours due to decline in drug content in the formulation. On the contrary, patch A_2 since contained PZ base, which is less soluble in phosphate buffer (pH 6.6) results into less solubilized drug molecules at a time (in comparison to A_1) and thus released slowly from A_2. Higher drug release from A_1 than from DMS A_3 and A_4 may also be explained similarly.

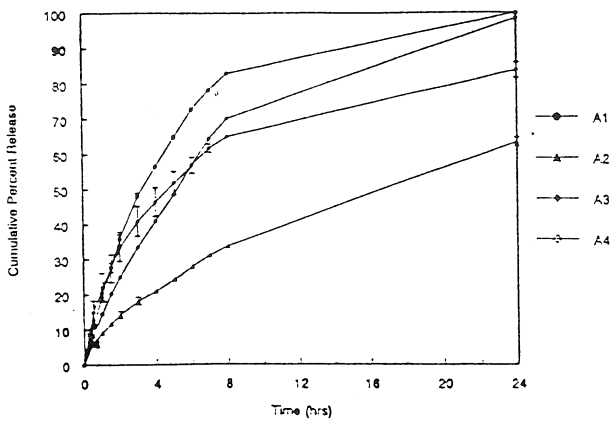

Fig. 4. *In-vitro* release profiles of pentazocine/ pentazocine hydrochloride from different disperse matrix systems/patches in phosphate buffer of pH 6.6

Second reason may be that the increased degree of ionization of carboxyl groups of CMC (anionic polymer) in the environment of pH 6.6 phosphate buffer, may result into formation of complex between the cationic drug i.e. PZ and anionic polymer, i.e. CMC (6), and the complex formation thus results into slow drug release from patch A_2 than A_1. The DMS of HPMC (Batch A_3) showed a slight burst effect in the first hour followed by slow drug release. Batch A_3 though exhibited higher drug release till 6 hours than A_4, but beyond 6 hours formulation A_4 provided higher extent of drug release than A_3 till 24 hours. The overall higher drug release from batch A_4 containing CP 974P : PVA in 1:2 ratio could be attributed to ionization of CP 974P at a pH environment (pH 6.6) higher than its pK_a value of 6. The ionization leading to increased swelling of the polymer causes the drug to diffuse out at a faster rate (7) from formulation A_4 specially in later stages of the study due to involvement of lag period for ionization, relaxation and more water uptake by carbopol polymer. However, in case of DMS A_3, since no uncoiling of polymeric backbone takes place in pH 6.6 environment, HPMC polymer being non-ionic, after an initial burst effect (which may be due to faster release of drug from the surface of the patch), drug is released slowly with almost constant rate and is controlled by the swelling of the polymer, followed by drug diffusion through swelled polymer and then further followed by slow erosion of the polymer.

To examine further the release mechanism of PZ/PZH from patches/DMS matrix systems, the results were analysed according to the following equation (8).

$$M_t/M_\infty = Kt^n$$

The value of n as estimated by linear regression of log (M_t/M_∞) versus log(t) of different formulations are shown in Table 5. The calculated value of n lies between 0.5 and 1.0 for all the formulations, indicating non-Fickian drug release kinetics, which is an indicative of drug release mechanisms involving combination of both diffusion and chain relaxation mechanisms(9).

In conclusion, the fabricated formulations show significant bioadhesive properties and could potentially be used as prolonged and controlled release delivery systems for administration of PZ through buccal route. Further, its potential to improve bioavailability of PZ, in comparison to its peroral administration, could be established after *in vivo* studies of these formulations in animals and/or human.

Table 5. Kinetic constant (K), diffusional exponent (n) & correlation coefficient (r^2) following linear regression of log $(M_t/M_¥)$ versus log (t) of patches/disperse matrix systems

S. No.	Batch No.	N	K	r^2
1.	A_1	0.727	0.199	0.995
2.	A_2	0.621	0.091	0.999
3.	A_3	0.528	0.222	0.999
4.	A_4	0.750	0.147	0.996
5.				

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