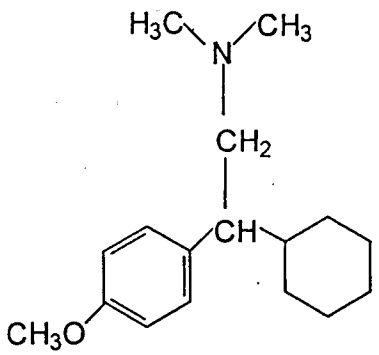

Venlafaxine

excipients used in the formulations. Phosphomolybdic and tungstic acids in the FCR preparation involve the following chemical species [6-7].

$3H_2O.P_2O_5.13WO_3.5MoO_3.10H_2O$ and $3H_2O.P_2O_5.14WO_3.4MoO_3.10H_2O$

VFX probably effects a reduction of one, two or three oxygen atoms from tungstate and/ or molybdate in FCR thereby producing one or more of the possible reduced species which have a characteristic intense blue color.

In conclusion, the proposed method is simple, rapid, accurate, specific and the reagents used in the method are cheaper. Further, the procedure does not involve any critical reaction conditions like heating and extraction as mentioned in the reported spectrophotometric method. Hence it may be used for the routine analysis of VFX in the pharmaceutical dosage forms.

REFERENCES

1. Reynolds, J.E.F. Eds., In; Matrindale, The Extra Pharmacopoeia, 31st Edn., The Pharmaceutical Society, London, 1996, 337.
2. Krishnan, P.V.V., In; CIMS, Drug Profile, Biogard Pvt Ltd., Bangalore, 2001, 25.
3. Budavari, S., Eds; The Merck Index,12th Edn.,Merck & Co., Whitehouse Station, NJ 1996,1695.
4. Appalaraju, S., Sarasambi, P.S. and Karadi, A.B., **Asian. J Chem.**, 2002, 14, 467.
5. Massart, D.L., Vandegingle, B.G. M., Deming, S.N., Michette, Y. and Kaufman, L., In; Chemometrics, A Text Book, Elseveir, Amsterdam, 1998, 293.
6. Folin, O. and Ciocalteu, D., **J. Biol. Chem.**, 1927, 73, 627.
7. Petreson, G.L., **Anal. Biochem.**,1979, 100, 201.

Transdermal Delivery of Ampicillin Sodium Patch Made from Volatile Vehicle

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The permeation of ampicillin sodium patch from ethanol/pH4.7 buffer solution containing antinucleant polymers across mouse skin, was investigated. The *in vitro* release of ampicillin sodium was determined under open condition at 25° and 65% relative humidity. Therefore the influence of evaporation of vehicle components on the permeation of ampicillin sodium was examined. Evaporation of the vehicle led to drastic compositional changes leading to supersaturation. However, supersaturation solutions started to crystallize reducing the thermodynamic activity of ampicillin sodium. Antinucleant polymers where used in the preparation of volatile vehicles in order to maintain the increased activity state of the drug.

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Carboxymethylcellulose and hydroxypropylmethylcellulose were efficient antinucleant polymers to increase the permeation of ampicillin sodium.

Ampicillin sodium is a semi synthetic antibiotic, possessing a broad spectrum of activity and is indicated in the treatment of wide range of bacterial diseases. It is active against a variety of Gram positive and Gram negative bacteria including *Haemophilus influenzae*. At present ampicillin is administered orally and by Intravenous route but this gives rise to side effects such as oesophageal ulceration, disturbance of normal gut flora, pain at site of injection[1].

It is anticipated that these side effects could be overcome by the delivery of ampicillin via the skin. Transdermal drug delivery has definite advantages over other routes of administration because of easy access, convenience of use and patient compliance[2]. The success of a transdermal drug delivery system (TDDS) will depend on the ability of the drug to penetrate the stratum corneum at a rate sufficient to achieve concentration in the systemic circulation, necessary for the desired therapeutic effect. One of the approaches to overcome this challenge is administration of skin permeation enhancers[3,4]. Penetration enhancement through use of supersaturation provides an attractive alternative[5]. Supersaturation is that state where drug concentration in a vehicle is greater than the saturated solubility. Therefore supersaturated solutions increases the activity of a drug, as it has a greater leaving tendency, producing an increased flux[6]. The main advantage of this method over other techniques is that it is inexpensive and does not greatly disturb the skin.

Supersatured solutions are physically unstable by their nature. The drug tends to crystallize upon preparation of the solution. The remarkable effects of antinucleant polymer in stabilizing supersaturated solutions have been utilized to demonstrate marked improvement in transdermal delivery from supersaturated systems[7,8]. Many methods for preparing supersaturated solutions have been identified[6]. In this study supersaturated solutions were prepared by the removal of volatile solvents by evaporation method[5]. Ethanol/ pH 4.7 buffer co-solvent system as the volatile vehicle was mixed in different proportions in the presence of antinucleant polymers which stabilize the supersaturated solutions. The effects of the supersaturation on the *in vitro* transdermal delivery of ampicillin sodium across excised mouse skin in an open condition were evaluated by using Franz-diffusion cell.

Gift sample of ampicillin sodium IP was obtained from Karnataka Antibiotics Ltd., Bangalore. Hydroxypropylmethyl-cellulose (HPMC) of 20 cps, sodium alginate, carboxymethylcellulose (CMC) of 1500 cps, Polyethylene glycol (PEG 400) was obtained from Bharat Coats, Chennai. All other reagents and chemicals used were of analytical grade.

Excess ampicillin sodium was added to a series of ethanol/pH 4.7 acetate buffer co-solvent systems ranging from 15 to 60% (V/V). The suspensions were stirred using magnetic stirrer for 2 h at 100 rpm. The samples were analysed by UV spectroscopy at 214 nm. and the ratio having maximum solubility was selected.

The films were fabricated by casting method using 2% polymer in ethanol and pH 4.7 acetate buffer solution[9]. 3 ml of the solution containing the drug, polymer was pipetted into a glass mould lined with aluminium foil. The mould was kept at open condition 25° and 65% RH for 2 d. The dried patches were then taken for *in vitro* release studies. Various patches were prepared by the above mentioned method using sodium alginate, HPMC, CMC, PEG 400 as polymers. The formulation details and physico chemical parameters of the films are summarised in Table 1.

The permeation of ampicillin sodium was determined by using Franz Glass diffusion cell. Freshly excised mouse skin was allowed to equilibriate with the buffer solution for about 30 min and then mounted on the receptor compartment with the stratum corneum side facing upwards into the donor compartment[9]. The patch to be evaluated was placed over the skin and covered with aluminium foil. The receptor compartment was then filled with phosphate buffer saline pH 7.4. The available diffusion area of cell was 2.5 cm^2 The receptor compartment was maintained at 37±1° and stirred by a magnetic stirrer at 100 rpm. At 3,6,24,30 and 48 h, 1 ml of the receptor solution was withdrawn and replaced with an equal amount of fresh buffer solution. The samples were analysed by UV spectroscopy at 214 nm.

The solubility of ampicillin sodium increased following the increase of ethanol proportions from 15% till 40% which was then found to decrease at 60%. Hence the ratio 40:60 of ethanol and pH buffer 4.7, respectively was selected to prepare the patches.

TABLE 1: PHYSICOCHEMICAL PARAMETERS AND *IN VITRO* PERMEATION DATA OF THE FILMS

Formulation Code	Polymer Used	Drug Content* (g)	Thickness* (μ)	Weight* (mg)	Flux* (μg /cm²/h)
A.	HPMC	19.10±0.21	155.0±0.24	187.0±0.25	16.0±0.80
B.	CMC	19.15±0.22	152.2±0.51	186.0±0.82	19.7±0.3
C.	PEG 400	19.55±0.42	160.0±0.22	187.0±0.42	15.5±0.2
D.	SA	19.30±0.15	150.4±0.12	170.0±0.21	12.9±0.3

Data obtained from evaluation of various formulations, A-hydroxypropylmethylcellulose (HPMC), B-carboxymethylcellulose (CMC), C-polyethyleneglycol 400 (PEG 400), D-sodium alginate (SA), *-Each data represents the mean ±S.D. (n=3).

Prepared patches were flexible and uniform in structure. Drug content was found to be fairly uniform in all formulated patches. Drug content in the prepared patches were found to be 19.1±0.23 g.

The permeation of ampicillin sodium from volatile vehicles (ethanol/pH 4.7 buffer, 40:60 v/v) are as shown in Fig. 1. The volatile vehicle without polymers (control group) shows an initial increase in ampicillin sodium permeation for 8 h followed by constant permeation. The initial increase of ampicillin sodium seen in this experiment is due to partitioning of ampicillin sodium from volatile solution into the skin. As the solvent evaporated the thermodynamic activity of ampicillin sodium increased and become greatest at permeation. However the ampicillin sodium permeation gradually leveled off, indicating that the initial high rate of permeation was not sustained. Presumbaly this was because of the further evaporation of volatile vehicle, precipitated excess drug as a deposited film on the skin.

The precipitation limited the amount of ampicillin sodium that could be absorbed and led to poor permeation of drug from the formulation because it could not effectively partition into the skin. In the presence of antinucleant polymers the permeation of ampicillin sodium was found to increase in the following order CMC>HPMC>PEG 400>SA with a flux [μg/cm²/h (±SD) of 19.7±0.3, 16.0±0.80, 15.5±0.2 and 12.9±0.3, respectively. The increase in the permeation may be due to crystal growth retardent polymer which would have slowed down the transformation of the drug from its high energy state to the stable crystalline form.

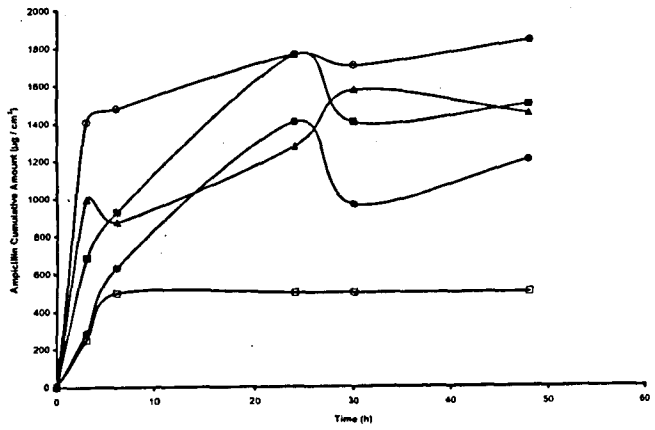

Fig 1 : *In vitro* permeation profiles of ampicillin sodium from ethanol / pH 4.7 buffer volatile vehicle (40:60, v/v) in the presence of 2% polymers.

Permeation profiles of ampicillin sodium across mouse skin from polymeric membrane systems of control (□), CMC (○), HPMC(■), PEG 400(▲) and SA(●). Study was carried out in franz-diffusion cell at 37±1°, samples were analyzed spectrophotometrically at 214 nm.

REFERENCES

1. William, A.P., In; Hardman, J.G., Limbird, L.E., and Gilman, G.A., Eds., Goodman and Gilman's The Pharmacological Basis of Therapeutics 10th Edn., The Mcgraw Hill companies, Inc.: USA, 2001, 1201.
2. Shyamala, B. and Sree, H., **Indian J. Pharm. Sci.**, 2000, 6, 424.
3. Huang, Y.B., Wu, P.C., Ko, H.M. and Tsai, Y.H., **Int. J. Pharm.**, 1995, 126, 111.
4. Fang, J.Y., Tsai, M.J., Huang, Y.B., Wu, P.C. and Tsai, Y.H., **Drug Dev. Res.**, 1997, 40, 56.
5. Fang, J.Y., Wu, P.C., Tsai, Y.H. and Kuo, C.T., **Int. J. Pharm.**, 1999, 176, 157.
6. Pellett, M.A., Castellano, S., Hadgraft, J. and Davis, A.F., **J. Control. Release**, 1997, 46, 205.
7. Davis, A.F. and Hadgraft, J., **Int. J. Pharm.**, 1991, 76, 1.
8. Konodo, S., Yamanako, C. and Suginoto, I., **J. Pharmacobio. Dyn.**, 1987, 10, 743.
9. Munden, B.J., Decay, G.H. and Banker, G.S., **J. Pharm. Sci.**, 1964, 53, 395.