ELSEVIER

International Journal of Pharmaceutics 132 (1996) 267–270

international journal of pharmaceutics

Short communications

Apparatus for preparing adhesive-dispersion transdermal patches on a laboratory scale

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Received 26 June 1995; accepted 11 July 1995

Abstract

Current methodology in use at a number of laboratories engaged in research on transdermal systems relies heavily on cast films or screen coating as opposed to knife coating, which is the method of choice in the adhesive tape industry. This report deals with the fabrication of a knife coating assembly from commonly available, inexpensive materials and its use in the preparation of transdermal patches of testosterone. Three series of formulations of the 'adhesive-dispersion' variety were prepared and coated on to fabric. Uniformity of thickness, weight and content was estimated within batches and between batches and found to be satisfactory. The apparatus is capable of preparing 10–100 cm/min of coated tape having a width of 0.5–2 cm. Thickness control up to 0.05 mm of wet mass (about 0.03 mm dry coating) may be achieved.

Keywords: Transdermal; Adhesive-dispersion; Knife coating

The simplest form of a transdermal patch, the adhesive-dispersion controlled release system (Chien, 1987) is often the most difficult to prepare on the laboratory scale. Various researchers have used different techniques to achieve a uniform coating of the pressure sensitive adhesive (PSA) formulation on to a backing membrane. All of these are variations of methods that may be summarized as knife and blade-, air knife-, bar-, roll- or gravure-coating and calendering. To this may be added another method adapted from the printing industry (at least in India), namely screen coating. A wide gap nevertheless exists between industrial equipment available for the purpose of coating (Satas, 1982), and the typical batch sizes that a development laboratory is interested in preparing. This leads to the adoption of manual methods of coating, which often suffer from the drawback of exhibiting an unacceptable degree of inter-batch and inter-operator variation.

It was therefore considered worthwhile to prepare a rudimentary apparatus from commonly available and inexpensive materials and validate its performance with respect to the preparation of

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SSDI 0378-5173(95)04262-Z

transdermal patches containing testosterone. The adhesive dispersion formulations were prepared by mixing the required amount of the drug with (a) natural rubber and terpene-phenol resin PSA; (b) an acrylate-based formulation (Vamulsion DEV 4000, Vam Organic Chemicals, India); and (c) a vinyl acetate terpolymer adhesive (Emdilith DM-45, Mafatlal Dyes and Chemicals, India). These were designated as the RBR, ACR and VAC series, respectively. All formulations were pseudoplastic but had a similar apparent viscosity.

The coating apparatus was comprised of the following components:

Take-off roll: a desktop tape dispenser was used to take off fabric for coating. A web of cotton fabric was mounted on the roll. Uniformity of dimensions was ensured by cutting along a single weft revealed upon pulling out a thread to create a 'ladder'.

Tension roller: the fabric web was maintained under tension so as to provide an even surface for coating. This was accomplished using a wooden roller (rolling pin) weighing 150 g placed on the web as it issued from the take-off roll.

Coating platform or apron: an evenly ground strip of aluminum was placed over the saw-tooth cutter of the dispenser and checked for true horizontal orientation using a spirit level. It was then sealed in place using a cyanoacrylate adhesive.

Coating knife: two strips of aluminum were placed on either side of the coating platform. These strips had matched grooves cut into them. Room-temperature vulcanizing silicone rubber (Metroark, India) was poured into the grooves and allowed to cure. A finely ground knife blade was then inserted into the grooves. The blade could be adjusted to the desired height above the platform by placing Feller gauge strips of the required thickness between the two and pressing the blade down firmly. The cured silicone rubber was elastic enough to allow the blade to be adjusted as described and, at the same time, firm enough to restrict its displacement during the coating operation.

Drive and wind-up roll: a synchronous motor (240 V, single phase, 50 Hz, 125 mA) was used to wind up the web from under the knife. It had a maximum RPM rating of 60 and could generate a maximum torque of 3 kg · cm. Since the revolutions of such a motor do not vary with the load (within an upper limit) imposed upon it, the setup was considered appropriate for maintaining a uniform coat application rate for typical batch sizes. The apparatus and control circuit of the motor are shown in Fig. 1.

The coating procedure was as follows. The assembly was placed on a level surface and the fabric web was passed under the knife and its leading edge secured to the rotor shaft of the drive with surgical plaster. The power output of the motor was adjusted to obtain the required linear rate of web motion (10–100 cm/min). A puddle of freshly prepared adhesive mass was then placed on the section of the web lying on the platform and the power switched on. The puddle was replenished manually during the operation. Strips of 20 cm length were obtained by this procedure. These were allowed to dry at 37°C for 18–24 h before being covered with silicone release liner (Bhati, India). Patches of desired dimensions were either cut or punched out of the strips using a shoemaker's leather punch.

Patches thus prepared were evaluated for coating thickness and weight as well as the variation of these parameters within and between batches. Thickness was measured with a dial gauge with a least count of 1 μm (Mitutoyo, Japan) and weights were recorded using a balance with a least count of 0.1 mg (Afcoset, India). Testosterone content and uniformity were assessed using high performance thin layer chromatography (Camag, Switzerland) using the procedure for identification of steroids described in BP 1993 (British Pharmacopoeia, 1993). Solvent extracts of the patches were diluted to an expected concentration of 10 μg/ml of testosterone and applied on C-18 reverse phase TLC plates (Merck, India). Chromatograms were developed to a solvent front of 15 cm and focused bands were quantitated by measuring absorbance at 239 nm and comparing with values of standard bands of concentrations ranging from 3 to 25 μg/ml run on the same plate.

The composition of formulations of the RBR, ACR and VAC series is shown in Table 1. These formulations were optimized to exhibit a similar

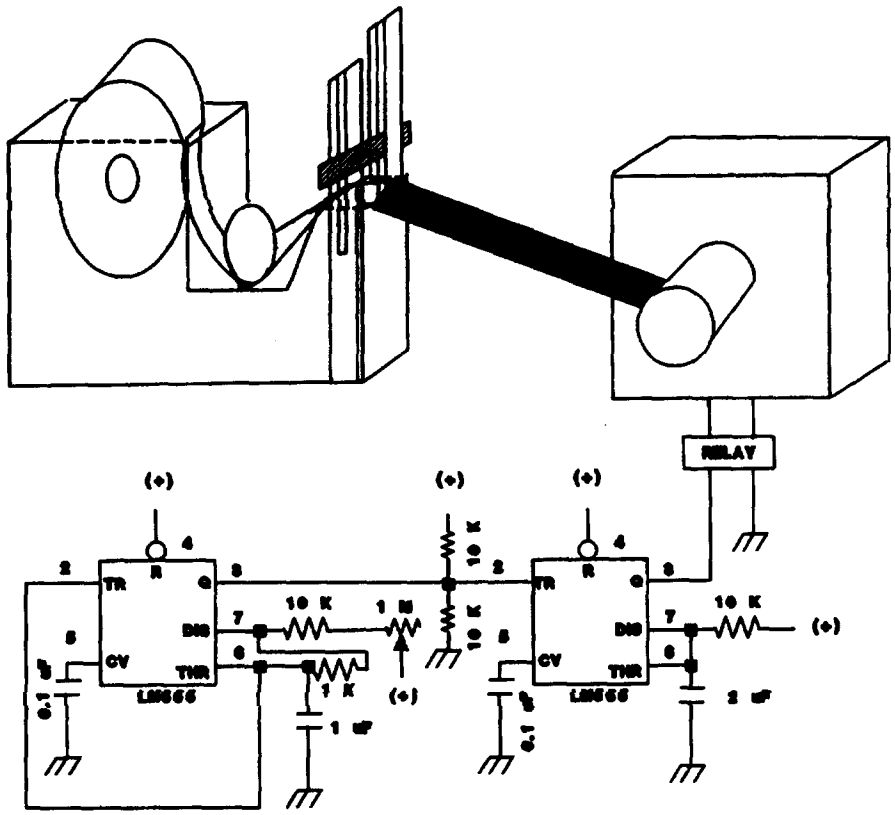

Fig. 1. Coating assembly and speed control circuit for motor.

degree of pressure sensitive adhesion as evaluated by subjective criteria, as well as parameters such as in vitro drug release.

In order to demonstrate the uniformity within a batch, we have listed the values of the percent coefficient of variation calculated for estimates of thickness and weights of 20 patches from each batch. This was observed to be normally distributed in all batches prepared after process optimization, within a 5% limit. Some batches showed skewing towards greater than average thickness, but the limit indicated was never violated. Weight distribution was always found to be truly Gaussian, regardless of whether patches were punched or cut out of the coated fabric. The estimation of both weight and thickness highlighted the distinction between non-uniformly coated and improperly cut or punched batches.

Variation of these parameters between four batches of each series was tested by Behren's method for calculating significance in the difference between group means (Fisher and Yates, 1963). Variation in the parameters being evaluated may arise from a multiplicity of sources, such as incorrect mixing, coating, unitization, or extraction during assay to name a few. Accordingly, Behren's method was preferred over other methods of computing variance such as *t*-tests or ANOVA. Batches of any particular series did not show significant variation, but inter-series variation was significantly different.

In the absence of official criteria for dose uniformity of transdermal patches, we have not attempted to fix values on the allowable extents of variation. Nevertheless, the experience with the evaluation of in-vitro drug release profiles of units from multiple batches prepared using the apparatus described here is reassuring.

Table 1
Variation within 4 different batches that showed no significant difference in mean values of thickness, weight and content within each series of formulations

Composition		B. no.	Thickness (mm)	% CV	Weight (g)	% CV	Assay (mg)	%CV
(1) Natural rubber	100	RBR1	0.118	0.034	0.3747	0.038	4.56	0.214
Capolyte 110	70	RBR2	0.108	0.011	0.3601	0.027	4.61	0.137
Zinc oxide IP	20	RBR3	0.112	0.026	0.3725	0.034	4.48	0.205
Light mineral oil IP	20	RBR4	0.114	0.031	0.3736	0.036	4.43	0.163
Testosterone BP	15	-	-	-	-	-	-	-
Additives and toluene	*qs*	-	-	-	-	-	-	-
(2) Vamulsion	100	ACR1	0.122	0.018	0.4134	0.030	4.74	0.241
Zinc oxide IP	22	ACR2	0.116	0.023	0.4058	0.022	4.63	0.223
Mineral oil IP	10	ACR3	0.134	0.031	0.4391	0.041	4.57	0.187
Testosterone BP	15	ACR4	0.127	0.025	0.4188	0.035	4.66	0.163
Isopropanol	*qs*	-	-	-	-	-	-	-
(3) Emdilith	100	VAC1	0.439	0.027	0.0310	0.010	4.38	0.116
ZnO, min. oil	5,5	VAC2	0.442	0.031	0.0310	0.011	4.48	0.099
Testosterone BP	15	VAC3	0.441	0.019	0.0317	0.007	4.74	0.154
Isopropanol	*qs*	VAC4	0.435	0.007	0.0311	0.014	4.50	0.239

We conclude, therefore, that the apparatus reported here may be used by the research laboratory for preparing appropriately sized batches of transdermal tape in a reproducible manner.

Acknowledgements

Financial support from NII core funds, and the generosity of Dr. Jagbir Singh, Vam Organic Chemicals Ltd. who provided the sample of Vamulsion; Mr. Rohit and Mr. Sandeep Gupta of Brij Textiles who provided natural rubber and Capolyte resin samples; and Mafatlal Dyes and Chemicals Ltd. who gave us the Emdilith sample; are gratefully acknowledged.

References

British Pharmacopoeia, Her Majesty's Stationery Office, London, 1993, pp. 64–65.

Chien, Y.W., Developmental concepts and practice in transdermal therapeutic systems. In Chien, Y.W. (Ed.) *Transdermal Controlled Systemic Medications*, Marcel Dekker, New York, 1987, pp. 25–82.

Fisher, R.A. and Yates, F., *Statistical Tests for Biological, Agricultural and Medical Sciences*, 6th Edn. Longman, Harlow, UK, 1963, p. 61.

Satas, D., Coating. In Satas, D. (Ed.) *Handbook of Pressure-Sensitive Adhesive Technology*, Van Nostrand Reinhold, New York, 1982, pp. 498–532.