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Preformulation Stability and Permeation Studies of Transdermal Patches of Salbutamol

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Stability and skin permeation of salbutamol base from adhesive matric transdermal patches containing antioxidants and skin permeation enhancers was studied. Skin permeation was enhanced with increase in salbutamol content and oleic acid content in the patches. Accelerated stability testing indicated that patches containing butylated hydroxy toluene and thiourea had an adequate stability profile.

FOR chronic management or prophylactic therapy of asthma particularly nocturnal asthama, long acting formulations particularly transdermal delivery would be of benefit.[1,2] In comparison to oral delivery which has the disadvantage of variable and limited period of residence at the site of absorption as well as potential for dose-dumping, the transdermal route provides more reliable and reproducible delivery. Recent advances in skin permeation enhancement suggest a potentically wider scope in terms of number and types of drugs deliverable by transdermal route.[3]

0.5 ml of the formulations containing 10 mg/ml of salbutamol (SL), 40 mg/ml of pressure sensitive adhesive (psa) and other ingredients as given in Table I were poured on a 5 sq.cm. area on a backing membrane and allowed to dry in air. The patches were packed in sealed pouches prepared from Scotchpak(R) film and stored at 45° (15 days) and 55° (10 days, 20 days). **Preliminary compatibility evaluations** were carried out by extracting the drug

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from the stored patches into methanol and TLC was performed on silica gel G plates using a solvent system consisting of methanol : toluene : ammonia (80:16:4). Spots were developed by placing the plates in an iodine chamber. An aqueous solution of SL was intentionally degraded at 55° for 20 days and TLC performed on the degraded sample. An Rf value of 0.72 (± 0.03) was obtained for SL whereas a spot for the degradation product(s) was observed at the origin. F4, F9 and F10 did not show a degradation spot under all storage conditions, whereas, F7 showed a degradation spot only after storage at 55° for 15 days. A stability indicating HPLC method[4] was used for **preliminary stability evaluation** of F4, F7, F9 and F10. The chromatograms gave a retention time of 5.3 min. for SL and 7.5 min. for the degradation product(s). Extracts from freshly prepared patches as well as patches stored as in Table II were injected. No peak for the degradation product(s) was obtained for F4, F9 and F10 but was obtained for F7. The mean extraction of the drug from the patches stored at various temperatures, expressed as a percentage of drug extracted from freshly prepared patches was calculated and the results are given in Table II. Statistical analysis $\alpha = 0.05$) showed that no detectable degradation occured in F4, F9 and F10. Further evaluations were carried out on these patches only. **Drug content** was evaluated by dissolving the matrix in ethylacetate and reading the absorbance at 278 nm. **Thickness uniformity** was determined by measuring the thickness at five siteson three patches each of F4, F9 and F10. **Weight** of the adhesive matrix of each formula was determined in triplicate from the difference in weight of the backing membrane with and without the adhesive matrix on it. The results are given in Table II. The low % c.v. indicate that the patches had good uniformity. A **primary skin irritation test** was performed as described earlier[5] using F4, F9 and F10 as test patches and Adhesive Tape USP as the control patch. The three test patches showed much lower irritation than the control patch. The **U Peel strength** of F4, F9 and F10 on human skin was determined using a pulley arrangement[6] and the values are given in Table II. Patches prepared from psa alone gave much higher peel stength (> 300g) suggesting that although F4, F9 and F10 had adequate adhesiveness to human skin the additives had a significant effect of decreasing the strength of adhesion to skin. **In vitro skin permeation studies** were done on formulations that did not contain antioxidants because of a possibility of permeation of antioxidants through the skin and their presence in the receptor compartment in amounts that could cause interference with the uv- spectrophotometric method. **In vitro** skin permeability studies were done using an Erweka skin permeation system and Erweka diffussion cells. In order to avoid guinea pig skin variability from biasing the results each replicate in a study used three skin pieces from adjoining abdominal sites of the same guinea-pig with the three different formulations being tested on the three skin peices. For three replicates in each set three male guinea pigs in the weight range of 300-400g were used. Thus observed differences between replicates would include differences in skin from three different guinea pigs whereas observed differences amongst F4, F9 and F10 within a replicate would include within skin (same guinea pig) variability, error, as well as differences in the three formulations. Isotonic physiological buffer (pH 7.4) was used as the receptor fluid. The system was preequilibrated and then maintained at 37° using a Julabo constant temperature circulating bath. Sampling was done by withdrawing the entire contents of the receptor compartment and the samples analysed by uv-spectrophotometry at 225 nm. It was found that lauryl alcohol and Tween 80 did not enhance the skin permeation, however, each of sodium lauryl sulphate and oleic acid (OA) resulted in a significant enhancement. Investigations on patches containing OA were conducted in two sets and are reported here. In set I the effect of increasing drug content, 5,10, and 15mg/5 sq.cm. patch in the matrix containing OA, 4mg/patch was evaluated and the patches were thus designated S.5-OA.4, S-10-OA.4 and S.15-OA.4. In set II the effect of increasing OA, O, 4 and 12 mg/patch at a high loading dose of SL (15 mg/patch)

Table I: Formulations used in capatibility and stability studies

Formulation Code	Citric acid	BHA	Propyl gallate	BHT	Thiourea	Oleic acid	Tween 80	Lauryl alcohol
F1	+[1]	—[2]	—	—	—	+	+	—
F2	—	+	+	—	—	—	+	—
F3	—	—	+	—	—	+	+	+
F4	+	+	—	—	—	—	+	+
F5	+	+	+	—	—	+	—	—
F6	—	+	—	—	—	+	—	+
F7	+	—	+	—	—	—	—	+
F8	—	—	—	—	—	—	—	—
F9	+	—	—	—	+	—	—	—
F10	—	—	—	+	+	—	—	—
F11	+	—	—	+	—	—	—	—

1 + Indicate the presence of the ingredient in the following concentrations :

Citric acid	:	1 mg/ml	Butylated hydroxy anisole	:	1 mg/ml
Propyl gallate	:	1 mg/ml	Thiourea	:	0.5 mg/ml
Butylated hydroxy toluene	:	1mg/ml	Oleic acid	:	8mg/ml
Lauryl alcohol	:	8mg/ml	Tween 80	:	8mg/ml

2. — Indicates the absence of the ingredient

was evaluated and these patches are abbreviated as S.15, S.15-OA.4, and S.15- OA.12. The results are given in Figure 1 and 2. Comparisons within a set were made by two-way ANOVA as well as Wilcoxon signed rank test. The analysis suggested that the effect of increasing the SL content as well as the OA content in the patch was significant at the 5% level of significance. The Tukeys test as well as the Wilcoxon signed rank test indicated that the enhancement was insignificant when the SL content was increased from 5 to 10 mg. However, enhancement was significant when SL content was increased from 5 to 15 mg. or from 10 to 15 mg. Similar statistical analysis of set II showed that enhancement was significant when OA content was increased from 0 to 4 mg and from 4 to 12 mg. Observations on the patches by light microscopy revealed that OA had an influence of dissolving most of the SL in the patch. Therefore, in addition to its influence on the stratum corneum, OA could have increased skin permeation rate by other mechanisms which may include increased concentration gradient of SL across the skin due to its dissolution by OA and possibly ion-pair formation between SL and OA.

On the basis of the results of the preliminary stability evaluation and skin permeation studies, the patch S.15-OA.12 containing 2% w/w BHT and 1%

Table II: Evaluation of Transdermal Patches

	Formation Code Parameter	F4	F7	F9	F10
1.	Mean % extraction*				
	(a) 0 days	100.0±6.4	100.0±4.8	100.0±8.0	100.0±4.9
	(b) 55° (15 days)	98.7±6.6	61.2±6.7	96.6±15.2	96.5±12.1
	(c) 45° (1 month)	104.6±5.6	74.5±4.5	104.3±7.4	98.6±8.0
	(d) 45° (2 months)	97.8±0.4	73.4±2.0	104.0±0.8	97.1±2.1
	(e) 37° (1 month)	105.5±13.4	96.8±8.6	105.8±14.3	96.0±5.8
	(f) 37° (2 months)	94.1±2.3	72.8±9.7	104.5±3.3	94.4±5.6
	(g) R.T. (6 months)	102.8±	67.9	98.3	103.4
2.	Weight (mg) (mean ± s.d.)	31.9±0.65 (2.03)	— —	27.1±1.26 (4.65)	25.3±0.65 (2.57)
3.	Thickness (μm) (mean ± s.d.)	197.0±0.09 (0.045)	— —	196.7±0.09 (0.045)	197.0±0.09 (0.045)
4.	Drug Content (mg) (mean ± s.d.)	5.09±0.071 (1.39)	— —	4.96±0.172 (3.46)	4.95±0.15 (3.07)
5.	180° peel strength (g)	23.3±2.9	—	30.7±5.7	32.5±5.0

* Mean percent extraction of drug expressed as percentage of that extracted from freshly prepared patches. Figures in brackets indicate % c.v.

w/w thiourea as antioxidants was subjected to short term **accelerated stability evaluation**. The pouched patches were stored in a 60° oven for 15 days. The HPLC method used in preliminary stability studies involved triple (15ml x 3) extraction into acetonitrile over a period of 24 h. This procedure did not result in high precision (% c.v. for F10 analysis was 4.9). The analytical method could be improved by extraction into methanol as follows. The patch was kept on a cellophane membrane which was then clamped on an Erweka diffusion cell. The receptor compartment filled with methanol was stirred for 1 h at 37 ± 0.5°. The solution was diluted and filtered through a 0.45 μm nylon filter and analysed by HPLC. This procedure resulted in a higher precision (% c.v. = 1.9). The first order rate constant for SL degradation at 60° was found to be 0.0053 ± 0.0017 day^{-1}. The 95% confidence interval for k_{60} was 0.004 to 0.00658 day^{-1}. Taking the highest possible value of k_{60} (0.00658 day^{-1}) and the literature value of energy of activation for SL degradation as 23 Kcal/mole, the value of k_{25} was calculated as 1.109×10^{-4} day^{-1}. The tentative period for 10% drug degradation was estimated to be 946 days, demonstrating that the patches were stable.

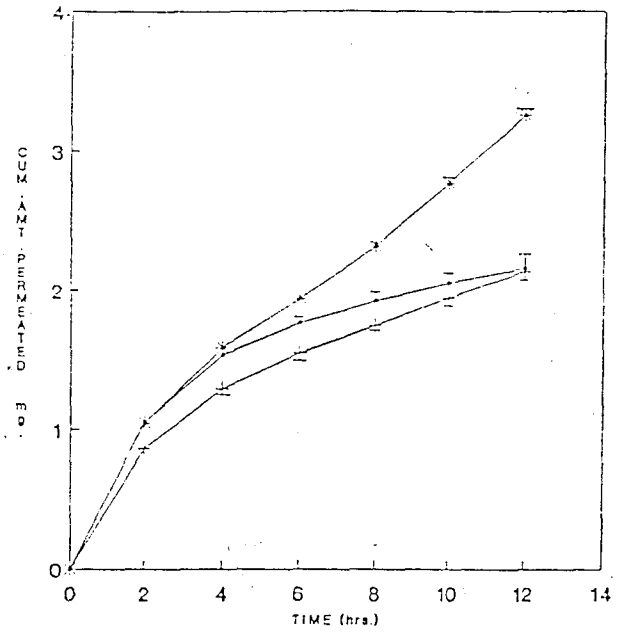

Fig.1: Effect of increasing drug to adhesive ratio on the skin permeation of salbutamol from adhesive matrix patches containing 4 mg oleic acid. Key : —o— S.5–OA.4, —+— S.10–OA.4, —*— S.15–OA.4 Bar represents S.E.M.

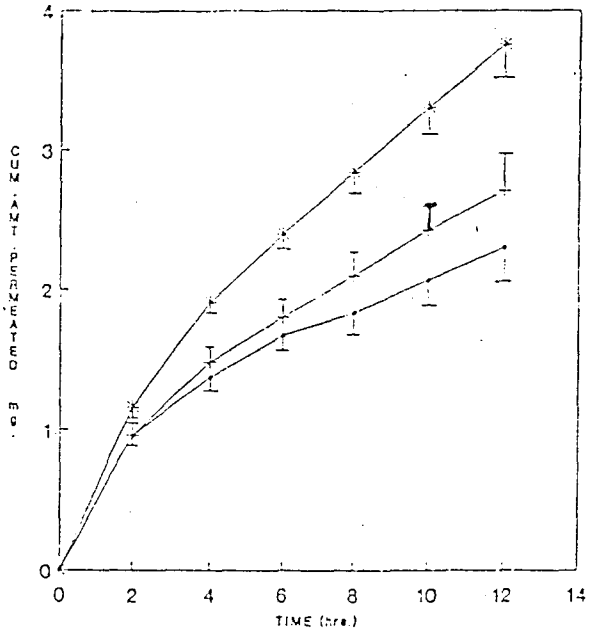

Fig. 2: Effect of increasing amount of oleic acid on the skin permeation of salbutamol at 15 mg. dose of salbutamol. Key : —o— S.15, —+— S.15–OA.4, —*— S.15–OA.12 Bar represents S.E.M.

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