

TABLE 64

Cumulative Amount of Diclofenac Sodium ( $\mu\text{g}/\text{cm}^2$ )				
Time	Diclo-9	Diclo-10	Diclo-11	Diclo-12
3 hours	7.5	1.5	33.4	257.7
6 hours	39.6	18.3	269.3	793.3
10 hours	63.2	49.3	654.4	1652.2
24 hours	34.6	227.7	1733.8	3257.7

[0407] The cumulative amount of diclofenac sodium across human cadaver skin at 24 hours increased from 34.6  $\mu\text{g}/\text{cm}^2$  to 3257.7  $\mu\text{g}/\text{cm}^2$  when the calculated excess NaOH concentration in the dried patch was increased from 0% to 1.8%. The cumulative amount of diclofenac sodium across human cadaver skin at 24 hours from the system containing 0.4% NaOH (Diclo-10) was 227.7  $\mu\text{g}/\text{cm}^2$ , which was about six times higher than that from the formulation without NaOH (34.6  $\mu\text{g}/\text{cm}^2$ , Diclo-9). This result indicated that the permeation of diclofenac sodium across human skin could be enhanced by a NaOH concentration as low as 0.4%.

[0408] The formulation of Diclo-10 provided up to 7-fold more diclofenac sodium flux than in the absence of NaOH (Diclo-9). The formulation of Diclo-11 provided up to 50-fold more flux, while the highest pH formulation evaluated, Diclo-12, provided up to 94-fold more flux than in the absence of NaOH.

[0409] The measured pHs at the skin/patch interface are listed below.

TABLE 65

pHs at the Interface between Skin and Patch				
Time	Diclo-9	Diclo-10	Diclo-11	Diclo-12
3 hours	*	11.0	*	10.3
6 hours	*	11.0	11.2	9.8
10 hours	8.5	10.9	10.7	10.2
24 hours	*	9.7	10.1	9.4

\* Could not be measured because there was not enough solution at the interface.

[0410] The pHs at the interface between skin and the patch remained about the same, even though the concentration of NaOH was increased from 0.4% to 1.8%. It was difficult to measure the pH of interface between skin and patch for the formulations without NaOH or with a low NaOH concentration because there was not enough solution on the top of the skin.

[0411] Since the pH measurement for the interface between the skin and patch may be difficult for low NaOH concentrations, the pHs of the receiver solutions were measured at various time points as references. The pHs of receiver solutions indicated that the pHs depend on the time interval between sampling, the NaOH concentration in the patch and the time point. The pHs at the 3-hour time point increased from 8.0 to 10.8 when the NaOH concentration in the patch was increased from 0.4% to 1.8%.

#### Example 20

[0412] An in-vitro skin permeation study was conducted using three alendronate sodium transdermal systems, designated, Al-1, Al-2 and Al-3, the compositions of which are set forth in Table 66.

[0413] Round disc samples were prepared in a manner similar to that described in the Methods section, except that the formulation was dried at a temperature of 65° C. and the discs were cut into discs having a diameter of  $\frac{9}{16}$  inch.

[0414] The theoretical percent weight for each ingredient after drying (calculated assuming all the volatile ingredients were completely removed during drying) is listed in Table 67.

TABLE 66

Component Weight and Weight Percent Based on Total Solution Weight			
	Al-1 g (wt %)	Al-2 g (wt %)	Al-3 g (wt %)
Alendronate sodium	0.30 (3.2)	0.30 (3.2)	0.30 (3.2)
Glycerin	1.00 (10.8)	1.00 (10.6)	1.00 (10.5)
NaOH	0	0.05 (0.5)	0.10 (1.1)
PIB adhesive (30% solid)	7.5 (80.6)	7.5 (79.8)	7.5 (78.9)
Heptane	0.50 (5.4)	0.50 (5.3)	0.50 (5.3)
DI water	0	0.05 (0.5)	0.10 (1.1)

[0415]

TABLE 67

Component Weight and Weight Percent Based on Dried Film Weight			
	Al-1 g (wt %)	Al-2 g (wt %)	Al-3 g (wt %)
Alendronate sodium	0.30 (8.5)	0.30 (8.3)	0.30 (8.2)
Glycerin	1.00 (28.2)	1.00 (27.8)	1.00 (27.4)
NaOH	0	0.05 (1.4)	0.10 (2.7)
PIB adhesive	2.25 (63.4)	2.25 (62.5)	2.25 (61.6)

[0416] Even though alendronate sodium may behave as an acid and react with NaOH, the amount of NaOH consumed by this reaction was not determined. For the ease of comparison, it was assumed that the reaction between alendronate sodium and NaOH was not significant. Therefore, the NaOH concentration listed in Table 67 equals the excess NaOH concentration, calculated as described in Example 2.

[0417] The pH of the patches was measured as described in the Methods section but using a 2.4  $\text{cm}^2$  circular patch. The pH of the alendronate sodium patch increased from 5.50 to 9.66 when the calculated excess NaOH concentration in the dried patch was increased from 0% to 2.7%.

TABLE 68

Excess NaOH Concentration (wt %) and pH			
	Al-1	Al-2	Al-3
Excess NaOH Concentration	0	1.4%	2.7%
pH	5.50	6.66	9.66

[0418] The in vitro permeation of alendronate sodium through human cadaver skin from these discs was measured as described in the Methods section. Three diffusion cells were used for each formulation. The receiver solution, PBS