as 150 rpm for six hours in the USP type II apparatus. Our findings also confirm the advantage of pills or pellets[4] over tablets as sustained release dosage forms.

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Synthesis and Evaluation of Polyacrylate Pressure Sensitive Adhesives

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In the fabrication of transdermal patches the cost of the pressure sensitive adhesive (PSA), including its application, release and prime coating, often surpasses the price of the backing many times.[1] Lalla et al.[2] have earlier reported the synthesis and evaluation of polyacrylate pressure sensitive adhesive. the solubility of the drug in the adhesive and the fraction of drug unionized can be important factors affecting the skin permeation rates of drugs from adhesive matrix types transdermal systems. Therefore, we have synthesized a neutral PSA (PSA I) and an acidic PSA (PSA II) by the method of solution polymerization.The formula are given in Table I.

THE monomers methyl methacrylate, methacrylic acid and 2- ethylhexy acrylate were obtained from Merck-Schuchardt. Methyl acrylate was procured from Fluka Chemie, while acrylic acid was obtained from Aldrich Chemical Co. Inc., USA. All solvents and other reagents used were of A.R. grade.

PSA I was synthesized in two different batches in order to test the reproducibility of the characteristics of the PSA prepared in two different batches. The stabilizers (hydroquinone and hydroquinone monomethyl ether) present in the commercially available monomers were removed by six washings with equal volume of 5% w/v sodium hydroxide solution; and their removal confirmed by a zero absorbance reading at 313.7 nm. The monomers were passed through anhydrous sodium sulphate bed to remove moisture.

The synthesis was carried out by solution polymerization at 70 ± 0.5° in a 3-necked round bottom flask while agitating the contents by an overhead teflon-blade stirrer, initially at 150 rpm but later at higher speeds as viscosity of the contents increased. At the end of 4 hrs for PSA I and 2 hrs for PSA II, the polymer precipitated. The excess methanol was decanted off and the copolymer dissolved in ethyl acetate.

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The excess benzoyl peroxide in the copolymers was removed by addition of methanol (for PSA I) or acetonitrile (for PSA II) which caused the precipitation of the copolymer. The solvents were decanted off and the process was repeated until the washings gave zero absorbance at 233 nm (for PSA I) or at 235.6 nm (for PSA II) The solution of purified pressure sensitive adhesive in ethyl acetate was spread on the surface of a release liner and allowed to dry in air.

The solubilities of the PSAs in different solvents, the intrinsic viscosity, the 180° peel adhesion strength[3], the rolling ball tack[3] and penetration[4] were determined as detailed elsewhere.[5] The 180° peel adhesion strength was determined using the foream of a female human volunteer as a test substrate.

Adhesive failure is defined as a failure of bond at the interface between the adhesive and the adhered. The failure of a bond within the adhesive is known as cohesive failure.[6] In order to test for adhesive/cohesive failure 5 sq. cm. patches of adhesive were prepared by the solvent evaporation technique on a backing membrane (Scotchpak film #1109, 3M Co.) and covered with a release liner. The average thickness of the patch as obtained by measurements with a micrometer screwguage was 0.200±0.014 mm. The thickness of the adhesive layer obtained by substracting the average thickness of the backing membrane and release liner was 0.084±0.005 mm. The patch was applied on the forearm of a human volunteer with light pressure and then peeled off. Care was taken such that the peeling off rate was approximately the same from patch to patch and the whole patch was removed in about 5 seconds.

Primary skin irritation test[7] was performed on intact skin of 7 healthy male rabbits weighing between 1.5-2.0 kg in order to compare the primary skin irritation potential of PSA I (batch I & batch II) with a marketed control-Adhesive Tape USP (Johnson and Johnson Ltd., Bombay). The test patch was placed on the right dorsal surface of each rabbit and the control was placed on an identical site on the left dorsal surface. After 24 hrs, the patches and controls were removed from the skin with the help of an alcohol swab and the skin was examined for erythema and oedema.

Table 1: Formulae for the synthesis of pressure sensitive adhesive.

Ingredients	Quantity Take (gm) Neutral PSA (PSA I)	Acidic PSA (PSA II)
Methyl acrylate	10	—
Methyl methacrylate	10	—
2-ethylhexy acrylate	30	31.5
Methacrylic acid	—	3.5
Methanol	27	18.9
Benzoyl peroxide	0.5	0.35

The neutral and acidic pressure sensitive adhesive did not show any apparent difference in their physical appearance. The agitational conditions in the synthesis of the two batches of neutral PSA could not be exactly reproduced because the stirring speed was increased manually as the viscosity of the contents of the flask increased. Thus, the yield was 66.6% and 78.2% w/w of the monomers for Batches I & II; respectively. The yield was 74.2% w/w of the monomers for PSA II. PSA I was soluble in ethyl acetate and isopropanol. PSA II was also soluble in ethyl acetate but only slowly soluble in isopropanol. Both the PSAs were insoluble in methanol, acetonitrile and water. The results of the intrinsic viscosity, peel adhesion strength, penetration value and rolling ball tack determination are given **in Table 2.** There was no significant difference in rolling ball tack between the two batches of the neutral PSA The instrinsic viscosity, 180° peel strength and penetration evaluation tests showed significant differences in the characteristics of the

Table 2: Characteristics of the pressure sensitive adhesive.

Property	PSA I (Batch I)	Adhesive PSA II (Batch II)	PSA II
Intrinsic viscosity	0.9625	0.875	0.67
180° peel strength (gm)	28.94 (5.14)	86.42 (7.87)	48.14 (7.57)
Penetration (mm)	5.37 (0.20)	4.52 (0.20)	4.74 (0.21)
Rolling ball tack (inches)	0.717 (0.06)	0.709 (0.07)	2.16 (0.08)

Figures in brackets indicate standard deviation.

Table 3: data from the primary skin irritation test.

Rabbit	Batch I		Batch II	
	Control	Test	Control	Test
1	1	2	1	2
2	1	1	1	1
3	1	2	1	3
4	1	2	1	3
5	1	1	1	1
6	1	1	1	2
7	1	1	1	1

two batches of the neutral PSA. Careful standardization of the process through more sophisticated control, especially on agitational intensity, may thus be required. The intrinsic viscosity and rolling ball tack of the acidic PSA was lower than the two batches of neutral PSAs; however, the 180° peel strength and penetration were between those of the two batches of neutral PSAs. The synthesized adhesive had adequate adhesion to skin. The patches fabricated from the synthesized PSAs and backing membrane showed adhesive failure when peeled from the skin and no adhesive residue was left on the skin surface.

In the primary skin irritation test, the grading system followed was as specified in USP XXII. The observations of the test are given in **Table 3.** The test and control patches did not show any oedema formation, giving the test patches a value of zero for oedema formation. The sign test[8] was performed

to compare the skin irritation potential of Batches I and II of PSA I with Adhesive Tape USP. The test showed that there was no difference in the level of skin irritation produced by the two batches of PSA I as compared to the control patch at the 5% level of significance.

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