STUDIES ON ANTIDIARRHEAL ACTIVITY OF INSOLUBLE POLYACRYLAMIDE

THERAPEUTIC agents of antidiarrheal control include the category of absorbents. Ispaghula mostly employed as bulk purgative is also of value in bacillary dysentery and chronic diarrhea. The action is purely mechanical and is due to the large amount of mucilage contained in the seeds[1]. Polycarbophil ingredient of Sorboquel (Schering) is chemically polyacrylic acid cross linked with divinyl glycol. It is insoluble in water and in common organic solvents but swells in water to a range of volumes depending primarily on the pH of the media[2]. This pharmacologically inert substance possessing the hydrosorptive property is used in diarrheal disorder to bind the free fecal water and consequently decrease the fluidity or looseness of stools. Orally administered polycarbophil exerts its most marked hydrosorptive action only on reaching the slightly acid or alkaline medium of the small intestine and colon. Insoluble polyacrylamide, employed in the studies as locally acting drug, exhibits similar characteristic as that of polycarbophil but with enhancement in swelling property.

Experimental

Castor oil was employed to create diarrhea in rats weighing 125 ± 20 g, while the insoluble polyacrylamide (G.C.I. Chemicals) of size 200/300 mesh was used as drug to protect the animals.

Procedure

Rats after being starved overnight with *ad libitum* access to water were given 1·5 ml of castor oil. Those responding by diarrheal action were selected for further studies, which were carried out after a week when each animal was challenged orally with 1·5 ml of castor oil and 2, 4, 8, 12, 16, 20, 24, 28, 32 and 40 mg/kg of polymer. Twenty rats were employed for each dose of the polymer. Individual animal was placed in metabolic cage and after 1, 2, 3, 4, 6 and 8 hours of castor oil plus polymer treatment absence of diarrhea was the criterion for drug effectiveness[4] (Table I).

ED_{50} with their confidence limits were calculated by Litchfield and Wilcoxon method[5] (Table II).

Water absorption capacity:—The polymer (100 mg) was kept in solutions of pH 1–10 for 8 hours. The mixture was then centrifuged and the polymer weighed and the amount of water absorbed was determined. The results are given in Fig. 1.

Results and Discussion

The hydrosorptive capacity of polyacrylamide was maximum above pH 8 (Fig 1). Orally administered polyacrylamide showed marked antidiarrheal action in the first hour at the ED_{50} value of 7·3 (5·74 to 9·26) mg/kg while, when the ED_{50} value was raised to 21·5 (20·1 to 23·0) mg/kg, no diarrhea was observed at any time during eight hours (Table II). Polycarbophil possesses maximum hydrosorptive capacity as 60 times of its own weight; when administered orally it exerts its profound hydrosorptive action only on reaching the slightly acidic or alkaline medium of the small intestine and colon. Polyacrylamide shows hydrosorptive power about 3 times more than polycarbophil which would suggest a basis to expect that polyacrylamide might exert more efficacious antidiarrheal activity than polycarbophil. Fields and Johnson[6] have found that certain water insoluble polyelectrolytes containing a particular type of imide will preferentially adsorb viruses contained in harvest. It will be of interest to further evaluate whether insoluble poly-

TABLE I

Time of the protective effect of the polymer against castor oil induced diarrhea in rats

Dose mg/kg	Protection[a] (%) Hours after Castor oil					
	1	2	3	4	6	8
2	0	0	0	0	0	0
4	30	0	0	0	0	0
8	50	0	0	0	0	0
12	70	50	40	30	10	0
16	85	80	75	55	45	40
20	100	90	90	70	60	55
24	100	100	95	80	75	65
28	100	100	100	95	90	80
32	100	100	100	100	100	95
40	100	100	100	100	100	100

[a] Twenty rats at each dose level for the observation period of 8 hours.

TABLE II

ED_{50} values and 95% confidence limits in mg/kg for the polymer in rats

Hours	ED_{50}	95% confidence limits
1	7·3	5·74 to 9·26
2	12·5	11·3 to 13·7
3	14·0	12·7 to 15·4
4	17·0	15·1 tc 19·0
6	18·5	16·9 to 20·1
8	21·5	20·1 to 23·0

acrylamide would adsorb viruses, bacteria or their toxins.

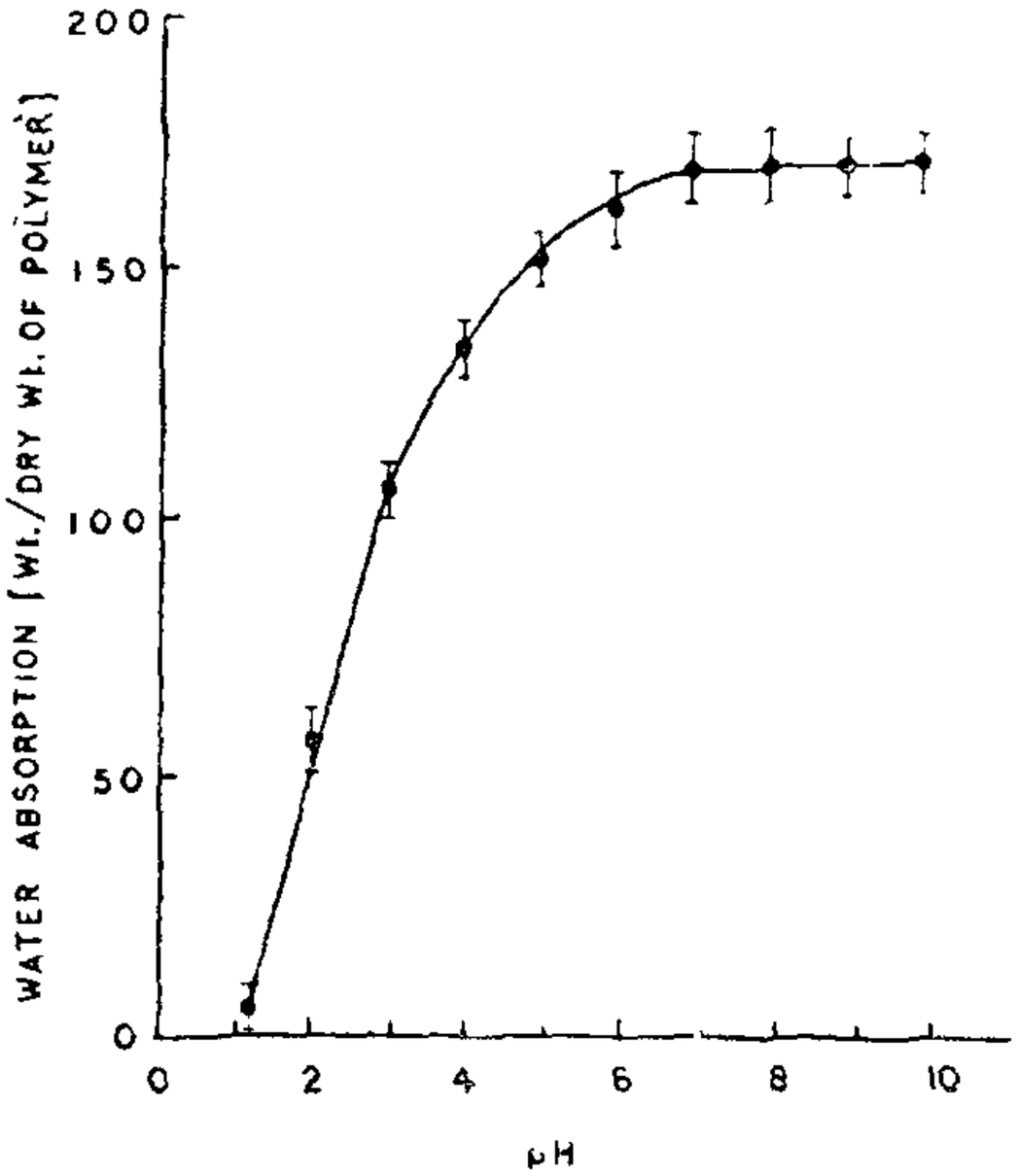

FIG. 1. Water absorption capacity of insoluble polyacrylamide at various pH. Each point represents a mean ± Standard error of 6 observations.

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Dept. of Pharmaceutical Sciences,
Nagpur University,
Nagpur 440 010,
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V. B. MATHUR.
D. M. BRAHMANKAR.

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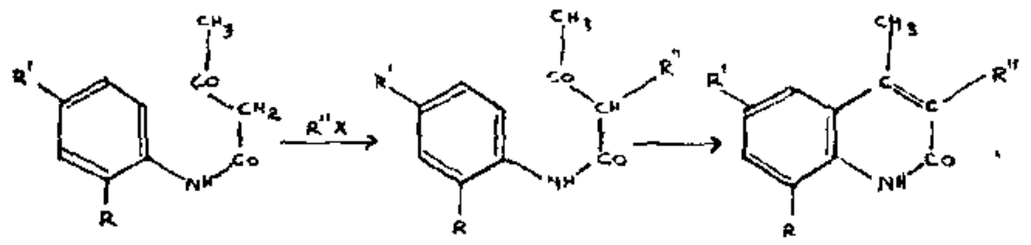
PHASE TRANSFER CATALYSIS IN THE ALKYLATION OF N-ARYLACETOACETAMIDES

ACETOACETANILIDE and similar anilides (I) can be smoothly alkylated with a variety of halogen compounds under the influence of benzyltriethylammonium chloride (BTEAC) catalyst to give *α*-substituted products (II) which constitute important intermediates in the synthesis of quinoline derivatives. The alkylation was done by using the anilide (1 mole), the alkylating agent (1 mole) and 50% aqueous sodium hydroxide (1 mole), in the presence of catalytic action of BTEAC. Methylene dichloride was used as the organic solvent and the alkylation was carried out by stirring the mixture, at 0–5° C. In all the cases examined, no O-alkylated or C-dialkylated products could be detected.



I II III

The yields of II in the different cases are tabulated below:

Compound alkylated	Halogen Compound	Yield of *α*-substituted compound
I	R″X	II %
R,R′=H	Br–CH_2–$COOC_2H_5$	80
R=OCH_3, R′=H	Br–CH_2–$COOC_2H_5$	60
R=H, R′=OCH_3	Br–CH_2–$COOC_2H_5$	80
R,R′=H	Br–CH_2–CH_2–CH_2–CH_3	16[a]
R,R′=H	Cl–CH_2–C_6H_5	60
R,R′=H	I–CH_2–CH(–CH_3)–CH_3	90

(*a*) 52% of acetoacetanilide was recovered unchanged.

The identity of II in almost all the cases was established by converting it to the known 3-substituted-2-quinolone (III) by the usual methods[1,2] excepting in the case of *α*-allyl acetoacetanilide which was converted into 4′ : 5′-dihydro-4 : 5′-dimethylfurano-(2′ : 3′-2 : 3) quinoline by the method of Raman[3].

No hydrolysis of ethyl bromoacetate occurred under the conditions of the reaction in contrast with the earlier observations about this reagent for alkylation of nitriles and ketones[3].

The present method provides a simple and convenient mode of preparation of *α*-alkyl derivatives of reactive anilides and is superior to the earlier methods[1,2,4]