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# CHEWABLE TABLETS OF ACETAMINOPHEN-PRODRUG APPROACH*

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## ABSTRACT

A prodrug of acetaminophen, viz. N-[4-(acetyloxy)phenyl] acetamide suitable for incorporation in a chewable tablet has been synthesized and its structure elucidated. Various characteristics required to be considered under preformulation studies of this dosage form have also been investigated. The results indicated that the material could be taken up for commercial exploitation.

## INTRODUCTION

The analgesic antipyretic acetaminophen (A) has been marketed in a variety of dosage forms. Its acrid taste restricts its use in chewable tablets.

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Earlier studies done to overcome this problem include the work of Repta & Hack[1] & Hussain et al.[2] Tastelessness and bioavailability were the criteria employed for such a molecular optimization. The N-[4-(acetyloxy)phenyl] acetamide (P.A.) derivative of A, which has been reported to possess low aqueous solubility[3] and nearly similar bioavailability to A[4] coincidently meets the requirements of a drug suitable for incorporation in chewable tablets. It was hence, considered of interest to prepare and evaluate this compound for incorporation in chewable tablets.

Important aspects of PA including its synthesis, structure & physico-chemical characteristics are presented here. Attempt has also been made to prepare a chewable tablet formulation containing this drug which has been evaluated subsequently.

## MATERIALS AND METHODS

Chemicals and solvents : All the chemicals and solvents used were of compendial grade or AR/CP grade manufactured by Glindia (BDH Chemicals) or SM Chemicals and were employed without further purification.

Synthesis of P.A. : Hundred grams (0.66 moles) of A was placed in a 500 ml round bottom flask containing mixture of 62 ml (0.66 moles) of acetic anhydride, 10 ml of reagent grade pyridine and 100 ml of isopropanol. The mixture was refluxed till a clear solution was obtained. It was then poured on 500 g of crushed ice and filtered. The precipitated P.A. was washed with chilled water till free from pyridine and acetic acid. The white solid

obtained was recrystallized from isopropanol - water (40:60) yielding glossy crystals, melting at 154 - 155°C.

Structure elucidation of P.A.

Elemental analysis : Heraeus microanalyser was used to estimate the percentage of carbon, hydrogen and nitrogen in P.A.

Calc. for C, H, N, (O) (%); C, 62.17; H, 5.74; N, 7.25;(O), 24.84

Found (%): C, 62.22; H, 5.73; N, 7.31; (O), 24.74

UV Spectrum : UV Spectrum of the compound in distilled water was recorded on a Perkin Elmer UV-VIS. Spectrophotometer model 550. It showed maximum absorbance at 240 nm with molar absorptivity of 12,096.

IR Spectrum : IR Spectrum of the compound in KBr was recorded on a Perkin Elmer IR-Spectrophotometer, model 1300.

NMR Spectra : $^{1}H$ NMR Spectrum of the compound in $CDCl_3$ was obtained on a Varian T-60 NMR spectrometer at 60 MHz using TMS as an internal standard.

$^{13}C$ NMR spectra (protons completely coupled, noise decoupled and off-resonance decoupled) of the compound in $CDCl_3$ were recorded on Brucker AM-500 FT NMR spectrometer at 125.7641 MHz with reference to TMS using $CDCl_3$ resonance at 77 ppm.

Mass Spectrum : Mass spectrum of the compound was obtained at electron impact of 70ev and temperature of 250°C on a Shimadzu QP-1000 mass spectrometer.

Physicochemical Characteristics

(1) Solubility : Solubility of P.A. was determined at 30 ± 1°C using method suggested by Lalla & Baichwal[5].

(2) Moisture sorption : One gramme sample of the prodrug was placed in an open tared petridish and exposed to 98%, 80%, 60%, 40% and 0.119% RH for a period of 30 days, at 30 ± 1°C. Weight of this dish was recorded at regular intervals of 24 hours and increase in weight (if any) was recorded.

Other Preformulation Studies

Heat of Solution : Heat of solution of P.A. was determined in a calorimeter by standard method using 5g of the sample in 1 litre purified water.

Micromeritics :Particle size was determined in Shimadzu Centrifugal Particle Size Analyser, Model SC-CP-2. Angle of repose was determined using method suggested by Craik[6], Packed and bulk densities were determined by standard methods.

Characterization of Polymorphs

X-ray powder diffraction : X-ray diffractograms of P.A. were recorded on a Philips X-ray unit at a scan speed of 3°/Min.

Thermal Analysis : DSC and TG Scans were recorded using Mettler TA-3000 thermal analysis system.

Infrared analysis : IR-Spectra of PA in KBr were recorded on Perkin Elmer IR spectrophotometer model 1300.

Purity Analysis using DSC : DSC-30 of Mettler TA-3000 thermal analysis system with built-in purity software was used for this

purpose. About 5 mg of P.A. seived through 40# screen was weighed directly into a DSC sample pan and subjected to a heat flux over a temperature range of 140 -160°C at a rate of 2k°/min under a purge of nitrogen with flow rate of 80 ml/min.

Hydrolytic behaviour in buffers & enzymes

Two ml solution of P.A. (0.04M) in spectroscopic grade dioxane was transferred to 100 ml volumetric flask and the volume was adjusted with the help of buffer of a desired pH value (1.2 to 8). Absorbance of the solution was measured at 290nm at different time intervals, in Perkin Elmer UV-VIS Spectrophotometer Model 550. The concentrations of A & P.A. were calculated from the absorbance values by extrapolation from the standard graph prepared using known concentrations of A & P.A..

DRUG-EXCIPIENT COMPATIBILITY : This was determined by using DSC-30 of Mettler TA-3000 thermal analysis system by investigating the thermal behaviour of powders containing P.A. admixed with dextrose monohydrate, dextrose anhydrous and ascorbic acid separately in 1:1 proportion and of P.A. in the tablet formulation. The work was based on the method reported by Lee and Hersey[7] employing DTA. About 5 mg. of sample was taken in an aluminium crucible covered with a pierced lid. The sample was heated at a rate of 5°K/min. using temperature programmes of 35-160°C and 35-200°C under nitrogen.

Preparation and evaluation of chewable tablets of P.A.

About 24 batches with varying composition were prepared; fourteen out of these were prepared by wet granulation using 10% starch

paste, 12% gelatine or 2% PVP solution; the remaining formulations ( including lead formulations A and B in Table - 3) were prepared by mixing P.A. with excipients and directly compressing the mixture on a single punch motor-operated tablet press using 12.5 mm flat faced punch set adjusting the die capacity to yield tablets weighing 550 mg with hardness of 7-8 $kg/cm^2$. Each tablet contained around 153.37mg of P.A. (equivalent to 120mg of acetaminophen). The tablets were studied for physical and organoleptic characteristics. Average weight, weight variation, hardness and friability were determined by standard methods; appearence was observed visually while the taste was evaluated in a panel of 5 volunteers.

Drug content : Drug content was determined in about 550mg of accurately weighed powder obtained after crushing 5 tablets. The sample was transferred to 1 l volumetric flask and the volume was adjusted with distilled water to the mark. After shaking the flask for about 30 minutes, the solution was filtered through G-4 sintered glass funnel. The absorbance of 0.5 ml of this filtrate after dilution with water to 10ml was measured spectrophotometrically at 240nm. in a Perkin Elmer UV_VIS spectrophotometer model 550 against distilled water as blank.

Accelerated stability studies on chewable tablets of P.A.; Qualitative detection of P.A. by TLC : This was done using the method reported by Koshy et al[5].

Quantitative determination of P.A. : Powdered sample (about 550 mg equivalent to 153.377 mg. of P.A.) was stirred with 25 ml of chloroform for 10 min. and filtered into a 250 ml volumetric flask. The volume was adjusted to the mark with chloroform. Five ml of this solution was loaded on 19 mm x 450 mm silicic acid column (prepared by mixing 10 gm of silicic acid with 7 ml of water) previously washed with 100 ml of chloroform.[4] The developement and the elution was done by addition of 50 ml of chloroform. The eluate was collected in a 500 ml round bottom flask and the solvent was completely removed by distillation under vacuum. The absorbance of the residue (after dissolving in water and suitably diluting) was measured spectrophotometrically at 240 nm.

Heat stability : Seven samples of 50 tablets each of formulation A were taken in petri dishes and were placed in desiccators containing saturated salt solutions giving RH of 60% at 30°C & 60% and 80% at 37°, 50° and 60°C respectively. It was planned to draw the samples at two weeks interval during ten weeks and examine the same for visual appearance, hardness and drug content.

On similar lines, tablets of formulation B were also investigated excepting that the temperatures maintained in this study were 30°, 37°, 50° and 55°C in absence of any specific moisture conditions.

Light stability : Stability to light under accelerated conditions was investigated in a light-stability cabinet

fabricated along the lines suggested by Lachman et al.[9,10]. Intensity of fluorescent light at different points in the cabinet was measured using a Megatron - luxmeter Type DA-10, Mark II. It was found to be 986 foot candles at a distance of 18" from the bank of fluorescent tubes. Samples of formulation `B' were exposed to this intensity for a period of two months. The temperature recorded was 32°C and could not be lowered further. The samples were also placed at a distance of about 18" from the bank of UV light. The samples were drawn at 2 weeks interval and evaluated as described under `Heat stability of tablets' for formulation A.

## RESULTS AND DISCUSSION

Structure elucidation : The mass spectrum of P.A. shown in Figure 6 gave the molecular ion peak at m/e 193 which corresponds to the molecular weight. Combustion analysis showed the compound to have C = 62.22%, H = 5.73%, N = 7.31% (and O = 24.74%). The molecular formula worked out to be $C_{10}H_{11}NO_3$. IR-spectrum (Figure 1) showed C=O bands at 1725 $cm^{-1}$ and 1680 $cm^{-1}$ respectively. A peak at m/e 43 suggested two CH C=O groups in view of the C=O peaks in infrared and singlets at 169.5 ppm and 168.3 ppm and quartets at 21 ppm and 24.33 ppm, respectively in the off-resonance decoupled $^{13}C$ NMR spectrum (Figure 5). Position of C=O bands, together with one nitrogen and three oxygen atoms in the formula indicated presence of an ester and an amide group; N-H stretch at 3340 $cm^{-1}$

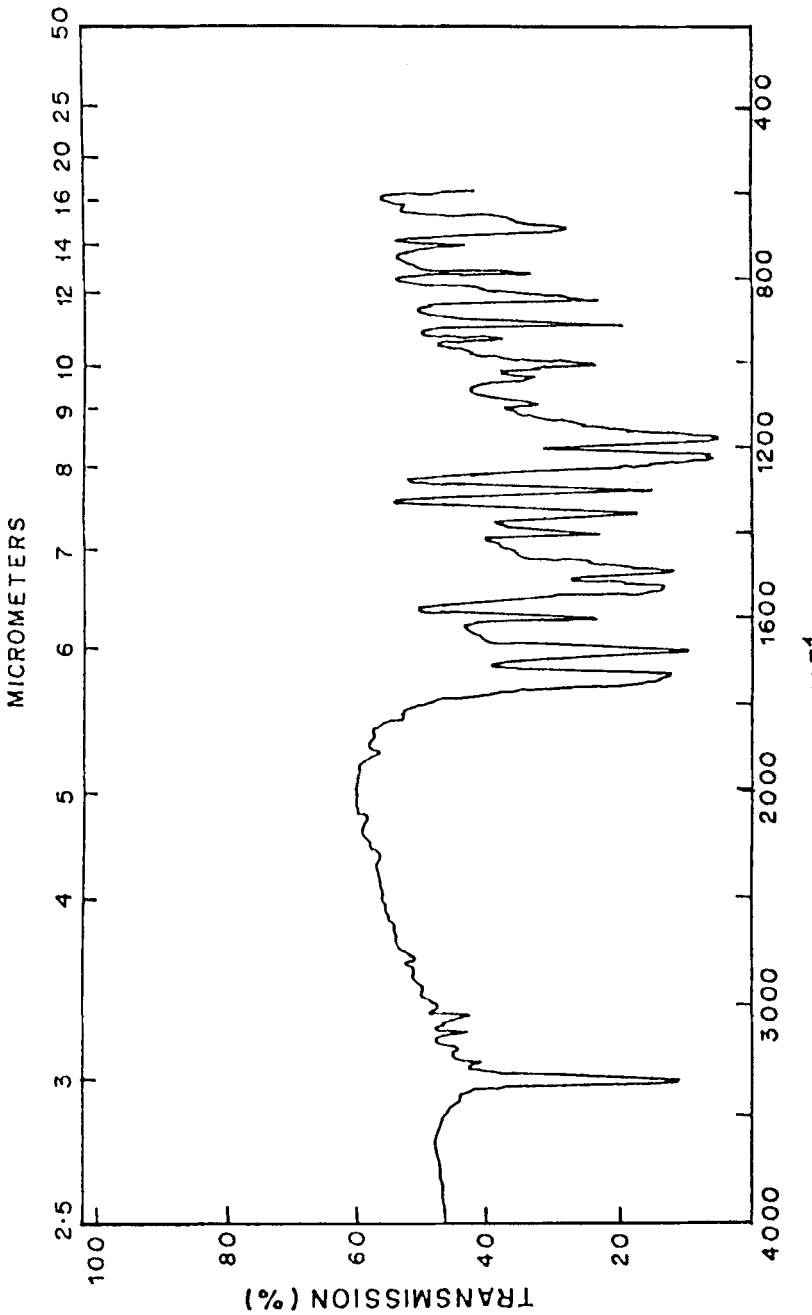


FIGURE : 1 Infrared spectrum of P.A. sample in KBr disc.

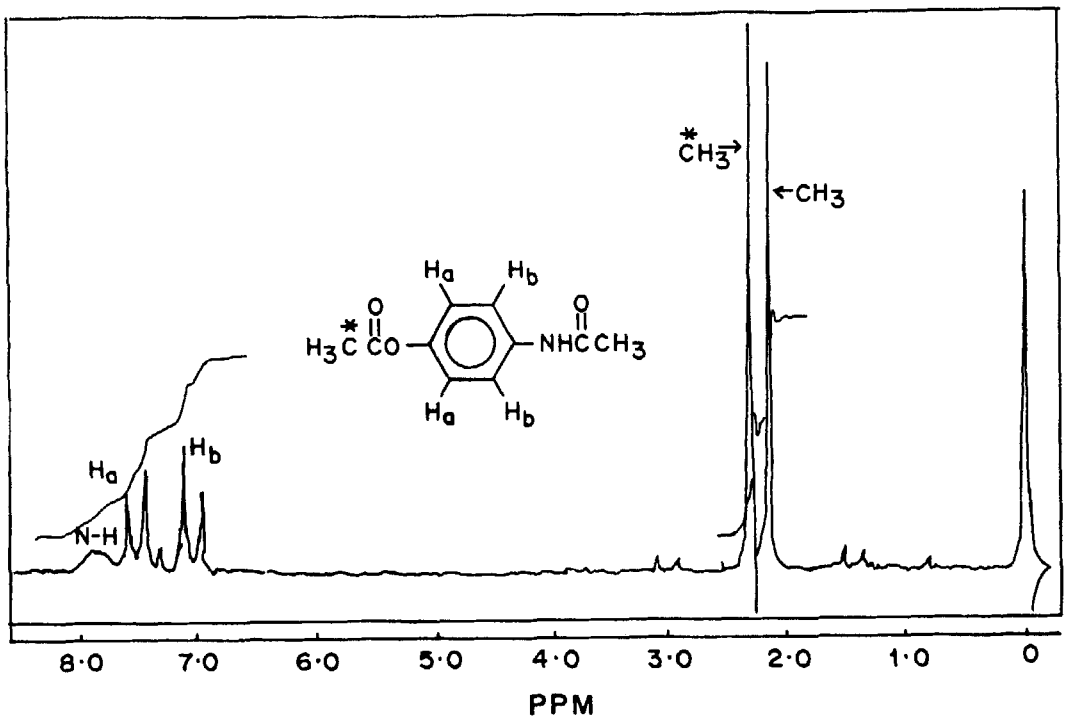


FIGURE : 2 $^{1}H$ NMR spectrum of P.A. . Solvent $CDCl_3$, 60 MHz, sweep width 500 Hz.

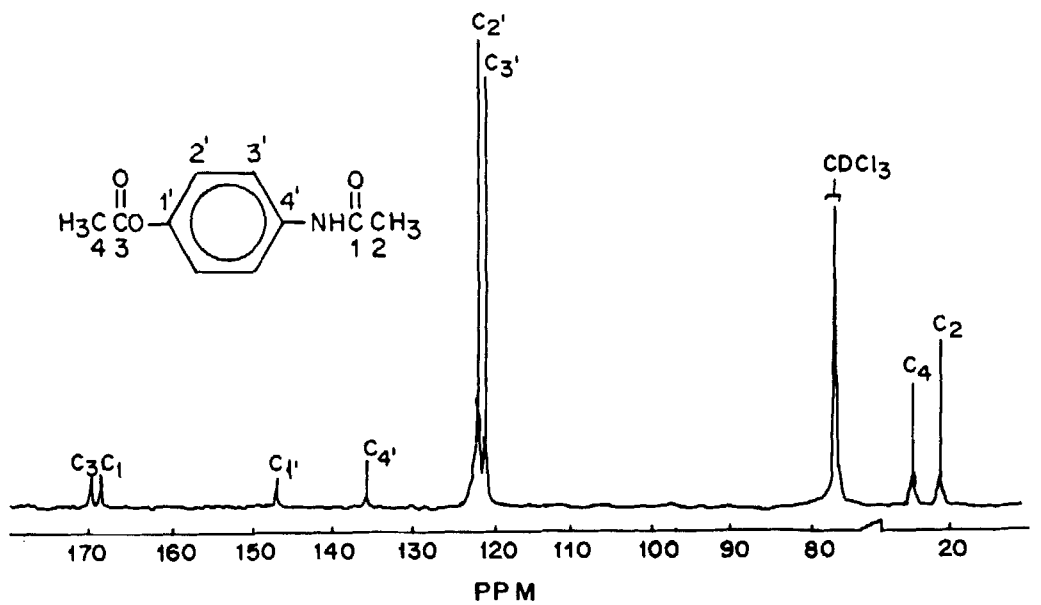


FIGURE : 3 Noise decoupled $^{13}C$ NMR spectrum of P.A. . Solvent $CDCl_3$, 125.7641 MHz, sweep width 21380.88 Hz.

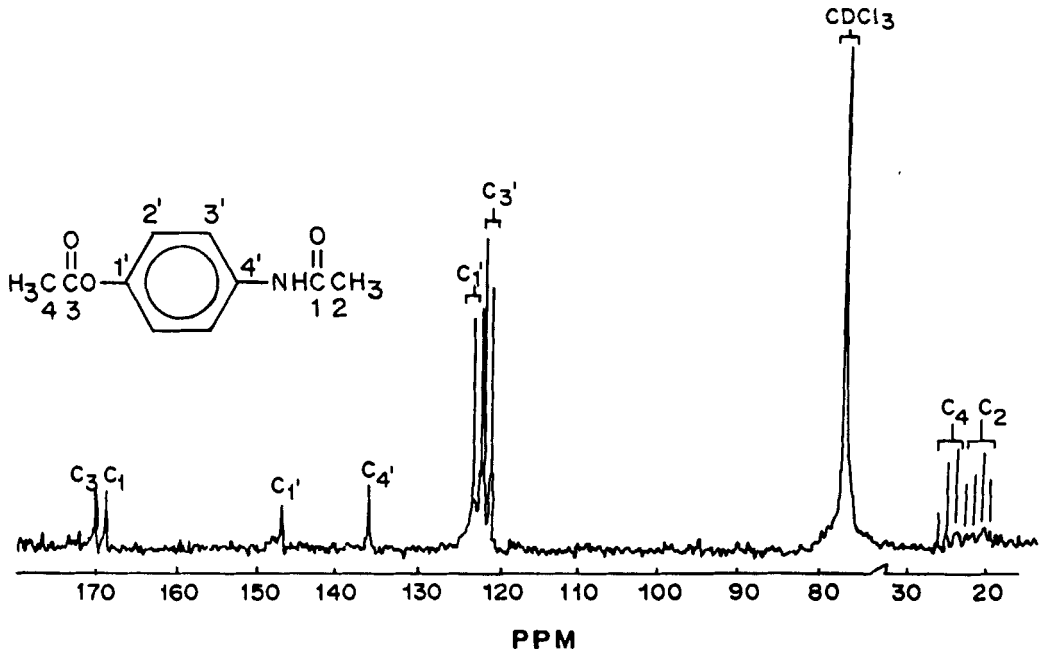


FIGURE : 4 $^{13}C$ NMR spectrum of P.A. with the protons completely coupled. Solvent $CDCl_3$, 125.7641 MHz, sweep width 21380.88 Hz.

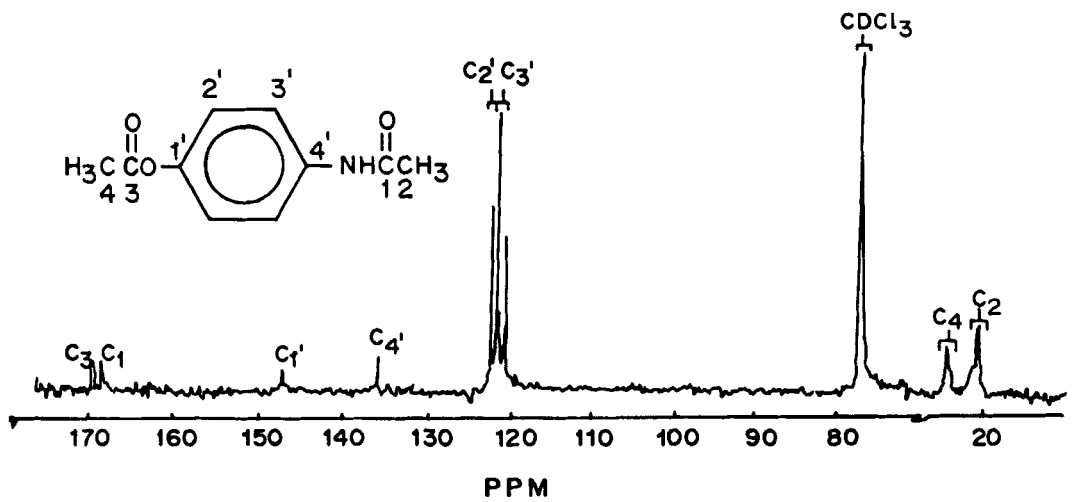


FIGURE : 5 Off-resonance decoupled $^{13}C$ NMR spectrum of P.A. . Solvent $CDCl_3$, 125.7641 MHz, sweep width 21380.88 Hz.

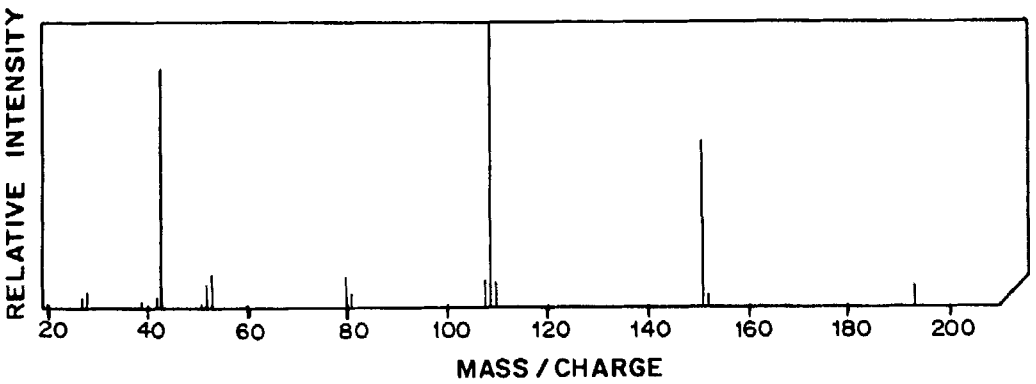


FIGURE : 6 Electron impact mass spectrum of P.A. .

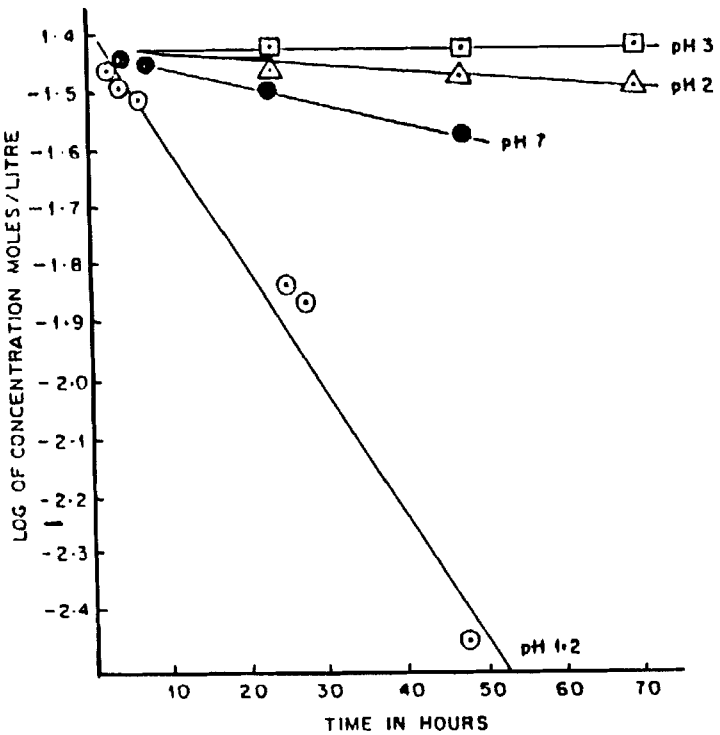


FIGURE : 7 Typical first-order plot for hydrolysis of P.A. at various pH levels at 30 ± 2°C.

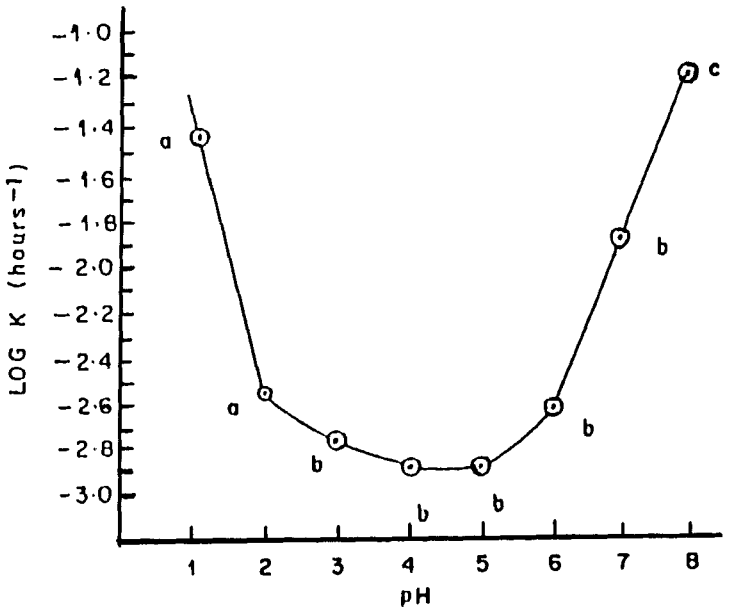


FIGURE : 8 pH-rate profile for hydrolysis of P.A. at 30 ± 2° C. a: HCl-KCl buffer; b: citric acid-phosphate buffer; c: $NaH_2PO_4$-$Na_2HPO_4$ buffer.

in IR-spectrum further pointed out that the amide was a secondary amide. Presence of an aromatic ring is indicated by $^1H$ NMR spectrum (Figure 2) of the compound, which showed multiplet between $\delta$ 6.97 and $\delta$ 7.6 (4H) characteristic of a p-disubstituted benzene ring and the general appearance of infrared spectrum which showed a small peak at 3040 $cm^{-1}$, strong peaks at 1590, 1520 and 1490 $cm^{-1}$ and several peaks in the low frequency (high wavelength) region. In noise decoupled $^{13}C$ NMR spectrum (Figure 3), eight carbon atoms and in $^{13}C$ NMR spectrum with the protons

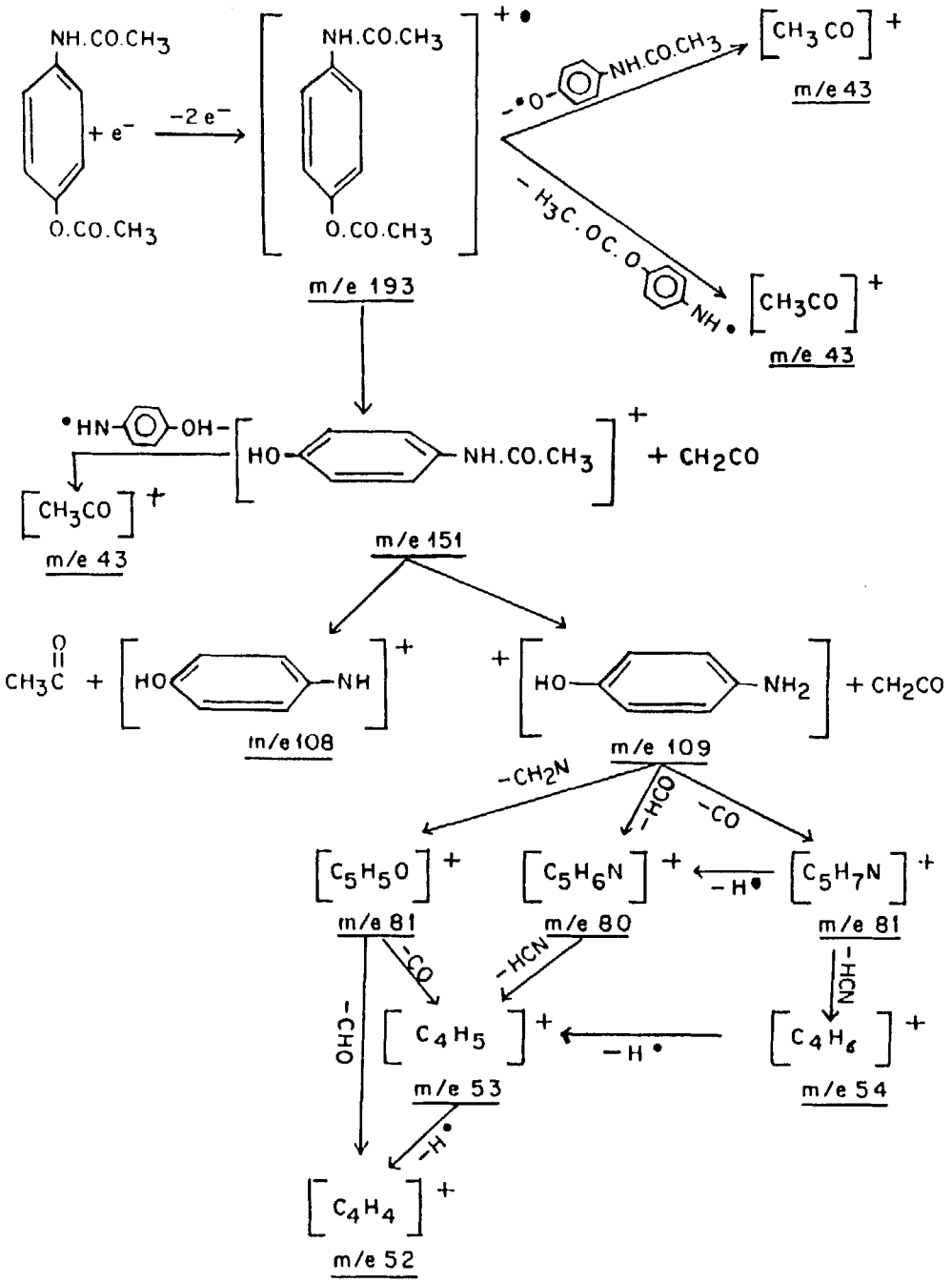


PLATE : 1 Proposed fragmentation pattern for P.A. .

completely coupled (Figure 4), eight protons were observed. The discrepancy between this count and the molecular formula confirmed the para substitution in benzene ring.

Based on above discussion, the structure of the compound assigned was:

Detailed study of mass spectrum assisted in determining fragmentation pattern of the compound shown in plate 1. It showed principle peaks at m/e 193,151,109 (base peak), 108,81,80,53,52 and 43.

The solubility data of P.A. is included in Table 1. Apparently, the amount dissolved does not bear any correlation with the dielectric constants of the solvents. As regards moisture sorption, samples stored at room temperature under varying conditions of humidity for one month failed to show any significant changes in the initial weight of the samples indicating that P.A. was non-hygroscopic. Negative heat of solution of this compound (-7.2 cal/gm) indicated that drug itself had a pleasant mouth feel. Dissolution of the saccharides was associated with endothermic changes. The loading of the drug with the saccharides (1:1) had additive effect. However, in presence of lubricants, binders, etc. in the formulation, the value fell substantially. The results have been depicted in Table 2. The average particle size was found to be 30 to 35 microns.

TABLE : 1

Solubility of P.A. in Different Solvents.

| No | Solvent | Dielectric Constant[12] $\epsilon$ | Solubility (mg/ml) |
|---|---|---|---|
| 1 | Water | 78.3 | 0.33 |
| 2 | Methanol | 32.6 | 72.99 |
| 3 | Ethanol | 24.3 | 45.87 |
| 4 | Acetone | 20.7 | 81.50 |
| 5 | n-Propanol | 20.1 | 50.00 |
| 6 | Ethyl methyl ketone | 18.45[13] | 62.50 |
| 7 | Isopropanol | 18.3 | 33.67 |
| 8 | Ethyl acetate | 6.02 | 27.80 |
| 9 | Chloroform | 4.806 | 49.02 |
| 10 | Diethyl ether | 4.335 | nil |
| 11 | Benzene | 2.275 | 1.50 |
| 12 | Carbon tetrachloride | 2.238 | nil |
| 13 | Dioxane | 2.209 | 51.02 |

TABLE : 2

Heat of Solution of Bases and Formulations

| Materials | Heat of solution Cal/g |
|---|---|
| P.A. | -7.2 |
| Mannitol | -30.1 |
| Mannitol + P.A. | -33.9 |
| Dextrose | -25.1 |
| Dextrose + P.A. | -30.7 |
| Lactose | -21.2 |
| Lactose + P.A. | -25.8 |
| Sucrose | -5.4 |
| Sucrose + P.A. | -10.3 |
| Sorbitol | -23.2 |
| Sorbitol + P.A. | -28.5 |
| Formulation A & B | -5.0 |

All Combinations of Saccharides and P.A. were in proportion of 1:1.

TABLE :3

Compositions of Formulations A & B

| Sr. No. | Ingredient | Formulation (%) A | B |
|---|---|---|---|
| 1. | P.A. | 27.9 | 27.9 |
| 2. | Dextrose anhydrous | 37.12 | - |
| 3. | Dextrose Monohydrate | - | 36.65 |
| 4. | Ascorbic acid | 13.63 | 13.63 |
| 5. | Glycine | 4.0 | 4.0 |
| 6. | Saccharine Sodium | 0.2 | 0.2 |
| 7. | Cellulose powder | 10.73 | 11.0 |
| 8. | Spray dried Orange flavour | 1.8 | 1.8 |
| 9. | Talc | 4.0 | 4.0 |
| 10. | Magnesium Stearate | 0.62 | 0.62 |
| 11. | Disodium EDTA | - | 0.2 |

Angle of repose, coefficient of friction, aerated bulk density, packed bulk density and percentage compressibility were found to be $43.67^{\circ}$ , 0.69, 0.29 g/cm$^3$, 0.54 g/cm$^3$ and 45.71% respectively (average of 3 readings). The results indicated that P.A. had poor flowability and compressibility.

The result of X-ray, thermal & infrared analysis indicated that the compound existed in at least three polymorphic forms, viz. I, II & III. The details of this study are being published elsewhere. Thermograph of P.A. showed two thermal events viz a small endotherm around $126^{\circ}$C and a major endotherm at about $154^{\circ}$C (denoting the melting point). In fact, the thermal event at $126^{\circ}$C

is due to a complete solid-solid transition of form I into II. By using TGA, it has been established by us that P.A. doesnot decompose prior to or during melting. Hence, the use of DSC which is simple quick and accurate for purity determination is valid. Results were found to be reproducible. Purity of double recrystallized sample pf P.A. from water:isopropanaol (1:0.67) was found to be 99.83% while the melting point and heat of fusion were found to be 154.3°C and 160.29 J/G respectively.

Figure 7 shows typical first order plots for hydrolysis of P.A. in buffers with pH values of 1.2, 2, 3 and 7.The pH rate profile of P.A. shown in Figure 8 indicated the minimum rate of hydrolysis at pH 4 and 5, respectively. At pH levels investigated, $t_{1/2}$ was found to be greater than 10 hrs. The results of studies on hydrolysis of P.A. with pancreatic lipase indicated complete conversion of this derivative of A in less than 15 min thus confirming adequacy of bioavailability.

P.A. was found to be compatible with the excipients. This was concluded from the thermographs which did not show any deviation from the anticipated peaks.

Of the 24 different formulations tried and given to the taste panel, formulation A and B were acceptable to all of them. Some formulations containing citric acid, although acceptable to the taste panel could not be considered for further study due to processing problems. When stored at higher humidity & temperature tablets of formulation A showed softening and complete

discoloration within a week. Results could not be quantitated since the tablets stuck to each other. However, TLC showed an additional spot corresponding to A.

In tablets of formulation B, appearance of brownish specks was noted after deactivation of silica gel in the desiccators. This discoloration was attributed to ascorbic acid which is sensitive to moisture within the formulation & in the atmosphere. These findings are in conformation with the observations about behaviour of ascorbic acid made by de la Vega[14], Poulsen[15] and Blaugh et al[16]. TLC of tablets of formulation B stored at 55°C for the eight and ten weeks exhibited an additional spot corresponding to A. Drug content found was 98.72% and 97.36% respectively.

As regards the stability to light, the tablets stored did not show any degradation when exposed to high intensity fluorescent light or a bank of UV tubes when stored in closed containers containing activated silica gel.

Due to unsuitability of dextrose in formulations A & B it is proposed that this material be substituted by relatively non-hygroscopic saccharide, viz. Mannitol. The manufacturing and packaging of these formulations be done under controlled conditions of temperature & humidity.

From the foregoing discussion, it is observed that P.A. is a good candidate for incorporatiom into a chewable tablets.

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