1680, 1660. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1,03 (d, ^{3}J = 6,7 Hz, 6 H, HC(CH_3)$_2$); 1,14 (t, 3 H, CH_2CH_3); 2,29 (s, 3 H, CH_3); 2,89 (sept, ^{3}J = 6,7 Hz, 1 H, $HC(CH_3)_2$); 3,02 (m, 2 H, CH_2CH_3); 4,68 (bs, 1 H, $CHCH_2CH_3$); 6,48 (bs, 1 H, NH); 6,53 (s, 1 H, Chinonimin-H*); 6,80 (bs, 1 H, NH); 6,98 (s, 1 H, Chinonimin-H); 7,35 (s, 1 H, Phenyl-H); 8,22 (s, 1 H, Phenyl-H). UV/Vis (CH_2Cl_2, nm): λ_{max} (log ε) = 278 (4,20), 330 (3,77), 513 (3,62).
$C_{20}H_{22}N_3ClO_2$ (371,9)

2.3. 6-Chlor-1,1-dioxo-7-N-[(1-methyl-4-(1-methylethyl)-1,4-cyclohexadie-non-6-yliden)amino]-1,2,3,4-tetrahydro-1,λ^6-benzo-1,2,4-thiadiazin (**14**)

Ausbeute: 304 mg (16%) rotviolette Kristalle vom Schmp. 196 °C. Dc: $R_f = 0,23$. MS (70 eV) m/z (rel. Int.): 380 (M^+, 100), 365 (20), 351 (14), 344 (22), 337 (12), 316 (42), 162 (30), 118 (60). IR (KBr, cm^{-1}): 3380, 3260, 3070, 1660, 1540. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1,07 (d, ^{3}J = 6,8 Hz, 6 H, HC(CH_3)$_2$); 2,37 (s, 3 H, CH_3); 2,95 (sept., ^{3}J = 6,8 Hz, 1 H, $HC(CH_3)_2$); 5,09 (m, 2 H, CH_2); 6,53 (s, 1 H, Chinonimin-H*); 6,73 (bs, 1 H, NH); 6,90 (bs, 1 H, NH); 7,02 (s, 1 H, Chinonimin-H); 7,42 (s, 1 H, Phenyl-H); 8,34 (s, 1 H, Phenyl-H). UV/Vis (CH_2Cl_2, nm): λ_{max} (log ε) = 275 (4,18), 320 (sh), 502 (3,54).
$C_{17}H_{18}N_3ClSO_3$ (379,9)

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Determination of maprotiline hydrochloride in tablets by ion-pair extraction using bromthymol blue

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Maprotiline hydrochloride (**1**) is a tetracyclic antidepressant. Various methods have been reported for the assay of **1**: colorimetry [1–3], fluorimetry [4, 5], HPLC [6], GC [7], GC-MS [8], immunoassay [9] and RIA [10]. Reported colorimetric methods are based on dithiocarbamic acid copper complex formation [1] and the reaction of the maprotiline base with π acceptors, 7,7,8,8-tetracyanoquinodimethane [2] and *p*-chloranil [3]. The last two methods require extraction of the base and heating for the reaction.

This paper describes a more simple and rapid spectrophotometric method for the determination of **1** in tablets through the formation of an ion-pair with bromthymol blue (BTB, **2**). The ion-pair formed was highly colored and could easily be extracted with dichloromethane. The absorption specrum in dichloromethane showed a maximum at 409 nm. Maximum color intensity was obtained at pH 6.0 using phosphate buffer. A 2.5 fold excess of the reagent was found to be sufficient to complete the reaction. The absorbance of the final solution was stable for at least 24 h at room temperature in the dark. The composition of the ion-pair formed was determined by Job's Curve and molar ratio methods. The stoichiometric ratio of **1** and **2** was found to be 1 : 1. The calibration graph was rectilinear in the concentration range of 2–16 $\mu g \cdot ml^{-1}$ of **1** ($A = 0.0609\,c - 0.005$, $r = 0.9994$).

In order to increase the sensitivity, a tetrabuthylammonium hydroxide (TBAH) (**3**) solution was added to the ion-pair in dichloromethane. The absorbance of the resulting blue solution due to the TBAH-BTB ion-pair was measured at 630 nm. The calibration graph was rectilinear in the concentration range of 2–7 $\mu g \cdot ml^{-1}$ of **1** ($A = 0.1442\,c - 0.064$, $r = 0.9996$).

The developed ion-pair extraction method was applied to commercially available tablets. Tablet excipients did not interfere. The results were statistically compared with those obtained with the official USP 23 HPLC method [11] using t and F tests at 95% confidence level. There were no significant differences between the proposed and the USP method with respect to the mean values and standart deviations (Table).

Preliminary experiments were done in order to analyse **1** in urine by the proposed method in the case of overdose. Absorbance values of the blank were found to be quite

Table: Comparison of the results obtained by the spectrophotometric and the HPLC method for the determination of maprotiline hydrochloride in tablets

Method	Mean (μg)	RSD
Spectrophotometry	24.87	0.53
HPLC	24.90	0.36
F = 2.15**		
t = 0,42***		

* Each tablet contained 25 mg of **1**
** Tabulated F = 6.39
*** Tabulated t = 2.31

high and variable because of the interferences of some naturally occurring amines in urine. Therefore, some modifications of the method are necessary. This subject is now under investigation.

Experimental

1. Apparatus and chemicals

Maprotiline hydrochloride of pharmaceutical grade was used. The other reagents were of analytical grade. Absorbance measurements were made with a Shimadzu UV-160 A UV visible spectrophotometer.

2. Solutions

The stock solution of **1** (1.27×10^{-4} M) was prepared in water. The solution of **2** (6.4×10^{-4} M) was prepared in phosphate buffer solution of pH 6.0. A solution of 20% **3** in methanol was used.

3. Procedure

3.1.1. Preparation of calibration graphs

Suitable aliquots of the stock solution of **1** (0.25–2 ml) were transferred to stoppered glass tubes and 1 ml of **2**-solution and 3 ml of phosphate buffer (pH 6.0) were added. The volume was brought to 5 ml with phosphate buffer. The mixture was extracted with 5 ml of dichloromethane for 2 min with a vortex mixer. The absorbance of the dichloromethane layer was measured at 409 nm against a blank solution prepared similarly.

3.1.2. Preparation of calibration graphs using TBAH

Suitable aliquots of the stock solution of **1** (0.50–1.75 ml) were transferred to stoppered glass tubes and 1 ml of **2**-solution and 3 ml of phosphate buffer (pH 6.0) were added. The volume was brought to 5 ml with phosphate buffer. The mixture was extracted with 10 ml of dichloromethane for 2 min with vortex mixer. To 3 ml of the solution, 25 µl of **3**-solution were added. The absorbance of the dichloromethane layer was measured at 630 nm against a blank solution prepared similarly.

3.1.3. Assay procedure for tablets

Tablet powder equivalent to one tablet (each tablet contains 25 mg of **1**) was accurately weighed and transferred into a 500 ml calibrated flask. Water (200 ml) was added, then the mixture was shaken mechanically for 20 min and diluted with water to the volume, mixed and filtered. The filtrate (1 ml) was analysed similarly as described in section 3.1.1. beginning with "1 ml of **2**-solution". The amount of **1** in tablets was calculated from the regression equation obtained from the calibration graph.

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Preparation and evaluation of benzyl benzoate-loaded poly-ε-caprolactone nanoparticles

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Aqueous suspensions of polymeric nanoparticles have been used for pharmaceutical applications such as drug targeting [1, 2]. They can be produced either by polymerisation [3, 4] or by dispersion of preformed polymers [5, 6]. The main difficulty encountered in the colloidal suspension systems was the separation of the nanoparticles from the liquid medium. This paper describes two methods to separate nanoparticles from the aqueous phase, namely ultracentrifugation and flocculation [7]. The later technique was performed in the presence of electrolytes and gave similar results. The determination of benzyl benzoate (BB) in nanoparticles and in the supernatant can be performed without derivatization by GC-MS [8].

BB determinations were performed simultaneously in the aqueous phase and in the sediment, on aliquots of the same sample of nanoparticle suspension at a concentration of 5 µl BB per ml suspension. When 10 ml of a nanoparticle suspension were ultracentrifuges at $50{,}000 \times g$ for 45 min, a very low concentration (1,39%) of BB was found in the aqueous phase, and 98,61% of the BB was entrapped in the polymer particles (encapsulated). When a sample of nanoparticles (10 ml) was flocculated directly by addition of electrolytes, the percentage of free BB was 1.16%, against 98.84% BB associated with the polymer. This result was expected because BB is a lipophilic compound which is not soluble in water. When the formulations were tested for release *in vitro* at pH = 7.4 (Fig.), it was found that BB and phenobarbitone were released in a biphasic pattern, characterized by an initial and variable rapid release period followed by a continuous and much slower release phase. The best ratio between free and encapsulated BB was obtained in the case of 4 ml BB/100 ml suspension. Ten ml of the nanoparticle suspension were flocculated. For this sample four successive determinations allowed calculation of the inter-assay precision (RSD). The results were as follows: 0.363 µl BB per ml

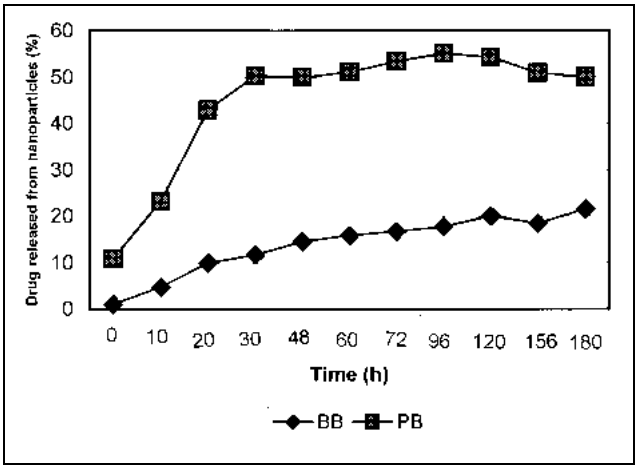

Fig.: *In vitro* release profile of benzyl benzoate (BB) and phenobarbitone (PB) from nanoparticle suspensions