ment of an OP of NE which can deliver the drug with a controlled rate for longer duration in order to achieve better therapeutic benefits with improved patient compliance and minimum side effects.

Different OP data for 30% ($t_{30\%}$) and 60% ($t_{60\%}$) drug release are shown in the Table. Release profiles are shown in the Fig. Conventional tablets (Nimulid®) delivered the drug faster and $t_{30\%}$ and $t_{60\%}$ were achieved in 0.5 and 1.85 h, respectively. The OP delivered the drug with a comparatively slower but almost constant rate for 12 h.

In our earlier investigation, when OP does not contain DSP and SBC, but contained NaCl, only 4% of NE release was observed in 12 h and was attributed to the poor water solubility of the drug. So, NE solubility was modulated by incorporation of different buffers in the osmotic core, and much higher drug releases were observed from batch I (65%), II (75%) and IIIa (71%) in 12 h. Batches II and IIIa exhibit more controlled drug release profiles than batch I.

Drug release data shown in the Table indicate that formulation IIIc coated with a microporous membrane gave faster and higher (73% in 12 h) drug release than OP IIIa and IIIb coated with SP membranes. Batch IIIa coated with cellulose acetate gave a higher (71% in 12 h) drug release than IIIb (42% in 12%) coated with ethyl cellulose. This is attributed to the lower water permeability of ethyl cellulose compared to cellulose acetate [5]. A portion of SBC was coated with enteric coating polymer CAP in batches IIIa, IIIb and IIIc, with an idea to make available uncoated SBC for dissolution of NE in the stomach and coated SBC for dissolution of NE in intestine so as to achieve a constant delivery rate of NE in all parts of the GIT.

Thus, we conclude that poorly water soluble drugs like NE can be formulated well as potential prolonged and controlled release OP using an optimum amount of selective osmotic agents and buffers.

Experimental

NE was a gift of Recon Ltd, India. Nimulid® (100 mg) tablets (Panacea Biotech Ltd. India), best quality chemicals and polymers were purchased. Each batch size of tablets was 500. All the materials (Table) were passed through sieve no. 60 (mean dia. 250 μm), granulated using a 2% w/w ethanolic solution of PVP, dried, mixed with SLS and talc and compressed on a Manesty E2 tableting machine using 11 mm standard concave punches. Tablets were coated in standard coating pan (Edwards and Co., London) using a coating solution as described in the Table and dried overnight at 40 ± 2 °C. An orifice was drilled through all SP coated OP using microdill [6].

All the OP were evaluated for various parameters as shown in the Table and were evaluated *in vitro* (5 runs for each batch) on an USP XXI dissolution apparatus II using 900 ml of pH 7.4 phosphate buffer maintained at 37 ± 0.5 °C and stirred at 50 r.p.m. Withdrawn samples were analysed on a Jasco UV/VIS spectrophotometer (model 7800) at 394 nm, the actual concentration of NE in the samples were read from a calibration curve prepared from pure NE in pH 7.4 phosphate buffer.

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Effects of *Quercus ilex* L. and *Punica granatum* L. polyphenols against ethanol-induced gastric damage in rats

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Local traditional medicine uses widely tannins-rich plants against gastric discomfort and diarrhea, among these plants are *Quercus ilex* roots bark and *Punica granatum* fruit peel. Crude extracts of some medicinal plants of which the main constituent is tannin prevent formation of gastric lesions induced by HCl, ethanol, indomethacin, reserpine and serotonin [1, 2]. Several polyphenols including tannic acid, ellagic acid, flavone, flavanone and quercetin have been reported to protect the stomach against necrotizing agents [3–6]. In this study, we examine the effects of polyphenols extracted from *Quercus ilex* roots bark and *Punica granatum* fruit peel on ethanol-induced gastric damage in rats.

In control animals, 15 min treatment with absolute ethanol were sufficient to induce extended hemorrhagic lesions mainly in the glandular region of the stomach. Animal pretreatment with *P. granatum* and *Q. ilex* polyphenols led to a marked dose-dependent protection of the stomach (Fig.). The number of lesions was slightly reduced but

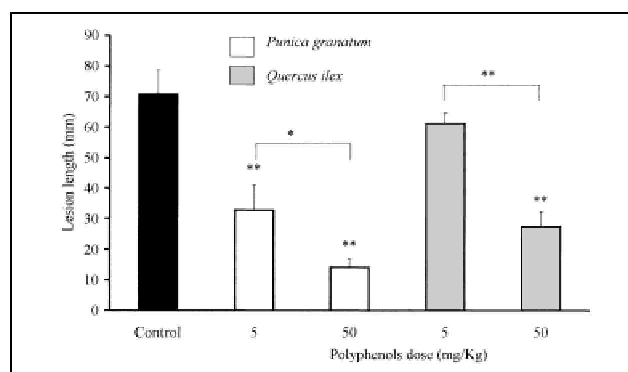

Fig.: Effect of polyphenols extracted from *Punica granatum* fruit peel and *Quercus ilex* roots bark on ethanol-induced gastric lesions in rats. Bars are means + SEM. *P < 0.05; **P < 0.001

without reaching a significant level (P > 0.05). However, both the severity and the length of the lesions were reduced. The protection afforded by *Q. ilex* was observed only with the high dose (60% protection). Total lesions length was reduced by both doses of *P. granatum* polyphenols; the percent protection was 53 and 80% for 5 and 50 mg/kg respectively.

The observed results are in agreement with previous reports showing gastroprotective effects of plant polyphenols [3–6]. The difference in efficiency of *P. granatum* and *Q. ilex* extracts is probably due to differences in their composition and/or in concentration of the same active molecule(s). The mechanisms underlying cytoprotection by polyphenols seems to reinforce the gastric defence barrier: (a) inhibition of the parietal proton pump [4], (b) stimulation of mucus secretion [7] probably by increasing prostaglandin E2 production [8], (d) maintenance of an efficient blood supply [2].

Experimental

Quercus ilex L. roots bark was collected from Babor National Park (Algeria). *Punica granatum* L. fruit peel was collected from fruits available on

the local market. The plant samples were air dried at room temperature and then finely powdered. The powder (10 g) was extracted with 70% acetone overnight and filtered. The filtrate was evaporated under reduced pressure below 40 °C. The aqueous residue was lyophilised and stored in a dessicator at −20 °C. Total polyphenols present in the lyophilisates was determined by the modified Prussian bleu assay [9, 10] using tannic acid as a standard. The extraction yield was 229 and 118 mg of equivalent tannic acid per gram of *P. granatum* and *Q. ilex* dry matter, respectively.

Fasted male Wistar rats (200–300 g) were randomly divided into 5 groups of 10 rats. The first four treated groups received 5 or 50 mg of polyphenols per kg body weight by oro-gastric intubation; whereas control group received proportionate amount of water by the same route. One hour later, all animals were gavaged with absolute ethanol (5 ml/kg). Fifteen min after administration of the necrotizing agent, animals were killed by cervical dislocation and their stomach rapidly removed. Each stomach was opened along the greater curvature, pinned flat on a corkboard and fixed with 10% formalin. Stomachs were photographed at about 2.3 magnification for lesions evaluation. The total length hemorrhagic lesions was evaluated in blind conditions.

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Orthoforin: The main degradation product of hyperforin from *Hypericum perforatum* L.

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Hyperforin is well documented in literature [1–5]. Recent publications show, that it is a highly important principle of the antidepressant activity of alcoholic Hypericum extracts [6–8]. Pure hyperforin is highly unstable in solution as well as in the solid state due to oxidation. The isolation, purification and structure elucidation of the main degradation product is described here.

The mass spectrum of pure hyperforin, which was treated in methanolic solution by a stream of compressed air for 6.5 h is shown in Fig. 1. The main oxidation product at 551.6 Da in the APCIneg. mode showed a total mass increase of 16 Da compared to hyperforin (535.8 Da). Other signals at 567.6, 583.7 and 599.3 Da indicated further oxidation processes. The main degradation product is an intermediate product undergoing further degradation which could be shown by prolonged oxidation experiments. The oxidized sample was separated by preparative chromatography. The main degradation product was collected between 11.8 and 12.5 min, resulting in a HPLC-purity of 99.9%. Other minor oxidation products were obvious in the chromatogram. Storage in methanol for 4 weeks at −20 °C showed a degradation of only 1%. Structure elucidation was performed using one- and two-dimensional ^{1}H and ^{13}C NMR techniques (COSY, HMBC, HMQC, NOESY). In contrast to the spectrum of hyperforin the ^{13}C signals of one olefinic side chain are missing and new signals at 83.0 and 88.8 ppm are detected. Furthermore, narrow signals for C-2, C-3 and C-4 indicate that there is no tautomerism as in the enol system of hyperforin. Since the major parts of the spectra of orthoforin do not strongly differ from those of hyperforin, a cyclic ether without changes in the central bicyclic ring system is suggested to be present in orthoforin. HMBC correlations between

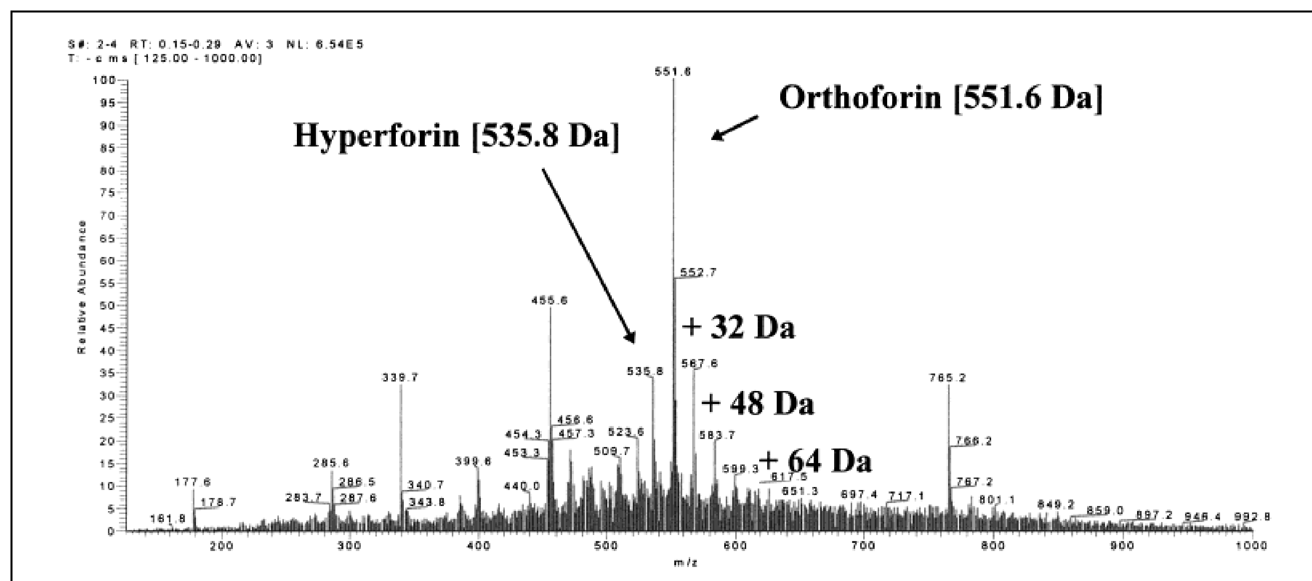

Fig. 1: The mass spectrometric APCIneg.-scan of hyperforin, after 6.5 h of oxidation with compressed air. The main degradation product orthoforin (551.6 Da) shows a mass gain of +16 Da compared to hyperforin. Additionally, signals of 567.6, 583.7 and 599.3 Da can be detected. This could be an indicator for further oxidation processes on the side chains.