

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

7,000

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Conventional and Novel Pharmaceutical Dosage Forms on Prevention of Gastric Ulcers

Işık Özgüney

Department of Pharmaceutical Technology

Faculty of Pharmacy, University of Ege

Turkey

1. Introduction

Peptic ulcer formation in either the stomach or duodenum is due to an imbalance between erosive factors such as hydrochloric acid and pepsin and the ability of the gastroduodenal mucosal to protect and heal itself (1). Unlike duodenal ulcers, in which the importance of acid secretion is indisputable, gastric ulcers can develop despite only minimal amounts of acid.

On the other hand, it has become apparent that consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) and stomach colonization by *Helicobacter pylori* (*H.pylori*) are the two most common causes of peptic ulcer disease. The prevention and management of NSAID related gastrointestinal (GI) complications are well recognized and in many cases successfully treated. However, the understanding and treatment of *H. pylori*-induced ulcers are still in progress (2).

2. NSAIDs induced gastric ulcers

NSAIDs are mainly indicated for mild to moderate pain of somatic origin. Due to their anti-inflammatory effect, they are among the agents most frequently used against musculoskeletal and rheumatic disorders throughout the world (3). Other indications include osteoarthritis, soft-tissue injury, renal colic, postoperative pain, and dental procedures. The efficacy of NSAIDs may vary by patient and by indication. In case of inefficacy, substitution by a NSAID from a different chemical class is a reasonable therapeutic option.

In 1899, acetylsalicylic acid was released to the pharmaceutical market (4). Almost 40 years passed before it was realized that aspirin may damage the gastric mucosa (5). Later, drugs having similar effects were recognized and thus termed 'aspirin-like drugs' or NSAIDs. The main therapeutic actions proved to be analgesic, antipyretic and anti-inflammatory through inhibition of the cyclooxygenase (COX) enzyme system (6,7). During the past 15 years the number of NSAIDs has doubled. Along with the discovery in 1990 of the inducible form of the cyclooxygenase system, i.e. COX-2 (8), and development of COX-2-specific inhibitors, NSAIDs may now be classified as either (i) non-selective NSAIDs, i.e. aspirin and non-

aspirin NSAIDs; (ii) COX-2 preferential inhibitors; and (iii) COX-2-specific inhibitors (coxibs) or COX-1-sparing NSAIDs (9).

NSAIDs may be grouped as salicylates (with as prominent member aspirin itself), arylalkanoic acids (diclofenac, indomethacin, nabumetone, sulindac), 2-arylpropionic acids or profens (ibuprofen, flurbiprofen, ketoprofen, naproxen), *N*-arylanthranilic acids or fenamic acids (mefenamic acid, meclofenamic acid), pyrazolidine derivatives (phenylbutazone), oxicams (piroxicam, meloxicam), sulfonanilides (nimesulide), and others (10). As a group, NSAIDs are structurally diverse and differ in pharmacokinetic and pharmacodynamic properties, but ultimately they share the same mode of action. Like aspirin, nonaspirin NSAIDs inhibit the production of prostaglandins by blocking the COX enzyme, causing analgesic, antipyretic, and anti-inflammatory benefits, but at a risk for increased gastric bleeding (11). Two COX isoforms have been identified and referred as COX-1 and COX-2. The inducible COX-2 is an important regulator to generate prostaglandins that mediate inflammation and pain, whereas the constitutive COX-1 is responsible for maintenance of the integrity of gastric mucosa and platelet aggregation (1).

However, aspirin and nonaspirin NSAIDs differ fundamentally in the way the COX enzyme is inhibited. Aspirin inhibits COX by noncompetitive and irreversible acetylation, where an acetyl group is covalently attached to a serine residue in the active site of the COX enzyme, rendering the COX enzyme permanently inaccessible for the biotransformation of arachidonic acid into PG H₂.

Conversely, nonaspirin NSAIDs competitively and reversibly inhibit the COX enzyme during only part of their dosage interval. This distinction is exemplified by their differential effects on platelet aggregation (10).

The gastroduodenal adverse effects include dyspepsia without endoscopically proven damage, asymptomatic endoscopic lesions of submucosal haemorrhage, erosions and ulcers, and-most important-ulcer complications (3). It is highly likely that the ulcerogenic effects of NSAIDs are directly related to their ability to suppress prostaglandin synthesis in the stomach. Prostaglandins play an important role in the GI tract: they mediate several components of mucosal defence (blood flow, mucus and bicarbonate secretion and mucosal immunocyte function). There is a good correlation between the ability of an NSAID to suppress gastric prostaglandin synthesis and its ulcerogenic action. NSAIDs, including acetyl salicylic acid, also have topical irritant properties that may contribute to their ability to damage the gastric mucosa. The majority of NSAIDs are weak acids with an ionisation constant in the range of 3.5. In the strongly acid environment of gastric juice, drugs are non-ionized and freely cross the cell membrane into the mucosal cells. The elevated intracellular pH promotes dissociation to its ionized form with subsequent intra-epithelial accumulation. The phenomenon of ion trapping and/or ability of these drugs to uncouple oxidative phosphorylation represent two important steps in the topical irritancy of NSAIDs. Thus, intragastric acidic pH plays an important role in the topical or systemic adverse effects of NSAIDs on the gastroduodenal mucosa (12).

Established risk factors for NSAID-associated ulcer complications include patient-specific factors such as advanced age, female gender, a history of peptic ulcer, and drug-specific factors such as the use of non-selective NSAIDs (type, dose, duration, multiple use) and concomitant anticoagulant drugs or corticosteroids. Probable risk factors comprise *H. pylori* infection and heavy consumption of alcohol, whereas use of selective serotonin re-uptake inhibitors, smoking and a number of other factors have also been proposed to contribute. Knowledge of absolute risk estimates is important for clinical decision making (3).

There is consistently clear evidence that advanced age is a major risk factor for complicated ulcer disease. The risk increases at least linearly with age in both NSAID-unexposed and NSAID-exposed individuals (13,14).

There is good evidence from meta-analysis that males have a two-fold higher risk of ulcer complications compared to females (15). However, among NSAID users, women have both a greater relative risk (RR) than men (RR 5.0 versus 3.5) (15) and a higher absolute risk, with number needed to harm (NNH) among women being about 50 versus 75 in men (13).

Patients with a history of peptic ulcer have an overall almost six-fold increased risk of ulcer complications (15, 16). Even though the relative risk of NSAID use is lower in patients without a history of ulcers than in patients with a prior ulcer (odds ratio (OR) 5.0 versus 2.5), NSAIDs are still more dangerous (17) due to the higher base-line risk of ulcer complications among the latter.

Heavy alcohol use was found to be associated with an increased risk of bleeding peptic ulcer (18,19). Previous dyspepsia may be associated with an increased risk of ulcer complications (20). NSAID-related dyspepsia is often treated with a proton pump inhibitor to heal a possible underlying ulcer. Some data suggest that the use of H₂-receptor antagonists can mask dyspepsia that may herald an ulcer bleeding. In clinical practice, therefore, proton pump inhibitors are often preferred (3).

The interaction between *H. pylori* and the use of NSAIDs in the development of gastroduodenal ulcers is less clear. *H. pylori* infection and NSAID use may represent independent but synergistic risk factors (21,22). A recent meta-analysis of 21 studies that evaluated the relationship between *H. pylori* and NSAIDs in the development of gastroduodenal ulcers found that the risk for uncomplicated ulcers was 4 times as high in *H. Pylori* positive compared with *H. pylori*-negative patients, irrespective of NSAID use (OR, 4.03), and 3 times as high in NSAID users compared with nonusers, irrespective of *H. pylori* status (OR, 3.10) (22). Furthermore, the risk of uncomplicated ulcers was almost twice as high among *H. pylori*-positive compared with *H. Pylori*-negative NSAID users (OR, 1.81), and 17.5 times higher among *H. pylori*-positive NSAID users compared with *H. pylori*-negative nonusers. Possible explanations for the increased risk of ulcers in *H. pylori*-positive NSAID users are deterioration of the mucosal barrier caused by inflammation, increased acid secretion, a higher level of apoptosis in the infected mucosa, and decreased gastric adaptation to NSAIDs (23).

Patients with rheumatoid arthritis seem to be at increased risk of having ulcer complications compared with patients with osteoarthritis (24). This difference may, however, be explained at least partly by use of higher doses of NSAIDs in patients with rheumatoid arthritis. Some studies have indicated that patients with a history of heart failure are at increased risk of ulcer complications (25). Moreover, recent data suggest that diabetes mellitus may increase the risk as well (20).

Solid evidence from landmark studies (26, 14), and good meta-analyses (15, 16) indicate that the use of ibuprofen and diclofenac is associated with a lower risk of gastroduodenal adverse effects. The use of naproxen, indomethacin and aspirin constitutes an intermediate position, while the use of piroxicam and ketoprofen is associated with a higher risk. Moreover, clear evidence indicates that a high dose of an NSAID is associated with an enhanced risk of ulcer complications in a dose-dependent fashion. (13, 16, 27, 28, 29). Moreover, users of multiple NSAIDs are at the highest risk (OR 9.0; 95% confidence interval (CI), 5.9±13.6) followed by switchers (OR 6.2; 95% CI, 4.7±8.1) compared with single-NSAID users (OR 4.6; 95% CI, 3.9-5.4) (13).

Initially, it was suggested that short duration of NSAID therapy may be associated with a higher risk of ulcer complications (26,30) perhaps explained by gastric adaptation. However, recent cohort studies and meta-analyses indicate that the risk of ulcer complications remains constant during NSAID exposure (15,31,32). After discontinuation of NSAIDs the risk of ulcer complications declines rapidly, however, being increased during 2 months before returning to the base-line level.

Whether patients are exposed to NSAIDs or not, anticoagulants increase the risk of bleeding from pre-existing ulcers because of their antihaemostatic properties. NSAIDs are prescribed to anticoagulant users in about 13% of elderly subjects, and the risk of ulcer complications is heavily increased (Relative risk (RR) 12.7, 95% CI, 6.-25.7; excess risk 2.4%; and $NNH_{1yr} \sim 40$) (33). Anticoagulants alone also increased both the relative and the absolute risk (RR 4.3, 95% CI, 2.6-7.2; excess risk 0.68%; $NNH_{1yr} \sim 147$).

One out of seven elderly subjects may use both NSAIDs and corticosteroids (34). Other studies (13) have confirmed the relationship and estimated that the excess relative risk due to the interaction between NSAIDs and steroids accounts for almost 60% of all cases using both NSAIDs and steroids.

The use of selective serotonin re-uptake inhibitors (SSRI) seemed to increase the risk of upper GI bleeding threefold (OR 3.0; 95% CI, 2.1-4.4) (35). Concomitant use of NSAIDs, however, increased the risk substantially, with an OR of 15.6 (95% CI, 6.6-36.6), suggesting an important interaction between NSAIDs and SSRI.

With the discovery of the 2 COX isoenzymes, COX-1 and COX-2, it was hypothesized that the continuous production of local gastroprotective prostaglandins is mainly COX-1 dependent, while the inducible production of inflammatory prostaglandins is mainly COX-2 dependent. Most traditional NSAIDs were found to be nonselective inhibitors of both COX isoforms (36). An ideal NSAID would selectively inhibit the inducible COX-2 isoform, thereby reducing inflammation and pain, without acting on the constitutive COX-1 isoform, thereby minimizing toxicity. On the basis of this hypothesis, several COX-2-selective NSAIDs were developed in the 1990s. Celecoxib (Celebrex®), rofecoxib (Vioxx®), and valdecoxib (Bextra®) received FDA approval for use in rheumatoid arthritis and osteoarthritis, while celecoxib and rofecoxib were also approved for use in acute pain. Two other COX-2 selective NSAIDs, etoricoxib (Arcoxia®) and lumircoxib (Prexige®), received European approval for use in rheumatoid arthritis, osteoarthritis, and acute gout or osteoarthritis, respectively. COX-2-selective NSAIDs demonstrate comparable analgesia and anti-inflammatory effects to nonselective NSAIDs in patients with rheumatoid arthritis and osteoarthritis (36-40). At their defined therapeutic doses, COX-2-selective NSAIDs show at least a 200- to 300-fold selectivity for inhibition of COX-2 over COX-1 (36). Many studies have evaluated the efficacy of COX-2-selective NSAIDs on reducing the risk of NSAID ulcers. In 2000, 2 pivotal outcome studies, the Celecoxib Long-term Arthritis Safety Study (CLASS) and Vioxx Gastrointestinal Outcome Research study (VIGOR), demonstrated that COX-2-selective NSAIDs decrease the risk for both endoscopic NSAID ulcers and serious NSAID ulcer complications when compared with nonselective NSAIDs (41,42).

The Multinational Etoricoxib and Diclofenac Arthritis Long-term program was a pooled intent-to-treat analysis of 3 randomized comparisons of etoricoxib (60 or 90 mg daily) and diclofenac (150 mg daily) in 34,701 rheumatoid arthritis or osteoarthritis patients (43). Overall, GI events were significantly less common with etoricoxib than with diclofenac.

In the Therapeutic Arthritis Research and GI Event Trial, 18,325 osteoarthritis patients were randomized to lumiracoxib 400 mg once daily, naproxen 500 mg twice daily, or ibuprofen

800 mg 3 times daily for 52 weeks (44). In the patients not taking aspirin, the cumulative incidence of serious NSAID ulcer complications (bleeding, perforation, or obstruction) was significantly lower with lumiracoxib than with naproxen or ibuprofen (hazard ratio, 0.21; 95% CI, 0.12 to 0.37). However, there was no significant difference in the patients concurrently taking aspirin. Furthermore, there were more myocardial infarctions with lumiracoxib, especially as compared with naproxen (0.38% versus 0.21%), although the differences were not statistically significant.

Several tentative conclusions may be drawn from these and other studies. First, the use of COX-2-selective NSAIDs significantly reduces the risk of NSAID ulcers and of serious NSAID ulcer complications. However, long-term efficacy remains debatable. Second, concurrent use of low-dose aspirin for primary or secondary prevention of cardiovascular or cerebrovascular disease negates the gastroprotective effect of COX-2-selective NSAIDs. This observation may be directly related to effect of aspirin, which irreversibly blocks COX-1 in the GI tract (45). Third, the use of COX-2-selective NSAIDs increases the risk of myocardial infarction, as compared with the nonselective NSAID naproxen (10). The highly selective COX-2 inhibitors such as rofecoxib showed reduced GI side effects but their possible role in increasing cardiac adverse effects has resulted in the withdrawal of rofecoxib and valdecoxib from the market (1).

3. Strategies to enhance the safety profile of NSAIDs

Two strategies have been employed to enhance the safety profile of NSAIDs: the use of concomitant medication to protect the gastroduodenal mucosa and the development of safer anti-inflammatory drugs: COX-2 selective inhibitors, nitric oxide-donors NSAIDs, phospholipid-coupled NSAIDs, N-enantiomers of NSAIDs (12). The other way to enhance the safety profile of NSAIDs is to use rectal drug delivery systems or modified release formulations. These are less ulcerogenic included methods to reduce topical effects such as enteric coating, rectal administration, or sustained release oral formulations. It is now well established that the point prevalence of peptic ulcer disease in patients receiving conventional NSAID therapy ranges between 10 and 30%, which is a 10- to 30-fold increase over that found in the general population (46). In a study that examined the prevention of NSAID-related ulcer complications in 8843 arthritis patients, it was reported that, over a 6-month trial period, 0.76% of patients (or 1.5% annually) experienced upper GI complications (25). The US Food and Drug Administration (FDA) similarly estimates that 2-4% of patients taking conventional NSAID for one year experience symptomatic ulcer or potentially life-threatening ulcer complications (47). The Arthritis, Rheumatism and Aging Medical Information Systems (ARAMIS) reported that the overall annual incidence of hospitalization for GI events was 1.3%, the rate was 6 times higher in patients with RA who were taking NSAID than in those who were not (24). Despite a reduction in the rate of hospitalisation (24,48), it has been established that 1 out of 175 users of conventional NSAIDs in the USA will be hospitalised each year for NSAID-induced GI damage (49). The mortality of hospitalised patients remains about 5-10%, with an expected annual death rate of 0.08% (24).

4. Suppository formulations

The advantages of suppositories as conventional formulations compared to other dosage forms are reduction of side effects, such as GI irritation and avoidance of disagreeable taste,

first pass effect, and undesirable effects of meals on drug absorption (50-54). There are indications for using this route of administration such as when the oral administration of medication is difficult due to non-compliance of patient or when GI motility is severely impaired. In addition the oral route can not be used in some patients due to oral or oesophageal injuries or ulceration and in convulsing neonates rectal administration is easier than parenteral or oral administration (55,56).

After dissolving a suppository containing NSAID in the rectal fluids and absorption by the rectal mucosa, the NSAID will be distributed to the various body compartments. The upper haemorrhoidal vein will drain the drug into portal system while the middle and lower haemorrhoidal veins drain it directly into the inferior vena cava which explains why the drug bioavailability may be modified according to the position of the suppository into the rectum. At least a part of the drug absorbed will bypass the liver and its first pass metabolism (which is of great importance for high clearance drugs but not for low clearance drugs such as most of the NSAIDs) will be decreased. It was known that, NSAIDs are variably, but usually well absorbed rectally, thereby reducing the risk of GI ulceration and NSAID suppositories are one approach, besides many others, that is proposed to limit NSAID-induced gastropathy. This proved to be true at least in one study conducted on 45 normal volunteers who received either indomethacin or placebo suppositories, or oral indomethacin. Both suppositories seemed to be better tolerated than oral formulation (57).

Ersmark H. et al. (58) have used in their study piroxicam and indomethacin suppositories for painful coxarthrosis. Six orthopaedic clinics in Sweden made a comparison of the effects and side effects of Piroxicam (20 mg) and Indomethacin (100 mg) suppositories in 261 patients with painful coxarthrosis on the waiting list for total hip replacement. The study was designed as a single blind study over 4 weeks. Amount of pain and range of motion was registered before the trial and compared with findings after 4 weeks, including reported side effects. Both drugs gave satisfactory pain relief without any appreciable variation on weightbearing or at rest. On the other hand, the trial showed a significant difference ($p = 0.0033$, Student's-test) between the two drugs as regards the frequency of side effects from the lower gastrointestinal tract, where piroxicam had a lower rate compared with indomethacin. No serious complications occurred; 16 patients dropped out, 8 in each group. Carrabba M. et al. (59) compared the local tolerability, safety and efficacy of meloxicam 15 mg suppositories with piroxicam 20 mg suppositories over a 3-week period in a single-blind, randomized study in patients with osteoarthritis. They found that local adverse events occurred in 11.9% of patients receiving piroxicam and 6.9% of those receiving meloxicam. Overall, GI adverse events were the most frequent of all 11.9% of piroxicam-treated patients. In both groups, about 90% of global tolerability assessments were classified, by the investigator and the patient, as either very good or good. They concluded that meloxicam 15 mg suppositories showed excellent local tolerability accompanied by good safety and efficacy in osteoarthritis, which was comparable to that of an established NSAID administered by the rectal route, and to that previously observed with oral formulations of meloxicam 15 mg.

Hatori M. et al. (60) used in their study 231 patients aged 16 to 75 years with osteoarthritis of the knee joint. Each patient received 20 mg of piroxicam daily as a suppository administered before sleep; 75% of the patients were treated for 14 days or longer. Overall treatment outcome was excellent in 34% according to physicians' ratings and in 36% according to the patients' self-ratings, good in 39% and 41%, fair in 22% and 17%, and unimproved in 5% and

7%, respectively. Side effects were reported by 3% of the patients. They concluded that treatment of osteoarthritis with piroxicam suppositories is safe and effective.

Aärynen M. and Palho J. (61) studied with 15 patients having rheumatoid arthritis or osteoarthritis. They received a single dose (20 mg) piroxicam (Felden) as suppository. Serum piroxicam concentrations were assayed by fluorometry 1, 2, 4, and 8 h after the installation of the suppository, the mean values being 1.3, 1.9, 1.8, and 1.8 mg/l, respectively. Then the patients continued on oral piroxicam 20 mg daily for maximum 3 weeks, and serum piroxicam levels (mean 6.3 mg/l) were checked at the end of this period. Nine patients then continued on piroxicam suppositories 20 mg daily for one week, and serum piroxicam levels (mean 4.5 mg/l) were again assayed at the end of this maintenance. Pain at rest, pain on motion, and joint movement restriction were scored on day 1, after oral maintenance, and after rectal maintenance. Reduced scores were found with time, but the only statistically significant effect was in the overall subjective pain relief measured after oral maintenance. Rectal irritation was recorded in one patient. They concluded that a) absorption of piroxicam from suppository was adequate, b) it was possible to maintain adequate serum piroxicam levels by repeated administration of suppository for one week, and c) the GI toleration was acceptable in these patients selected for showing poor tolerance towards other nonsteroidal antiinflammatories.

In a placebo-controlled double-blind trial analgesic effectiveness and tolerability of alpha-methyl-4-(2-thienyl-carbonyl)phenylacetic acid (suprofen, Suprol) 300 mg suppositories were evaluated for 45 informed patients suffering from chronic pain due to osteoarthritis; the subjects were treated rectally, t.i.d., for 10 days. Suprofen proved to be statistically significantly superior to placebo in all the variables considered for evaluation of the analgesic effect, i.e., pain intensity and relief scores, sum of pain intensity differences, total pain relief, global assessments by investigator and patient. In particular, the efficacy of suprofen was judged by the physician good or very good in 86.3% of the patients. Similar frequencies of rectal side-effects were observed in both treatment groups, with slightly but not significantly higher incidence in the group treated with suprofen. Haematologic and clinical chemistry laboratory tests showed no statistically significant alterations due to the treatment (62).

Efficacy and toleration of piroxicam suppositories 20 mg, given once daily for 4 weeks were assessed in 96 patients suffering from degenerative joint disease and 20 patients suffering from rheumatoid arthritis. The mean scores of objective parameters measured (tenderness, swelling, limitation of movement) decreased significantly 2 and 4 weeks after initiation of therapy. Patients' self-evaluation of pain and stiffness also significantly improved during the trial. Overall evaluation of efficacy and toleration were excellent or good in more than 80% of patients. Local toleration was excellent in all but two patients (63).

In a 15 day double-blind clinical trial 39 patients affected with rheumatic disease have been enrolled to evaluate the therapeutic effect of rectal administration of Piroxicam, in comparison with Indomethacin. At the end of the study, 20 patients had been treated with Piroxicam and 19 with Indomethacin. Nine patients in the Indomethacin group and one in the Piroxicam group dropped-out. Both drugs safety resulted good in the patients who completed the study, whereas 5 out of 10 dropped-out patients stopped the trial in consequence of severe side-effects of Indomethacin. Piroxicam induced a very good improvement in 76% of the patients, moderate in 19% and no improvement in 5%; Indomethacin induced a very good improvement in 75% of the patients, moderate in 15% and no improvement in 10%. No significative modifications resulted from the control of the

laboratory blood tests. Piroxicam (30 mg/die) showed a therapeutic activity similar to Indomethacin (100 mg/die). The rectal administration of Piroxicam can be then considered a very good alternative to the oral one, particularly in the patients in which oral use of NSAID is counter-indicated (64).

Ketoprofen administered via the rectal route seemed to be valuable when given at night to patients with various rheumatic syndromes and may be particularly useful for patients who show gastric intolerance of the capsules. Anal intolerance was noted in 12% of the patients (65).

The relative risks associated with anti-inflammatory drug prescription for patients with an earlier history of drug-associated gastro-intestinal disturbance have been investigated by Bunton RW. et. al (66) in a retrospective study. Under these circumstances ibuprofen was well tolerated. The risks associated with modified salicylates (principally aspirin in enteric-coated form) and indomethacin suppositories also appeared to be relatively slight.

Together with NSAIDs a lot of other drugs such as alendronate sodium (ALD) have GI side effects. ALD is a bisphosphonate medication used in the treatment and prevention of osteoporosis. Absorption of ALD as oral formulation is very poor (0.5-1%). Its bioavailability can decrease with food effect. It has some GI adverse effects such as gastritis, gastric ulcer, and esophagitis. Asikoglo et al. (67) developed in their study a rectal formulation of ALD as an alternative to oral route and investigated the absorption of it by using gamma scintigraphy. For this reason, ALD was labelled with Technetium-99m (^{99m}Tc) by direct method. They found that the rectal absorption of ^{99m}Tc -ALD from suppository formulation was possible. According to their results, this formulation of ALD can be suggested for the therapy of osteoporosis as an alternative route. Asikoglu et al. (68) developed in another study a vaginal suppository formulation of ALD and they showed that the vaginal absorption of ^{99m}Tc -ALD from suppository formulation was also possible.

It was known that sustained release (SR) suppositories together with suppositories are other important formulations to reduce the GI side effects. In the case of drugs that are rapidly eliminated from the systemic circulation, frequent administration would be needed to maintain the therapeutic plasma concentration. To reduce the frequency of dosing, several approaches have been performed to prepare SR suppositories by using various polymer such as chitosan (69), Eudragit (70-72), cellulose acetate phthalate (73), carboxyvinyl polymer (74), and various hydrogel formulation (75,76), were also investigated. Özgüney et. al. (77) prepared SR suppositories of ketoprofen (KP). Since KP produces gastro-intestinal side effects and its administration rectally is considered as a serious alternative to the oral route (75). KP is an appropriate model drug for formulation of controlled release dosage forms due to its short plasma elimination half-life and poor solubility in unionized water, which affects its bioavailability (78). They designed KP SR suppositories according to the $3^2 \times 2^1$ factorial design as three different KP:Eudragit RL 100 ratios, three particle sizes of prepared granules and two different PEG 400:PEG 6000 ratios. The conventional KP suppositories also prepared with Witepsol H 15, Massa Estarinum B, Cremao and the mixture of PEG 400:PEG 6000. The dissolution studies of suppositories prepared was carried out according to the USP XXIII basket method and it was shown that the dissolution time was sustained to 8 hours. In addition, they determined antiinflammatory activity of SR suppository as significantly extended according to the conventional suppositories.

Güneri et. al. (79) reported that formulation of sustained-release suppositories using ibuprofen-ethylcellulose microspheres was attempted. Ibuprofen was an appropriate candidate for sustained-release formulation because of its short half-life (1.8-2 hrs) and

undesired GI effects when it is administrated through oral route, such as peptic ulceration and GI bleeding.

There are a lot of studies on SR suppositories prepared with NSAIDs to reduce their GI side effects (80,81).

Liquid suppository formulations are newer SR suppository formulations according to the conventional suppository formulations. Conventional suppositories are solid forms which often cause discomfort during insertion. The leakage of suppositories from the rectum also gives uncomfortable feelings to the patients. In addition, when the solid suppositories without mucoadhesivity reach the end of the colon, the drugs can undergo the first-pass effect. To solve these problems, Choi et.al. (82) developed a novel in situ-gelling and mucoadhesive acetaminophen liquid suppository with gelation temperature at 30–36°C and suitable gel strength and bioadhesive force. Poloxamer 407 (P407) or/and poloxamer 188 (P188) were used to confer the temperature-sensitive gelation property. The mixtures of P407 (15%) and P188 (15–20%) existed as a liquid at room temperature, but gelled at 30–36°C. They studied bioadhesive polymers such as polyvinylpyrrolidone, hydroxypropylmethylcellulose, hydroxypropylcellulose, carbopol and polycarbophil to modulate the gel strength and the bioadhesive force of acetaminophen liquid suppositories. Choi et. al. (83) showed in their another study that liquid suppository A [P 407:P 188:polycarbophil:acetaminophen (15:19:0.8:2.5%)], which was strongly gelled and mucoadhesive in the rectum, showed more sustained acetaminophen release profile than did other suppositories and gave the most prolonged plasma levels of acetaminophen in vivo. Liquid suppository A also showed higher bioavailability of acetaminophen than did the conventional formulation and it did not cause any morphological damage to the rectal tissues.

Özguney et. al. (84, 85) prepared a liquid suppository formulation using P407, P188, ketoprofen and various amounts of different bioadhesive polymers (PVP, CMC, HPMC and Carbopol 934 P). Because of the gastro-intestinal side effects ketoprofen was chosen as active ingredient. They investigated the release and mechanical characteristics of the formulations. As to the obtained results of in vitro drug release studies, Carbopol has the biggest effect on release rate among the bioadhesive polymers. It was seen that the release rate decreased with increasing of Carbopol concentration. The release rate decreased between the formulations having highest or lowest concentrations of Carbopol in percent of 20 at 8. hour.

5. Enteric-coated formulations

Enteric-coated (EC) products are designed to minimize exposure of a drug to the acidic pH in the stomach, which could result in its degradation, or to decrease gastric side effects such as ulcers, perforations and bleeding due to the local effects of the drug on the gastric mucosa. Cellulose acetate phthalate is the polymer most commonly used for enteric coating. The core in such a formulation is coated with this polymer, which does not dissolve at a gastric pH. The dissolution of coating begins at a higher intestinal pH (generally at a pH higher than 5) as the tablet transits out of stomach into the intestine. Generally, the enteric-coated products are tablets. However, small beads or spheroids can be covered with an enteric coating and then these beads can be placed in a hard gelatin capsule (86). Ethylcellulose and cellulose acetate phthalate capsules in the form of Snap-Fit type hard gelatin capsules were developed for controlled release and enteric-coated dosage forms

respectively. The capsules were drilled in different diameters by using laser and filled with concentrated drug solution. In vitro and in vivo drug releases were investigated (87). In another study, the enteric-coated capsules were prepared using hydroxypropylmethyl cellulose phthalate and examined in vitro and in vivo drug releases (88,89).

Although diclofenac sodium (DFNa), is a conventional NSAID, it could be fully utilized without harmful side effects if it was properly formulated (90). When it comes to oral administration of DFNa, at least two requirements should be considered: (a) perfect drug retention under gastric conditions, and (b) sufficient drug release during intestinal residence time. To achieve these requirements, a variety of controlled release formulations for DFNa have already been reported. In terms of pH-responsive matrices, water-soluble matrix tablets containing DFNa coated with hydroxypropyl methylcellulose phthalate (HPMCP) for delayed release of DFNa (91) and DFNa-loaded pH-sensitive microspheres comprising of poly(vinyl alcohol) and poly(acrylic acid) interpenetrating network for the delivery of DFNa to intestines were prepared and evaluated in vitro (92). Novel enteric microcapsules were reported, and in vivo evaluation of dosage forms showed successful pharmacodynamic activities (93).

Due to the necessity to pass intact through the stomach for reaching the duodenum for absorption, the pantoprazole is formulated as solution for intravenous administration (lyophilized powder for reconstitution) or as gastric-resistant tablets (oral delayed-release dosage form). In the case of oral administration, the enteric coating prevents pantoprazole from degradation in the gastric juice (at pH 1–2, pantoprazole degrades in few minutes) (94). As a general rule, the multiple-unit products show large and uniform distribution; they are less affected by pH and there is a minor risk of dose dumping (95). Besides, these new drug delivery systems, as the polymeric microparticles, are also proposed to improve absorption, distribution, and bioavailability of acid labile drugs (96,97). As they rapidly disperse in the GI tract, they can maximize drug absorption, minimize side effects, and reduce variations in gastric emptying rates and intersubject variability (98,99).

Caldwell J.R. et al. (100) compared in their study efficacy and GI tolerability of a new enteric coated formulation of naproxen (NAP-EC) with standard immediate release naproxen (NAP-STD). For this reason one hundred seventy-nine patients with osteoarthritis and one hundred seventy-six patients with rheumatoid arthritis at high risk for developing GI side effects to NSAID therapy were enrolled in a double blind, parallel, multicenter study. All patients had either discontinued as NSAID during the previous one year or required cotreatment with antiulcer drugs for control of GI complaints related to NSAID use. The treatments were evenly divided in both diagnostic cohorts. As to the obtained results of their study, except for minor differences in alcohol consumption, baseline characteristics of patients in both treatment groups were statistically similar. Both naproxen formulations were highly efficacious by all variables of disease activity when changes were measured from baseline. No statistically significant between formulation difference was found in the primary efficacy variable, overall disease activity. Overall, between formulation differences in efficacy measures were few, though most favored NAP-STD. GI complaints were reduced by 15% (51% NAP-EC vs 60% NAP-STD, $p = 0.077$) and GI complaints thought to be drug related were reduced by 36% (16% NAP-EC vs 25% NAP-STD, $p = 0.024$). Withdrawals due to GI complaints were reduced by 37% in the NAP-EC group (12% NAP-EC vs 19% NAP-STD, $p = 0.054$), and withdrawals due to GI complaints judged to be drug related were reduced by 55% in the NAP-EC group (6% NAP-EC vs 12% NAP-STD, $p = 0.025$). They concluded that enteric coated naproxen is an effective treatment for osteoarthritis and

rheumatoid arthritis. All observed differences in GI tolerability favor NAP-EC over NAP-STD.

The damaging effect of enteric-coated and plain naproxen tablets on the gastric mucosa was studied in 12 healthy subjects before and after 7 days' treatment in a randomized, double-blind, double-dummy, cross-over trial. Both formulations of the drug caused mucosal lesions, but the extent of the damage was significantly decreased after enteric-coated naproxen as compared with plain tablets. The subjects' preference was significantly in favour of the enteric-coated naproxen tablets. The plasma naproxen concentration was significantly higher after treatment with enteric-coated naproxen than after treatment with plain tablets. In conclusion, the results of the study indicate that naproxen might damage the gastric mucosa by local and systemic effects and that the local effect might be prevented by enteric coating of the tablets (101).

Aabakken L. et al. (102) studied the GI side effects of three formulations of naproxen in 18 healthy male volunteers. In a Latin-square design crossover study, the subjects received 500 mg naproxen twice daily for 7 days as plain tablets, enteric-coated tablets, or enteric-coated granules in capsules. The ^{51}Cr -EDTA absorption test was performed before and at the end of each drug period, to evaluate changes in the distal gut. The test dose was instilled distally in the duodenum to prevent lesions in the stomach from interfering with the evaluation. Upper endoscopy was performed at the same intervals, scoring changes in the middle and distal duodenum separately from findings in the stomach and duodenal bulb. The nature and severity of adverse effects were recorded for each treatment period. Non-parametric methods were used for statistical evaluation. All drugs induced a significant increase in ^{51}Cr -EDTA absorption, but they did not detect any difference between the three formulations. All formulations were associated with a significant increase in all the endoscopic findings monitored. Enteric-coated tablets induced significantly less lesions than enteric-coated granules in the stomach and duodenal bulb, and an advantage over plain tablets was indicated. No difference was seen in the middle and distal duodenum. The proximal endoscopic scores were not correlated to those found in the middle and distal duodenum. Evaluation of the small and large bowel should probably be included in clinical studies of NSAIDs, but their findings suggest that the importance of transfer of mucosal lesions to the distal gut by enteric coating may have been overemphasized.

The effects of plain and enteric-coated fenoprofen calcium (Nalfon, Dista, Indianapolis, Ind.) on GI microbleeding were studied in 32 normal male volunteers in a randomized, open-label, parallel trial at two inpatient research facilities. A 1-week placebo (baseline) period preceded 2 weeks of fenoprofen therapy (enteric coated or plain, 600 mg q.i.d.). Fecal blood loss was measured by ^{51}Cr -tagged erythrocyte assay and averaged over days 4 to 7 (baseline) and 11 to 14 and 18 to 21 (active therapy). At one center GI irritation was evaluated endoscopically before and after active therapy. Endoscopy showed both formulations to cause mucosal damage not evident by subject-reported symptoms. Four of the 16 subjects developed asymptomatic duodenal ulcers. Mean daily fecal blood loss was significantly lower ($P = 0.03$) with enteric-coated (mean \pm SD, 1.104 \pm 0.961 ml/day) than with plain fenoprofen calcium (mean \pm SD, 1.686 \pm 0.858 ml/day), suggesting that tolerance of fenoprofen can be improved with administration in an enteric-coated form (103).

When administered on a chronic high-dosage regimen, enteric-coated aspirin granules produced significantly less gastric damage than plain aspirin or aspirin-antacid combinations. Clinically meaningful damage occurred in all subjects receiving plain aspirin, 93% of those receiving aspirin-antacid combination and only 27% and 20% of those

receiving enteric-coated aspirin granules qid and bid, respectively. All three aspirin formulations were taken as 1 g qid (4 g/day) and an additional group received enteric granules administered as 2 g bid (4 g/day). Gastric damage was assessed by means of endoscopy carried out after seven days of treatment. Enteric granules are equally safe when administered on a bid or qid regimen (at same total daily dosage) and, in a bid regimen, should provide a compliance advantage for patients on high-dose therapy for diseases such as rheumatoid arthritis (104).

6. Sustained and controlled release formulations

The development of oral sustained and controlled release formulations offers some benefits: controlled administration of a therapeutic dose at the desired delivery rate, constant blood levels of the drug, reduction of side effects, minimization of dosing frequency and enhancement of patient compliance (105).

The basic rationale for the development of controlled drug delivery is to modulate the magnitude and duration of drug action(s), and to dissociate it from the inherent properties of the drug molecule. To enable optimal design of controlled release systems, a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug is necessary.

In many cases, the development of SR dosage forms is somewhat empirical. It is often based on the sole objective of reducing the dosing frequency or fluctuation between peak and trough plasma concentrations (C and C_{max} respectively) associated with conventional tablet or capsule formulations. The development process tends to be based on an intuitive pharmacodynamic rationale assuming that the magnitude of response elicited by the drug is closely related to changes in its plasma concentration (106).

In general, almost all drugs cause side effects or have extraneous activity in addition to their primary therapeutic function. An important principle in the design of a proper delivery system for a drug is the consideration that each of the pharmacologic effects of the drug has its own pharmacodynamic profile. Furthermore, while a certain pharmacological effect is considered as a therapeutic response,

larger intensities of the same effect are regarded as undesired (and possibly toxic). Thus, an important advantage of SR formulations is that by narrowing the range of drug concentrations (especially, by reducing C_{max} levels) the delivery system enables the minimization of the adverse effects associated with elevated drug concentrations. This pharmacodynamic principle has been widely applied as a means to improve drug therapy (107). There are numerous examples to demonstrate modulation of adverse effect of NSAIDs by SR formulations (108-115).

Lipid-based formulations have attracted increasing attention for improvement of bioavailability of hydrophobic drugs in comparison with solid dosage forms (116). In fact, lipid microspheres composed of lecithin and soybean oil were tested as carriers for hydrophobic NSAIDs (117). Unlike many of NSAIDs, DFNa is basically watersoluble at neutral pH, making it difficult to exist in an oil-based formulation. Although self-emulsifying drug delivery system (SEDDS) composed of goat fat and Tween 65 was also applied to diclofenac (90).

Twenty-five inpatients with chronic inflammatory rheumatic disease were entered into a double blind crossover trial. Consecutive treatment regimens consisted of a single daily dose of Bi-Profenid 150 mg at 8 pm for 3 days and a single placebo tablet at 8 pm for 3 days. Order of treatment regimens was randomly assigned. Bi-Profenid proved highly superior to

placebo with a very significant (p less than 0.01) difference in effectiveness on nocturnal pain, morning stiffness and pain evaluated on the pain scale. During the short treatment period no significant clinical side-effects were recorded. The authors conclude that Bi-Profenid is effective at a daily dosage of 150 mg, thus enabling to adjust prescriptions to actual needs when pain is not continuous throughout the 24 hours (118).

Schumacher HR. et al. (119) described a new extended-release formulation that maintains therapeutic plasma ketoprofen concentrations for up to 24 hours. A single 200-mg capsule thus provides daytime and nighttime symptom control. Small pellets, enclosed in a gelatin capsule, are released in the stomach but release their contained ketoprofen only after reaching the nonacidic environment of the small intestine. Diurnal fluctuations in plasma concentrations of ketoprofen are reduced, and the drug does not accumulate in plasma with extended use. The half-life of the drug from this dosage form is not significantly affected by the increasing age of the patients. The efficacy of extended-release ketoprofen in British clinical trials has been comparable to that of conventional ketoprofen or naproxen. Safety profiles have been comparable to profiles of other NSAIDs; adverse effects have usually been mild and transient, although, as with other NSAIDs, ulcers and bleeding can occur. Extended-release ketoprofen appears to be a good choice for the symptomatic treatment of rheumatoid arthritis and osteoarthritis. Convenient once-daily administration may help improve patients' compliance.

An open study was carried out in 46 patients with osteoarthritis of the hip to compare the efficacy and tolerance of treatment with ketoprofen given either as 100 mg capsules twice daily or as 2 capsules of 100 mg ketoprofen in a controlled-release formulation given once daily. The results of subjective and objective assessments before and during 3-months' treatment in the 48 patients who completed the trial showed both treatments produced improvement in all parameters, except for the time taken for inactivity stiffness to develop, and there was no significant difference between treatments in terms of efficacy. The controlled-release preparation, however, was significantly better tolerated than the ordinary capsule form. Minor haematological and biochemical changes during treatment were noted but these were not of clinical importance. Six patients, 2 receiving the controlled-release and 4 receiving the ordinary formulation of ketoprofen, were withdrawn because of lack of efficacy or unacceptable side-effects (120).

A multi-centre, double-blind, crossover study was carried out in 80 patients with rheumatoid arthritis to compare the efficacy and side-effect profiles of two formulations of indomethacin. Patients were allocated at random to receive 75 mg indomethacin per day either as 1 controlled-release tablet at night or as 1 immediate-release capsule given 3-times a day for a period of 4 weeks before being crossed over to receive the alternative treatment for a further 4 weeks. Pain scores, daily symptomatology and the requirement for escape analgesia recorded by both investigator and patient indicated that controlled-release indomethacin tablets, 75 mg given at night, was as efficacious as immediate-release indomethacin capsules given 3-times daily. However, the controlled-release formulation had a superior side-effect profile with a reduced incidence of abdominal/epigastric pain compared to the immediate-release preparation (121).

Prichard PJ. et al. (122) have compared acute gastric bleeding caused by a new slow release preparation of indomethacin (indomethacin Continus) with that caused by aspirin and other indomethacin preparations. In a randomized crossover study, blood loss into timed gastric aspirates was determined in 20 healthy volunteers after receiving, over 96 h, either placebo, aspirin (600 mg four times daily; 17 doses) indomethacin BP (50 mg three times daily; 13

doses), Indocid-R (75 mg twice daily; 9 doses) or indomethacin Continus (75 mg twice daily; 9 doses). A venous blood sample was also taken during each treatment period for subsequent determination of alpha 1-glycoprotein, and for drug assay. Gastric bleeding on placebo was 1.4 (0.7-2.8) microliters 10 min⁻¹ (mean, 95% CI). Both aspirin and the indomethacin preparations caused significantly more bleeding (P less than 0.05). Rates of bleeding after aspirin, indomethacin BP, Indocid-R, and indomethacin Continus were respectively 22.0 (10.7-47.2) microliters 10 min⁻¹, 4.4 (2.2-9.1) microliters 10 min⁻¹, 10.8 (5.3-22.3) microliters 10 min⁻¹, and 5.1 (3.0-10.6) microliters 10 min⁻¹. 4. Rates of bleeding after indomethacin BP and indomethacin Continus, but not Indocid-R, were significantly less than after aspirin (P less than 0.01). Salicylate or indomethacin was detectable in the plasma of all subjects after the active treatment periods, except for one instance involving a subject allocated indomethacin BP. Indomethacin levels were significantly higher 2 h after Indocid-R than with indomethacin BP or indomethacin Continus. 6. alpha 1-acid glycoprotein levels were not significantly affected by prior treatment with aspirin or indomethacin.

GI blood loss was measured in 30 healthy male volunteers before and during 4 weeks of oral treatment with either tiaprofenic acid tablets 300 mg twice daily, tiaprofenic acid sustained action (SA) capsules 600 mg once daily, or indomethacin SR capsules 75 mg once daily, in an open parallel-group study of 38 days' duration. Autologous erythrocytes labelled with ⁵¹Cr were given intravenously on the first study day. GI blood loss was measured by comparing faecal and red blood cell ⁵¹Cr activity during the second and fourth weeks of drug treatment. Blood loss was significantly greater during treatment with all 3 active preparations than during the pretreatment period, but this comparison is of limited value because placebo was not given in parallel and because in 4 subjects, who had to have their erythrocytes relabelled, there was no pretreatment data. The tiaprofenic acid SA group had consistently lower blood loss than the tiaprofenic acid tablet group. Both these groups also had consistently lower blood loss than the indomethacin SR group, although the difference between the treatment groups was not significant. Blood loss during the fourth week of treatment was less than during the second week of treatment for both the tiaprofenic acid SA and indomethacin SR capsule groups. With tiaprofenic acid tablets, blood loss was very similar at weeks 2 and 4 but this result should be viewed with caution because data at week 2 were missing for 3 subjects. Thus, formulation of tiaprofenic acid as a sustained action capsule does not appear to increase gastric irritancy as measured by faecal blood loss (123).

Forty adult patients with coxarthrosis were treated for 30 days with oral diclofenac sodium at the daily dose of 150 mg: 20 of these were administered one 150 mg prolonged-release capsule per day, the other 20 received one 50 mg enteric-coated tablet every 8 hours. The presence and severity of several symptoms and signs (various pain types, cramps, morning stiffness, impaired function capacity), the intensity of pain through the Visual Analogical Scale and some laboratory tests (Erythrocyte Sedimentation Rate, C-reactive protein, Rheuma test) were controlled to monitor drug efficacy. The routine laboratory tests of blood, liver and kidney function, the GI tolerance of the two administered formulations and the appearance of any adverse event were controlled to monitor drug tolerability. Both administration schemes yielded very positive results as to treatment efficacy, although the prolonged-release capsule often induced a somewhat quicker response. At the end of the one-month treatment more than half of patients in both groups registered disappearance of several symptoms and a noticeable reduction of the remainder ones. Systemic tolerability was also good, with superimposable results in the two groups; GI tolerance on the contrary was better in the recipients of the prolonged-release capsules (2 cases of dyspepsia) with

respect to those treated with the enteric-coated tablets (2 cases of gastric pyrosis and 2 cases of gastralgia). No adverse events were registered (124).

A double-blind, double-dummy, crossover study was carried out in 8 centres to compare the efficacy and tolerability of 'controlled-release' ketoprofen tablets (200 mg) with that of indomethacin suppositories (100 mg) in out-patients with definite or classical rheumatoid arthritis. Patients were allocated at random to receive a daily bedtime dose of either 1 ketoprofen tablet or 1 indomethacin suppository plus the dummy of the other formulation for a period of 3 weeks. They were then crossed over to the alternative treatment for a further 3 weeks. Daily diary records were kept by patients of the number of night-time awakenings due to pain, pain severity at awakening in the morning and the duration of early morning stiffness. Treatment efficacy was also assessed at the end of each trial period by means of an articular index and by physician's and patient's overall evaluation of response. Adverse effects spontaneously mentioned by the patients or elicited by direct questioning using a symptom check-list were recorded. Statistical analysis of the results from 83 evaluable patients showed that the 'controlled-release' tablet formulation of 200 mg ketoprofen was equally as effective as the 100 mg indomethacin suppository in the treatment of rheumatoid arthritis, especially with regard to pain at awakening and morning stiffness. Side-effects in both groups were those commonly seen with non-steroidal anti-inflammatory drugs and, as expected, GI and CNS disturbances predominated. Overall, side-effects were fewer with ketoprofen than with indomethacin (125).

There are several histological studies which show that controlled release formulations of NSAIDs are alternatives for preventing of gastric lesions.

Nishihata T. et al. (126) showed in their study that the increased solubility of sodium diclofenac in a suppository base in the presence of lecithin resulted in a slow release of sodium diclofenac from the base. Rat rectal mucosal damage caused by sodium diclofenac was moderated by the administration of the lecithin suppository, probably due to the low concentration of sodium diclofenac in the rectal fluid due to a slow release of sodium diclofenac from the lecithin suppository.

A mefenamic acid-alginate bead formulation (127, 128) and mefenamic acid spherical agglomerates (129) prepared with various polymethacrylates were developed in different studies and evaluated histologically. Histological studies showed that the administration of mefenamic acid in alginate beads or spherical agglomerates prevented the gastric lesions. Another work reports on a new pharmaceutical formulation for oral delivery of diclofenac sodium (DFNa). Although DFNa itself is water-soluble at neutral pH, it was readily suspended in soybean oil via complex formation with an edible lipophilic surfactant and a matrix protein. The resulting solid-in-oil (S/O) suspension containing stably encapsulated DFNa in an oil phase markedly reduced the risks for GI ulcers upon oral administration even at the LD50 level in rats (ca. 50 mg/kg DFNa) (90).

7. H. pylori induced gastric ulcers

H. pylori is a gram-negative microaerophilic non-invasive spiral bacillus which has the ability to colonize the gastric mucosa (130). It causes indolent but chronic inflammation in the gastric mucosa and its clinical course is highly variable (131). It has a powerful urease enzyme which catalyses hydrolysis of urea to ammonia, enabling the bacteria to survive in the acid milieu. Although it induces a strong host local and systemic immune response (which is important in pathogenesis) it has also developed mechanisms to evade host

immunity. This means that following initial infection, which usually occurs in childhood, it is able to persist lifelong in the absence of effective treatment. This persistent infection and inflammation underlies disease, which usually occurs in adults. Worldwide, *H. pylori* colonizes >50% of the population and is by far the most important cause of peptic ulcers and gastric adeno-carcinoma. Its prevalence varies from more than 80% in developing countries to less than 20% in some developed countries, where it is steadily falling due to improved hygiene and sanitation, and possibly increased antibiotic use.

Only about 15% of individuals infected with *H. pylori* develop a peptic ulcer: who develops disease depends on bacterial, host and environmental factors (130). The infection is usually limited to the antrum, resulting in hypersecretion of acid and the development of duodenal ulcers, which is basically an acid injury. However, the infection sometimes spreads proximally, causing diffuse inflammatory damage to the gastric mucosa in the body of the stomach and resulting in a gastric ulcer. The inflammation induced by *H. Pylori* damages the natural defence of the gastric mucosa (131).

The risk of ulceration is higher with more virulent strains. The best-described virulence determinants are expression of active forms of a vacuolating cytotoxin (VacA) (132) and possession of a protein secretory apparatus called Cag (cytoxin-associated gene products) that stimulates the host inflammatory response (133). Cag⁺ strains interact more closely with epithelial cells and induce release of pro-inflammatory cytokines, thereby increasing inflammation. Host genetic susceptibility and environmental factors may affect the risk; for example, smoking is strongly associated with peptic ulceration in *H. pylori*-infected individuals (134). *H. pylori*-induced duodenal ulceration arises in people with antral-predominant gastritis (135). Gastric ulceration occurs on a background of pangastritis, often arising at the highly inflamed transitional zone between antrum and pylorus, particularly on the lesser curve. Identical hormonal changes occur, but acid production from the inflamed corpus is reduced or normal.

H. pylori appears to be responsible for 95% of the cases of gastritis and 65% of gastric ulcers (136). Although most individuals with *H. pylori* are asymptomatic, there is now convincing evidence that this bacterium is the major etiologic factor in chronic dyspepsia, *H. pylori*-positive duodenal and gastric ulcers and gastric malignancy (137, 138). Consequently, *H. pylori* eradication is now recognized to be the correct approach along with conventional therapies in the treatment of the disease. Options that have been considered to treat peptic ulcer disease include taking drugs such as antacids, H⁺-blockers, antimuscarinics, proton pump inhibitors and combination therapy for gastritis associated with *H. pylori*. The eradication of *H. pylori* is limited by its principle unique characteristics. Once acquired, it penetrates the gastric mucus layer and fixes itself to various phospholipids and glycolipids on the epithelial surface, including phosphatidylethanolamine (139), GM3 ganglioside (140) and Lewis antigen (141). For effective *H. pylori* eradication, therapeutic agents have to penetrate the gastric mucus layer to disrupt and inhibit the mechanism of colonization. This requires targeted drug delivery within the stomach environment. Although most antibiotics have very low in-vitro minimum inhibitory concentrations against *H. Pylori*, no single antibiotics has been able to eradicate this organism effectively. Currently, a drug combination namely "triple therapy" with bismuth salt, metronidazole and either tetracycline or amoxycillin with healing rates of up to 94% has been successfully used (142-144). The principle of triple therapy is to attack *H. pylori* luminally as well as systemically. The current treatment is based on frequent administration (4 times daily) of individual dosage forms of bismuth, tetracycline and metronidazole (Helidac Therapy, consisting of

262.4 mg bismuth subsalicylate, 500 mg tetracycline and 250 mg metronidazole). The associated limitations are the complex dosing regimen/frequency, large amount of dosage forms and reduced patient compliance. Therefore, a successful therapy not only includes the selection of the right drugs but also the timing and frequency as well as the formulation of the delivery system (2).

8. Dosage forms with prolonged gastric residence time

More than 50% of the pharmaceutical preparations on the market are for oral administration. The advantages of this route include the ease of administration, and avoidance of the pain and discomfort associated with injections. However, for drugs whose target is the stomach, such as antibiotics against *H.pylori* for local treatment of gastric ulcer, the development of oral drug delivery systems meets with physiological obstacles such as limited residence time and inefficient drug uptake by the gastric mucosa (145). Long-term monotherapy of gastric ulcer patients with amoxycillin is ineffective even at high daily doses, apparently due to limited contact time with the target site when administered in a conventional oral dosage form (138, 146-148).

The degradation of antibiotics in gastric acid may be the other reason of ineffectiveness (149). Local diffusion of the drug in the mucosa appears to be essential for achieving bactericidal levels in both healthy subjects (138) and patients: for example, more complete eradication of *H. pylori* was achieved by applying a new method of topical therapy in which an amoxycillin solution was kept in contact with the stomach for 1 h (150). The development of oral amoxycillin dosage forms with prolonged gastric residence time is therefore an attractive goal. Several strategies have been developed in order to prolong the gastric residence time of dosage forms and target the gastric mucosa, including the use of floating, floating in situ gelling, swelling, expanding and bioadhesive forms (151-156). A new strategy is proposed for the triple drug treatment (tetracycline, metronidazole and bismuth salt) of *Helicobacter pylori* associated peptic ulcers. The design of the delivery system was based on the swellable asymmetric triple layer tablet approach, with floating feature in order to prolong the gastric retention time of the delivery system. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt could be included in one of the outer layers for instant release. Results demonstrated that sustained delivery of tetracycline and metronidazole over 6-8 h can be easily achieved while the tablet remained afloat. The floating aspect was envisaged to extend the gastric retention time of the designed system to maintain effective localized concentration of tetracycline and metronidazole. The developed delivery system has potential to increase the efficacy of the therapy and improve patient compliance (2).

Floating in situ gelling system of clarithromycin (FIGC) was prepared using gellan as gelling polymer and calcium carbonate as floating agent for potentially treating gastric ulcers, associated with *H.pylori*. The in vivo *H. pylori* clearance efficacy of prepared FIGC and clarithromycin suspension following oral administration, to *H. pylori* infected Mongolian gerbils was examined by polymerase chain reaction (PCR) technique and by a microbial culture method. FIGC showed a significant anti-*H. pylori* effect than that of clarithromycin suspension. It was concluded that prolonged GI residence time and enhanced clarithromycin stability resulting from the floating in situ gel of clarithromycin might contribute better for complete clearance of *H. Pylori* (157). Rajinikanth P.S et al. (149) developed in their another study a intra-gastric floating in situ gelling system for controlled delivery of amoxicillin for the treatment of peptic ulcer disease caused by *H.pylori*. They

prepared gellan based amoxicillin floating in situ gelling systems (AFIG). The in vivo H. pylori clearance efficacy of the formulation was examined by the same technique. It showed a significant anti-H. pylori effect in the in vivo gerbil model. It was noted that the required amount of amoxicillin for eradication of H. pylori was 10 times less in AFIG than from the corresponding amoxicillin suspension. The results further substantiated that the prepared AFIG has feasibility of forming rigid gels in the gastric environment and eradicated H. pylori from the GI tract more effectively than amoxicillin suspension because of the prolonged GI residence time of the formulation.

A gastroretentive drug delivery system of DA-6034, a new synthetic flavonoid derivative, for the treatment of gastritis was developed by using effervescent floating matrix system (EFMS). The therapeutic limitations of DA-6034 caused by its low solubility in acidic conditions were overcome by using the EFMS, which was designed to cause tablets to float in gastric fluid and release the drug continuously. The release of DA-6034 from tablets in acidic media was significantly improved by using EFMS, which is attributed to the effect of the solubilizers and the alkalizing agent such as sodium bicarbonate used as gas generating agent. DA-6034 EFMS tablets showed enhanced gastroprotective effects in gastric ulcer-induced beagle dogs, indicating the therapeutic potential of EFMS tablets for the treatment of gastritis (158).

In another example, it was found that in normal volunteers ionexchange resins achieved excellent distribution in the gastric cavity and had a prolonged gastric residence time, 20-25% remaining for 5.5 h. (155). More recent results by the same group indicate that the mechanism by which resin particles adhere to the mucosa is unlikely to be chargebased, since they persist in the stomach regardless of whether they bear a non-adhesive polymer coating and regardless of whether the stomach contains food (156). Other authors have recently shown that ion-exchange resins also interact with other mucosal surfaces, such as the nasal mucosa (159). Because of this reason, microparticles consisting of amoxycillin-loaded ion-exchange resin encapsulated in mucoadhesive polymers (polycarbophil and Carbopol 934) were prepared.

As reported in this review, the drug delivery systems have an important role on prevention of NSAID related or H.pylori induced gastric ulcers.

9. References

- [1] H. Lu, D. Y. Graham. New development in the mechanistic understanding of peptic ulcer diseases. *Drug Discovery Today: Disease Mechanisms* 2006; 3(4): 431-437.
- [2] L. Yanga, J. Eshraghib, R. Fassihia. A new intragastric delivery system for the treatment of Helicobacter pylori associated gastric ulcer: in vitro evaluation. *Journal of Controlled Release* 1999; 57: 215-222.
- [3] C. Aalykke, K. Lauritsen. Epidemiology of NSAID-related gastroduodenal mucosal injury. *Best Practice & Research Clinical Gastroenterology* 2001; 15(5): 705-722.
- [4] H. Dreser. Pharmacologisches Uber Aspirin (Acetylsalicylsaure). *Pflügers Archiv* 1899; 76: 306-318.
- [5] A.H. Douthwaite & SAM Lintott. Gastroscopic observations of the effect of aspirin and certain other substances on the stomach. *Lancet* 1938; 2: 1222-1225.
- [6] J.R. Vane. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature New Biology* 1971; 231: 232-235.

- [7] J.R. Vane JR & R.M. Botting. Mechanism of action of nonsteroidal anti-inflammatory drugs. *American Journal of Medicine* 1998; 104: 2S-8S.
- [8] J.Y. Fu, J.L. Masferrer, K. Seibert et al. The induction and suppression of prostaglandin H₂ synthase (cyclooxygenase) in human monocytes. *Journal of Biological Chemistry* 1990; 265: 16 737-16 740.
- [9] C.J. Hawkey. COX-2 inhibitors. *Lancet* 1999; 353: 307-314.
- [10] H.E. Vonkeman, Mart A.F.J. van de Laar. Nonsteroidal Anti-Inflammatory Drugs: Adverse Effects and Their Prevention. *Semin Arthritis Rheum.* 2010; 39: 294-312.
- [11] R. Flower, R. Gryglewski, K. Herbaczynska-Cedro, J.R. Vane. Effects of anti-inflammatory drugs on prostaglandin biosynthesis. *Nat New Biol* 1972; 238:104-106.
- [12] M. Lazzaroni, G. Bianchi Porro. Prophylaxis and treatment of non-steroidal anti-inflammatory drug-induced upper gastrointestinal side effects. *Digest Liver Dis* 2001; 33 (Suppl 2): 544-558.
- [13] S.P. Gutthann, L.A. Garcia Rodriguez & D.S. Raiford. Individual nonsteroidal antiinflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation. *Epidemiology* 1997; 8: 18-24.
- [14] L.A. Garcia Rodriguez & H. Jick. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; 343: 769-772.
- [15] S. Hernandez-Diaz & L.A. Rodriguez. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiology. *Archives of Internal Medicine* 2000; 160: 2093-2099.
- [16] D. Henry, L.L. Lim, R.L. Garcia et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *British Medical Journal* 1996; 312: 1563-1566.
- [17] M.R. Griffin. Epidemiology of nonsteroidal anti-inflammatory drug-associated gastrointestinal injury. *American Journal of Medicine* 1998; 104: 23S-29S.
- [18] D.W. Kaufman, J.P. Kelly, B.E. Wiholm et al. The risk of acute major upper gastrointestinal bleeding among users of aspirin and ibuprofen at various levels of alcohol consumption. *American Journal of Gastroenterology* 1999; 94: 3189-3196.
- [19] J.P. Kelly, D.W. Kaufman, R.S. Koff et al. Alcohol consumption and the risk of major upper gastrointestinal bleeding. *American Journal of Gastroenterology* 1995; 90: 1058-1064.
- [20] J. Weil, M.J. Langman & P. Wainwright. Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. *Gut* 2000; 46: 27-31.
- [21] J.Q. Huang, S. Sridhar, R.H. Hunt. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic ulcer disease: a meta-analysis. *Lancet* 2002;359: 14-22.
- [22] G.V. Papatheodoridis, S. Sougioultzis, A.J. Archimandritis. Effects of *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs on peptic ulcer disease: a systematic review. *Clin Gastroenterol Hepatol* 2006; 4: 130-142.
- [23] P. Malfertheiner, J. Labenz. Does *Helicobacter pylori* status affect nonsteroidal anti-inflammatory drug-associated gastroduodenal pathology? *Am J Med* 1998; 104: 35-40S.

- [24] G. Singh & G. Triadafilopoulos. Epidemiology of NSAID induced gastrointestinal complications. *Journal of Rheumatology* 1999; 26 (supplement 56): 18-24.
- [25] F.E. Silverstein, D.Y. Graham, J.R. Senior et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine* 1995; 123: 241-249.
- [26] M.J.S. Langman, J. Weil, P. Wainwright et al. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; 343: 1075-1078.
- [27] J.L. Carson, B.L. Strom, K.A. Soper et al. The association of nonsteroidal anti-inflammatory drugs with upper gastrointestinal tract bleeding. *Archives of Internal Medicine* 1987; 147: 85-88.
- [28] M.R. Griffin, J.M. Piper, J.R. Daugherty et al. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Annals of Internal Medicine* 1991; 114: 257-263.
- [29] D. Henry, A. Robson & C. Turner. Variability in the risk of major gastrointestinal complications from nonaspirin nonsteroidal anti-inflammatory drugs. *Gastroenterology* 1993; 105: 1078-1088.
- [30] S.E. Gabriel, L. Jaakkimainen & C. Bombardier. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Annals of Internal Medicine* 1991; 115: 787-796.
- [31] T.M. MacDonald, S.V. Morant, G.C. Robinson et al. Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. *British Medical Journal* 1997; 315: 1333-1337.
- [32] G. Singh. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *American Journal of Medicine* 1998; 105: 31S-38S.
- [33] R.I. Shorr, W.A. Ray, J.R. Daugherty & M.R. Griffin. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. *Archives of Internal Medicine* 1993; 153: 1665-1670.
- [34] J.M. Piper, W.A. Ray, J.R. Daugherty & M.R. Griffin. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. *Annals of Internal Medicine* 1991; 114: 735-740.
- [35] F.J. De Abajo, L.A. Rodriguez & D. Montero. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *British Medical Journal* 1999; 319: 1106-1109.
- [36] G.A. FitzGerald, C. Patrono. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001; 345: 433-442.
- [37] P. Emery, H. Zeidler, T.K. Kvien, M. Guslandi, R. Naudin, H. Stead, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet* 1999; 354: 2106-2111.
- [38] G.W. Cannon, J.R. Caldwell, P. Holt, B. McLean, B. Seidenberg, J. Bolognese et al. Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. Rofecoxib Phase III Protocol 035 Study Group. *Arthritis Rheum* 2000; 43: 978-987.

- [39] W. Bensen, A. Weaver, L. Espinoza, W.W. Zhao, W. Riley, B. Paperiello et al. Efficacy and safety of valdecoxib in treating the signs and symptoms of rheumatoid arthritis: a randomized, controlled comparison with placebo and naproxen. *Rheumatology (Oxford)* 2002;41: 1008-1016.
- [40] C.W. Wiesenhutter, J.A. Boice, A. Ko, E.A. Sheldon, F.T. Murphy, B.A. Wittmer et al. Evaluation of the comparative efficacy of etoricoxib and ibuprofen for treatment of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2005; 80: 470-479.
- [41] F.E. Silverstein, G. Faich, J.L. Goldstein, L.S. Simon, T. Pincus, A. Whelton et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA* 2000; 284: 1247-1255.
- [42] C. Bombardier, L. Laine, A. Reicin, D. Shapiro, R. Burgos-Vargas, B. Davies et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000; 343: 1520-1528.
- [43] L. Laine, S.P. Curtis, B. Cryer, A. Kaur, C.P. Cannon. Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2007; 369: 465-473.
- [44] T.J. Schnitzer, G.R. Burmester, E. Mysler, M.C. Hochberg, M. Doherty, E. Ehram et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004; 364: 665-674.
- [45] B. Cryer, M. Feldman. Effect of very low dose daily, long-term aspirin therapy on gastric, duodenal, and rectal prostaglandin levels and on mucosal injury in healthy humans. *Gastroenterology* 1999; 117: 17-25.
- [46] J. Kremer. From prostaglandin replacement to specific COX-2 inhibition. A critical appraisal. *J Rheumatol* 2000; 27(Suppl 60): 9-12.
- [47] H.E. Paulus. FDA Arthritis Advisory Committee meeting: serious gastrointestinal toxicity of non-steroidal anti-inflammatory drugs. *Arthritis Rheumatol* 1988; 31: 1450-1451.
- [48] M.M. Wolfe, D.R. Lichtenstein, G. Singh. Gastrointestinal toxicity of non-steroidal anti-inflammatory drugs. *N Engl J Med* 1999; 340: 1888-1899.
- [49] J.F. Fries. NSAID gastropathy, epidemiology. *J Musculoskel Med* 1991; 8: 21-28.
- [50] T. Umeda, A. Matsuzawa, T. Yokoyama, K. Kuroda, T. Kuroda. Studies on sustained release dosage forms. I. preparation of indomethacin suppositories. *Chem. Pharm. Bull.* 1983; 31: 2793-2798.
- [51] T. Nakajima, Y. Takashima, K. Iida, H. Mitsuta, M. Koishi. Preparation and in vitro evaluation of sustained-release suppositories containing microencapsulated indomethacin. *Chem. Pharm. Bull.* 1987; 35: 1201-1206.
- [52] A.G. de Boer, D.D. Breimer, H. Mattie, J. Pronk, J.M. Gubbens-Stibbe. Rectal bioavailability of lidocaine in man: partial avoidance of "first-pass" metabolism. *Clin. Pharmacol. Ther.* 1979; 26: 701-709.
- [53] A.G. de Boer, F. Moolenaar, L.G.J. de Leede, D.D. Breimer. Rectal drug administration: clinical pharmacokinetics consideration. *Clin. Pharmacokin.* 1982; 7: 285-311.

- [54] T. Takatori, N. Shimono, K. Higaki, T. Kimura. Evaluation of sustained release suppositories prepared with fatty base including solid fats with high melting points. *Int. J. Pharm.* 2004; 278: 275-282.
- [55] C. King. Rectal drug administration. *Journal of Equine Veterinary Science* 1994; 14: 521-526.
- [56] S. Corveleyna, D. Henrsta, J. P. Remona, G. VAN DER Wekenb, W. Baeyensb, J. Haustraeteb, H. Y. ABOUL-Eneinc, B. Sustronckd, P. DEPREZ. Bioavailability of racemic ketoprofen in healthy horses following rectal administration. *Research in veterinary science.* 1999; 67 (2): 203-204.
- [57] J. P. Famaey. Suppositories for Arthritis. *Clinical rheumatology* 1992; 11 (1): 26-27.
- [58] H. Ersmark, B. Tjornstrand, G. Gudmundsson, H. D ppe, M. Fagerlund, B. Jacobsson, G. Ordeberg, L. Wallinder. Piroxicam and indometacin suppositories for painful coxarthrosis. *Clinical rheumatology* 1992; 11(1): 37-40.
- [59] M. Carrabba, E. Paresce, M. Angelini, A. Galanti, MG. Marini, P. Cigarini. A comparison of the local tolerability, safety and efficacy of meloxicam and piroxicam suppositories in patients with osteoarthritis: a single-blind, randomized, multicentre study. *Curr Med Res Opin* 1995; 13(6): 343-355 Erratum in: *Curr Med Res Opin* 1996; 13(7): 427-428.
- [60] M. Hatori, M. Sakurai , S. Kokubun, KP. Rijal. Piroxicam suppositories in the treatment of osteoarthritis of the knee joint. *Clin Ther.* 1990; 12(3): 227-229.
- [61] M. A rynen, J. Palho. Piroxicam capsules versus suppositories: a pharmacokinetic and clinical trial. *Arzneimittelforschung* 1986; 36(4): 744-747.
- [62] M. Viara, V. Menicanti, M. Nebiolo, N. Michos, C. Sarchi. Double-blind placebo-controlled study of the efficacy and tolerability of suprofen suppositories in patients with osteoarthritic pain. *Arzneimittelforschung* 1986; 36(7): 1113-1115.
- [63] G. Heynen, P. Dessain, Piroxicam suppositories for osteoarthritis and rheumatoid arthritis: an open multicentre study in 116 patients. *Eur J Rheumatol Inflamm.* 1983; 6(1): 134-138.
- [64] F. Macc , L. Milani, M. Dal Follo, L. Corbetta, G. Zeni, R. Zuin. Therapeutic action of Piroxicam administered rectally in rheumatic diseases. Controlled double-blind study. *Minerva Med.* 1984; 75(14-15): 811-819.
- [65] A. Fournie, C. Ayrolles. A clinical study of ketoprofen suppositories. *Rheumatol Rehabil.* 1976; Suppl:59-60.
- [66] R.W. Bunton, D.C. Barrett , D.G. Palmer. Reintroduction of anti-inflammatory drug therapy after drug-associated gastro-intestinal disturbances. *N Z Med J.* 1982; 95(714): 582-584.
- [67] M. A ıko lu, I.  zg ney,  .  zcan, O.  r ml , T. G neri, K. K seo lu, H.  zkılı . The absorption of ^{99m}Tc-alendronate given by rectal route in rabbits. *Pharmaceutical Development and Technology* 2008; 13(3): 213-20.
- [68] M. A ıko lu, D.  lem, T. G neri, K. K seo lu. Intravaginal Administration of Tc^{99m}-ALD sodium. 14th International Pharmaceutical Technology Symposium, 8-10 September 2008; P-60, pp: 233-236, Antalya/Turkey.
- [69] D. Ermi , N. Tarımcı. Sustained release characteristics and pharmacokinetic parameters of ketoprofen suppositories using chitosan. *Int. J. Pharm.* 1997; 147: 71-77.
- [70] D. Ermi , N. Tarımcı. Preparation and in vitro evaluation of sustained release suppositories of indomethacine. *Ankara Ecz. Fak. Derg.* 1998; 27: 11-21.

- [71] G.S. Arra, S.A. Biswanath, D.R. Krishna, S. Arutla, A.K. Bandyopadhyay. Development and Evaluation of Micropelleted Sustained-Release Suppositories of Terbutaline Sulfate. *Drug Dev. Ind. Pharm.* 1997; 23: 1233-1237.
- [72] N. , T. Yokoyama, Y. Kiyohara, K. Okumura, K. Kuroda. Evaluation of Indomethacin Sustained-Release Suppositories Prepared with a Methacrylic Acid-Methacrylic Acid Methyl Ester Copolymer-Polyethylene Glycol 2000 Solid Matrix. *Chem. Pharm. Bull.* 1988; 36: 430-434.
- [73] T. Umeda, T. Yokoyama, N. Ohnishi, T. Kuroda, Y. Kita, K. Kuroda, S. Asada. Studies on Sustained-Release Dosage Forms. III. Preparation of Nifedipine Suppositories and Bioavailability in Rabbits. *Chem. Pharm. Bull.* 1985; 33: 3953-3959.
- [74] Y. Azechi, K. Ishikawa, N. Mizuno, K. Takahashi. Sustained release of diclofenac from polymer-containing suppository and the mechanism involved. *Drug Dev. Ind. Pharm.* 2000; 26: 1177-1183.
- [75] D. Ermiş, N. Tarımcı. Ketoprofen sustained-release suppositories containing hydroxypropylmethylcellulose phthalate in polyethylene glycol bases. *Int. J. Pharm.* 1995; 113: 65-71.
- [76] N. Ohnishi, T. Yokoyama, T. Umeda, Y. Kiyohara, T. Kuroda, Y. Kita, K. Kuroda. Preparation of sustained-release suppositories of indomethacin using a solid dispersion system and evaluation of bioavailability in rabbits. *Chem. Pharm. Bull.* 1986; 34: 2999-3004.
- [77] I.Özgüney (Sarıgüllü), İ.Özcan, G. Ertan, T. Güneri. The preparation and evaluation of ketoprofen containing Eudragit RL 100 sustained release suppositories with factorial design. *Pharmaceutical Development and Technology* 2007; 12: 97-107.
- [78] M.L. Vueba, L.A.E. Batista de Carvalho, F. Viegas, J.J. Sousa, M.E. Pina. Influence of cellulose ether polymers on ketoprofen release from hydrophilic matrix tablets. *Eur. J. Pharm. Biopharm.* 2004; 58: 51-59.
- [79] T. Güneri, M. Arıcı, G. Ertan Preparation and diffusional evaluation of sustained-release suppositories containing ibuprofen microspheres. *FABAD J. Pharm. Sci.*, 2004; 29: 177-184.
- [80] G. Uzunkaya, N. Bergeşadi. In vitro drug liberation and kinetics of sustained release indomethacin suppository. *Il Farmaco* 2003; 58: 509-512.
- [81] T. Kuroda , T. Yokoyama, T. Umeda , A. Matsuzawa , K. Kuroda, S. Asuda. Studies on sustained-release dosage forms. II. Pharmacokinetics after rectal administration of indomethacin suppositories in rabbits. *Chem. Pharm. Bull.* 1982; 31: 3319-3325.
- [82] H.G. Choi, J.H. Jung , J.M. Ryu, S.J. Yoon, Y.K. Oh, C.K. Kim. Development of in situ-gelling and mucoadhesive acetaminophen liquid suppository. *International Journal of Pharmaceutics* 1998; 165: 33-44.
- [83] H.G. Choi, Y.K. Oh, C.K. Kim. In situ gelling and mucoadhesive liquid suppository containing acetaminophen: enhanced bioavailability. *International Journal of Pharmaceutics* 1998; 165: 23-32.
- [84] I. Özgüney, A. Kardhiqi, G. Ertan, T. Güneri. Development of in situ-gelling and thermosensitive ketoprofen liquid suppositories. *Proc. 7th Central European Symposium on Pharmaceutical Technology and Biodelivery Systems, Ljubljana, Slovenia, 2008.*

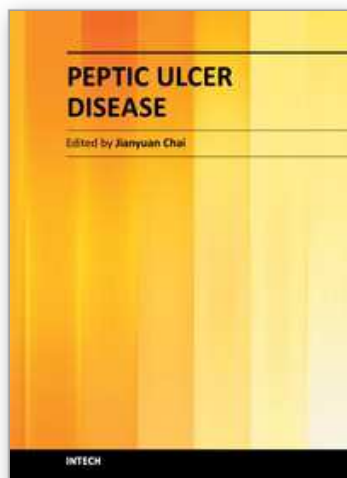
- [85] A. Kardhiqi, I. Özgüney. Mechanical properties of in situ-gelling and thermosensitive ketoprofen liquid suppositories. Proc. 15th International Pharmaceutical Technology Symposium, Antalya, Turkey, 2010.
- [86] Gibaldi's Drug Delivery Systems In Pharmaceutical Care, Edited by Archana Desai and Mary Lee. Published by American Society of Health-System Pharmacists, Bethesda, MD, 2007.
- [87] L. Kırılmaz. Two new suggestions for pharmaceutical dosage forms: ethylcellulose and cellulose acetate phthalate capsules. S.T.P. Pharma Sciences 1993; 3 (5): 374-378.
- [88] E. Ö. Çetin, E. Atlıhan, O. Çağlayan, M. Aşıkoğlu, L. Kırılmaz. A new alternative for enteric-coated dosage forms: hydroxypropylmethyl cellulose phthalate capsules. Proc. 11th Pharmaceutical Technology Symposium, İstanbul, Turkey, 2002.
- [89] O. Örümlü, E. Ö. Çetin, E. Atlıhan, F.G. Durak, Y.K. Dağdeviren, M. Aşıkoğlu, L. Kırılmaz. A new alternative for enteric-coated dosage forms: In vivo investigation of hydroxypropylmethyl cellulose phthalate capsules. Podium Presentations, The 4 th International Postgraduate Research Symposium on Pharmaceutics, İstanbul, Turkey, Acta Pharmaceutica Turcica Vol.46 Suppl. 2004.
- [90] H. Piao, N. Kamiya, J. Watanabe, H. Yokoyama, A. Hirata, T. Fujii, I. Shimizu, S. Ito, M. Goto. Oral delivery of diclofenac sodium using a novel solid-in-oil suspension. International Journal of Pharmaceutics 2006; 313: 159-162.
- [91] H.I. Kim, J.H. Park, I.W. Cheong, J.H. Kim. Swelling and drug release behavior of tablets coated with aqueous Hydroxypropylmethylcellulosephthalate (HPMCP) nanoparticles. J. Control. Release 2003; 89: 225-233.
- [92] M.D. Kurkuri, T.M. Aminabhavi. Poly (vinyl alcohol) and poly (acrylic acid) sequential interpenetrating network pH-sensitive microspheres for the delivery of diclofenac sodium to the intestine. J. Control. Release 2004; 96: 9-20.
- [93] S.S. Biju, S. Saisivam, N.S. Maria, G. Rajan, P.R. Mishra. Dual coated erodible microcapsules for modified release of diclofenac sodium. Eur. J. Pharm. Biopharm. 2004; 58: 61-67.
- [94] G.M. Ferron, S. Ku, M. Abell, M. Unruh, J. Getsy, P.R. Mayer, J. Paul. Oral bioavailability of pantoprazole suspended in sodium bicarbonate solution. Am. J. Health Syst. Pharm. 2003; 60 (13): 1324-1329.
- [95] S.Y. Lin, Y.H. Kao. Tablet study of spray-dried sodium diclofenac enteric-coated microcapsules. Pharm. Res. 1991; 8 (7): 919-924.
- [96] P. O'Donnell, J. McGinity. Preparation of microspheres by the solvent evaporation technique. Adv. Drug Deliv. Rev. 1997; 28: 25-42.
- [97] Y. Yamagata, M. Misaki, T. Kurokawa, K. Taira, S. Takada. Preparation of a copoly(DL-lactic/glycolic acid)-zinc oxide complex and its utilization to microcapsules containing recombinant human growth hormone. Int. J. Pharm. 2003; 251: 133-141.
- [98] K.A. Mehta, M.S. Kislalioglu, W. Phuapradit, A.W. Malick, N.H. Shah. Release performance of a poorly soluble drug from a novel, Eudragit®-based multi-unit erosion matrix. Int. J. Pharm. 2001; 213: 7-12.
- [99] R.P. Raffin, L.M. Colome', A.R. Pohlmann, S.S. Guterres. Preparation, characterization, and in vivo anti-ulcer evaluation of pantoprazole-loaded microparticles. European Journal of Pharmaceutics and Biopharmaceutics. 2006; 63: 198-204.
- [100] J.R. Caldwell, S.H. Roth. A double blind study comparing the efficacy and safety of enteric coated naproxen to naproxen in the management of NSAID intolerant

- patients with rheumatoid arthritis and osteoarthritis. Naproxen EC Study Group. *J Rheumatol*. 1994; 21(4): 689-95.
- [101] R.I. Trondstad, E. Aadland, T. Holler, B. Olaussen. Gastroscopic findings after treatment with enteric-coated and plain naproxen tablets in healthy subjects. *Scand J Gastroenterol*. 1985; 20(2): 239-42.
- [102] L. Aabakken, B.A Bjornbeth, B. Hofstad, B. Olaussen, S. Larsen, M. Osnes. Comparison of the gastrointestinal side effects of naproxen formulated as plain tablets, enteric-coated tablets, or enteric-coated granules in capsules. *Scand J Gastroenterol Suppl*. 1989; 163: 65-73.
- [103] J.R. Ryan, W.A. Riley, R. Vargas, W.W. Offen, C.M. Gruber. Enteric coating of fenopfen calcium reduces gastrointestinal microbleeding. *Clin Pharmacol Ther*. 1987; 42(1): 28-32.
- [104] F.L. Lanza, M.F. Rack, G.S. Wagner, T.K. Balm. Reduction in gastric mucosal hemorrhage and ulceration with chronic high-level dosing of enteric-coated aspirin granules two and four times a day. *Dig Dis Sci*. 1985; 30(6) :509-512.
- [105] Y. W. Chien, Controlled- and modulated-release drug-delivery systems. in: J. Swarbrick, J. C. Boylan (Eds). *Encyclopedia of Pharmaceutical Technology*, Marcel Dekker, New York, 2001; 203-226.
- [106] G. Castaneda-Henandez, G. Caille, P. du Souich. Influence of drug formulation on drug concentration–effect relationships. *Clin. Pharmacokinet*. 1994; 26: 135–143.
- [107] A. Hoffman. Pharmacodynamic aspects of sustained release preparations. *Advanced Drug Delivery Reviews* 1998; 33: 185–199.
- [108] A.T. Florence, P.U. Jani, Novel oral formulations: their potential in modulating adverse effects. *Drug Safety* 1994; 10: 233–266.
- [109] F.P. Maesen, J.J. Smeets. Comparison of a controlled-release tablet of salbutamol given twice daily with a standard tablet given four times daily in the management of chronic obstructive lung disease. *Eur. J. Clin. Pharmacol*. 1986; 31: 431–436.
- [110] I. Özgüney (Sarıgüllü), G. Ertan, T. Güneri. Dissolution Characteristics of Megaloporous Tablets Prepared with Two Kinds of Matrix Granules. *Il Farmaco* 2004; 59(7): 549-555.
- [111] E. Karasulu, H. Y. Karasulu, G. Ertan, L. Kırılmaz and T. Güneri. Extended release lipophilic indomethacin microspheres: formulation factors and mathematical equations fitted drug release rates. *European Journal of Pharmaceutical Sciences*. 2003; 19(2-3); 99-104.
- [112] L. Kırılmaz, A. Şahin, Z. Sarçin, F. Taneri. A preliminary investigation on the estimation of the sustained-release of indomethacin from agar beads. Part I., *Acta Pharm. Turcica*. 1997; XXXIX, (3): 119-132.
- [113] L. Yang, R. Fasihsi. Modulation of diclofenac release from a totally soluble controlled release drug delivery system. *Journal of Controlled Release* 1997; 44 (2-3); 135-140.
- [114] J. A. Herrera, A. Millán, R. Ramos, P. Fuentes, M. González. Evaluation of the effectiveness and tolerability of controlled-release diclofenac-potassium versus immediate-release diclofenac-potassium in the treatment of knee osteoarthritis. *Current Therapeutic Research* 2007; 68(2): 82-93.
- [115] M. Halsas, J. Hietala, P. Veski, H. Jürjenson, M. Marvola. Morning versus evening dosing of ibuprofen using conventional and time-controlled release formulations. *International Journal of Pharmaceutics*. 1999; 189(2,5): 179-185.

- [116] C.W. Pouton. Lipid formulations for oral administration of drugs: nonemulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. *Eur. J. Pharm. Sci.* 2000; 11: 93–98.
- [117] O. Ohmukai. Lipo-NSAID preparation. *Adv. Drug Deliv. Rev.* 1996; 20: 203–207.
- [118] J.M. Harrewyn, B. Amor. Double-blind comparative study of slow-release ketoprofen and a placebo in chronic inflammatory rheumatism. *Sem Hop.* 1983; 59(46): 3225–3228.
- [119] H.R. Schumacher. Ketoprofen extended-release capsules: a new formulation for the treatment of osteoarthritis and rheumatoid arthritis. *Jr Clin Ther.* 1994; 16(2): 145–159.
- [120] K.D. Morley, R.M. Bernstein, G.R. Hughes, C.M. Black, C.N. Rajapakse, L.A. Wilson. Comparative trial of a controlled-release formulation of ketoprofen ('Oruvail') and a conventional capsule formulation of ketoprofen ('Orudis') in patients with osteoarthritis of the hip. *Curr Med Res Opin.* 1984; 9(1): 28–34.
- [121] P. Bacon, R.A. Luqmani, C. Barry, D. Foley-Nolan, R. Grahame, J. West, B.L. Hazleman, A.O. Adebajo, G.R. Hughes, M. Abdullah et al. A comparison of two formulations of indomethacin ('Flexin Continus' tablets and 'Indocid' capsules) in the treatment of rheumatoid arthritis. *Curr Med Res Opin.* 1990; 12(2): 121–127. Erratum in: *Curr Med Res Opin* 1990; 12(3): 142.
- [122] P.J. Prichard, T.J. Poniatowska, J.E. Willars, A.T. Ravenscroft, C.J. Hawkey. Effect in man of aspirin, standard indomethacin, and sustained release indomethacin preparations on gastric bleeding. *Br J Clin Pharmacol.* 1988; 26(2): 167–72.
- [123] S.J. Warrington, J. Dana-Haeri, M.A. Horton, E.J. Thornton. Drugs Comparison of gastrointestinal blood loss in healthy male volunteers during repeated administration of standard and sustained action tiaprofenic acid and sustained release indomethacin. *Drugs* 1988; 35 Suppl 1: 90–94.
- [124] C. Varese, A. Palazzini. Open study of a diclofenac sodium prolonged-release in patients suffering from coxarthrosis. *Eur Rev Med Pharmacol Sci.* 1997; 1(1–3): 57–62.
- [125] P. Uddenfeldt, I. Leden, B. Rubin. A double-blind comparison of oral ketoprofen 'controlled release' and indomethacin suppository in the treatment of rheumatoid arthritis with special regard to morning stiffness and pain on awakening. *Curr Med Res Opin.* 1993; 13(3): 127–32.
- [126] T. Nishihata, H. Wada, A. Kamada. Sustained-release of sodium diclofenac from suppository. *International Journal of Pharmaceutics* 1985; 27 (2–3): 245–253.
- [127] F. Sevgi, B. Kaynarsoy, G. Ertan. An anti-inflammatory drug (mefenamic acid) incorporated in biodegradable alginate beads: development and optimization of the process using factorial design. *Pharm Dev Technol.* 2008; 13(1): 5–13.
- [128] F. Sevgi, B. Kaynarsoy, M. Özyazıcı, C. Pekçetin and D. Özyurt. A Comparative Histological Study of Alginate Beads as a Promising Controlled Release Delivery for Mefenamic Acid. *Pharmaceutical Development and Technology* 2008; 13: 387–392.
- [129] M. Özyazıcı, F. Sevgi, C. Pekçetin, B. Sarpaş and Ş. Sayın. Sustained release spherical agglomerates of polymethacrylates containing mefenamic acid: in vitro release, micromeritic properties and histological studies. *Pharmaceutical Development and Technology* (In Press). (doi: 10.3109/10837450.2010.550621).

- [130] D. Majumdar, J. Bebb, J. Atherton. *Helicobacter pylori* infection and peptic ulcers. *Medicine*. 2007; 35 (4): 204-209.
- [131] L. H. Lai, J. J.Y. Sung. *Helicobacter pylori* and benign upper digestive disease. *Best Practice & Research Clinical Gastroenterology*. 2007; 21 (2): 261-279.
- [132] J.C. Atherton, P. Cao, R.M. Peek, M.K.R. Tummuru, M.J. Blaser, T.L. Cover. Mosaicism in vacuolating cytotoxin alleles of *Helicobacter-Pylori* association of specific vaca types with cytotoxin production and peptic-ulceration. *J Biol Chemil* 1995; 270: 17771-17777.
- [133] J. Viala, C. Chaput, I.G. Boneca. et al. Nod1 responds to peptidoglycan delivered by the *Helicobacter pylori* cag pathogenicity island. *Nat Immun* 2004; 5: 1166-1174.
- [134] T.S. Chen , Y.C. Lee, F.Y. Li, F.Y. Chang. Smoking and hyperpepsinogenemia are associated with increased risk for duodenal ulcer in *Helicobacter pylori*-infected patients. *J Clin Gastroenterol* 2005; 39: 699-703.
- [135] S.F. Moss, S. Legon, A.E. Bishop, J.M. Polak, J. Calam. Effect of *Helicobacter-pylori* on gastric somatostatin in duodenal-ulcer disease. *Lancet* 1992; 340: 930-932.
- [136] A. Lee. The nature of *Helicobacter pylori*. *Scand. J. Gastroenterol*. 1996; 31(Suppl. 214): 5-8.
- [137] G.N. Tytgat. Current indications for *Helicobacter pylori* eradication therapy. *Scand. J. Gastroenterol*. 1996; 31(Suppl. 215): 70-73.
- [138] M.P. Cooreman, P. Krausgrill, K.J. Hengels. Local gastric and serum amoxicillin concentrations after different oral application forms. *Antimicrob. Agents Chemother*. 1993; 37: 1506-1509.
- [139] B.D. Gold, M. Huesca, P.M. Sherman, et al. *Helicobacter mustelae* and *Helicobacter pylori* bind to common lipid receptors in vitro. *Infect. Immun*. 1993; 61: 2632-2638.
- [140] B.L. Slomiany, J. Piotrowski, A. Samanta et al. *Campylobacter pylori* colonization factors shows specificity for lactosylceramide sulfate and GM3 ganglioside. *Biochem. Internat*. 1989; 19: 929-936.
- [141] T. Bore'n, P. Falk, K.A. Roth, et al., Attachment of *Helicobacter pylori* to human gastric epithelium mediated by blood group antigens. *Science* 1993; 262: 1892-1895.
- [142] A.L. Blum, *Helicobacter pylori* and peptic ulcer disease. *Scand. J. Gastroenterol*. 1996; 31(Suppl. 214): 24-27.
- [143] R.V. Heatley. The treatment of *Helicobacter pylori* infection. *Aliment. Pharmacol. Ther*. 1992; 6: 291-303.
- [144] A.T.R. Axon. *Helicobacter pylori* therapy: effect on peptic ulcer disease. *J. Gastroenterol. Hepatol*. 1991; 6: 131-137.
- [145] M. Cuna, M.J. Alonso, D. Torres. Preparation and in vivo evaluation of mucoadhesive microparticles containing amoxicillin-resin complexes for drug delivery to the gastric mucosa. *European Journal of Pharmaceutics and Biopharmaceutics* 2001; 51: 199-205.
- [146] D.Y. Graham, G.M.A. Borsch. The who's and when's of therapy for *Helicobacter pylori*. *Am. J. Gastroenterol*. 1990; 85: 1552-1555.
- [147] A. Ateshkadi, N.P. Lam, C.A. Johnson. *Helicobacter pylori* and peptic ulcer disease. *Clin. Pharm*. 1993; 12: 34-48.
- [148] J.C. Atherton, A. Cockayne, M. Balsitis, G.E. Kirk, C.J. Hawkey, R.C. Spiller. Detection of the intragastric sites at which *Helicobacter pylori* evades treatment with amoxicillin and cimetidine. *Gut* 1995; 36: 670-674.

- [149] P.S. Rajinikanth, J. Balasubramaniam, B. Mishra. Development and evaluation of a novel floating in situ gelling system of amoxicillin for eradication of *Helicobacter pylori*. *International Journal of Pharmaceutics* 2007; 335: 114-122.
- [150] K. Kimura, K. Ido, K. Saifuku, Y. Taniguchi, K. Kihira, K. Satoh, T. Takimoto, Y. Yoshida. A 1-h topical therapy for the treatment of *Helicobacter pylori* infection. *Am. J. Gastroenterol.* 1995; 90: 60-63.
- [151] N. Nagahara, Y. Akiyama, M. Nakao, M. Tada, M. Kitano, Y. Ogawa. Mucoadhesive microspheres containing amoxycillin for clearance of *Helicobacter pylori*. *Antimicrob. Agents Chemother.* 1998; 38: 2492-2494.
- [152] A.K. Hilton, P.B. Deasy. In vitro and in vivo evaluation of an oral sustained-release floating dosage form of amoxycillin trihydrate. *Int. J. Pharm.* 1992; 86: 79-88.
- [153] V.R. Patel, M.M. Amiji. Preparation and characterization of freeze-dried chitosan-poly(ethylene oxide) hydrogels for site-specific antibiotic delivery in the stomach. *Pharm. Res.* 1996; 13: 588-593.
- [154] S. Shah, R. Qaqish, V. Patel, M. Amiji. Evaluation of the factors influencing stomach-specific delivery of antibacterial agents for *Helicobacter pylori* infection. *J. Pharm. Pharmacol.* 1999; 51: 667-672.
- [155] S. Burton, N. Washington, R.J.C. Steele, R. Musson, L. Feely. Intragastric distribution of ion-exchange resins: a drug delivery system for the topical treatment of the gastric mucosa. *J. Pharm. Pharmacol.* 1995; 47: 901-906.
- [156] S. Thairs, S. Ruck, S.J. Jackson, R.J.C. Steele, L.C. Freely, C. Washington, N. Washington. Effect of dose size, food and surface coating on the gastric residence and distribution of an ion exchange resin. *Int. J. Pharm.* 1998; 176: 47-53.
- [157] P.S. Rajinikanth, B. Mishra. Floating in situ gelling system for stomach site-specific delivery of clarithromycin to eradicate *H. Pylori*. *Journal of Controlled Release* 2008; 125: 33-41.
- [158] S.W. Jang, J.W. Lee, S.H. Park, J. H. Kima, M. Yoo, D.H. Na, K.C. Lee. Gastroretentive drug delivery system of DA-6034, a new flavonoid derivative, for the treatment of gastritis. *International Journal of Pharmaceutics.* 2008; 356: 88-94.
- [159] M. Takenaga, Y. Serizawa, Y. Azechi, A. Ochiai, Y. Kosaka, R. Igarashi, Y. Mizushima. Microparticle resins as a potential nasal drug delivery system for insulin. *J. Control. Release* 1998; 52: 81-87.



Peptic Ulcer Disease

Edited by Dr. Jianyuan Chai

ISBN 978-953-307-976-9

Hard cover, 482 pages

Publisher InTech

Published online 04, November, 2011

Published in print edition November, 2011

Peptic ulcer disease is one of the most common chronic infections in human population. Despite centuries of study, it still troubles a lot of people, especially in the third world countries, and it can lead to other more serious complications such as cancers or even to death sometimes. This book is a snapshot of the current view of peptic ulcer disease. It includes 5 sections and 25 chapters contributed by researchers from 15 countries spread out in Africa, Asia, Europe, North America and South America. It covers the causes of the disease, epidemiology, pathophysiology, molecular-cellular mechanisms, clinical care, and alternative medicine. Each chapter provides a unique view. The book is not only for professionals, but also suitable for regular readers at all levels.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Işık Özgüney (2011). Conventional and Novel Pharmaceutical Dosage Forms on Prevention of Gastric Ulcers, Peptic Ulcer Disease, Dr. Jianyuan Chai (Ed.), ISBN: 978-953-307-976-9, InTech, Available from: <http://www.intechopen.com/books/peptic-ulcer-disease/conventional-and-novel-pharmaceutical-dosage-forms-on-prevention-of-gastric-ulcers>

INTech
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen