JPP Journal of Pharmacy and Pharmacology

JPP 2007, 59: 59–65

Received March 21, 2006
Accepted October 2, 2006
DOI 10.1211/jpp.59.1.0008
ISSN 0022-3573

Enteric-coated solid dosage forms containing sodium bicarbonate as a drug substance: an exception from the rule?

Jörg Breitkreutz, Tjwan Gie Gan, Bernd Schneider and Peter Kalisch

Abstract

Sodium bicarbonate (sodium hydrogen carbonate) is used as an oral medication in disorders such as mild metabolic acidosis and chronic kidney disease. The two commercial products on the German market, bicaNorm and Nephrotrans, and also newly developed multiple-unit pellet formulations, have been characterized in these investigations by in-vitro methods like disintegration and dissolution testing. Both marketed products containing sodium bicarbonate are of sufficient pharmaceutical quality according to the European Pharmacopoeia. However, they and the novel pellet preparations showed different drug release at moderately elevated pH values. Early drug release may cause dose dumping in the stomach and adverse drug effects from the developed carbon dioxide. The soft capsule preparation (Nephrotrans) released the smallest amount of sodium bicarbonate at pH 1 and 4.5 of all formulations tested. It appeared that oral dosage formulations of sodium bicarbonate were an exception to the rule: the monolithic soft capsule seemed to be superior to an enteric-coated tablet as well as to multiple-unit pellet formulations from the biopharmaceutical point of view. Our results correspond with individual reports on adverse effects from patients treated with the sodium bicarbonate products.

Introduction

Sodium bicarbonate, also called sodium hydrogen carbonate, is used as a pH regulatory agent in oral drug formulations for mild metabolic acidosis (Adrogué & Madias 1998) and for supportive therapy in chronic kidney diseases (Kraut & Kurtz 2005). In other diseases, such as lactic acidosis, treatment with sodium bicarbonate is controversial (Cuhaci et al 2000; Forsythe & Schmidt 2000). Infusions containing sodium bicarbonate are indicated in life-threatening conditions such as acute renal failure and acute asthma (Buysse et al 2005; Hoste et al 2005).

The oral administration of sodium bicarbonate is a pharmaceutical technological challenge: firstly, the drug must not be released in the stomach as the acidic gastric juice would immediately transform bicarbonate into carbon dioxide. The desired therapeutic effect would not be achieved and the produced gas could cause abdominal pain and flatulence. Secondly, sodium bicarbonate should be rapidly released from the solid dosage form into the intestinal fluid as residuals of bicarbonate in ileum and colon may cause diarrhoea and flatulence. Both criteria can be fulfilled by enteric-coated dosage forms of sodium bicarbonate. It is well known from the literature that numerous variables can affect the stability and functionality of enteric coatings (Petereit & Weisbrod 1999). External factors, such as mechanical forces, pH values and temperature, as well as inter-formulational interactions with external substances like buffer substances or macrogol (Breitkreutz 2000), may influence the drug release. Intra-formulational interactions (e.g. with solvents, plasticizers or core material) also influence the dissolution pattern (Raffin et al 1996). In sodium bicarbonate formulations the permeability of hydrogen ions has an extraordinary impact as traces of protons in the core could initiate gas forming and consequently cause film rupturing. Dose dumping would result.

Two different products for the oral administration of sodium bicarbonate are available on the German market. Both are single-unit dosage forms: a tablet containing 1g sodium

Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Universitätsstrasse 1, 40225 Düsseldorf, Germany

Jörg Breitkreutz

Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany

Tjwan Gie Gan, Bernd Schneider, Peter Kalisch

Correspondence: J. Breitkreutz, Institut für Pharmazeutische Technologie und Biopharmazie, Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany. E-mail: joerg.breitkreutz@uni-duesseldorf.de

bicarbonate (bicaNorm) and a soft capsule containing 0.5g sodium bicarbonate (Nephrotrans). Nephrotrans contains various triglycerides from plant origin, lecithin, sorbitol and mannitol. The soft capsule shell made from gelatine is enteric-coated by a hypromellose phthalate film coating. The bicaNorm enteric-coated tablets are composed of starch, microcrystalline cellulose, macrogols and polyvinylpyrrolidone for the tablet core, a hypromellose subcoat and a Eudragit L enteric coating layer. The monolithic character of both marketed products may be surprising as multiple-unit dosage forms are assumed to be superior in preventing dose dumping compared with monolithic formulations. Multiple-unit preparations have therefore become more popular in recent years. Actually, various complaints from patients indicate that dose dumping may happen when using the commercial products with sodium bicarbonate, indicated by gluttony, flatulence and abdominal pain. It appears from patients' complaints that there may be more adverse reactions with the enteric-coated tablet formulation than the enteric-coated soft gelatine capsule.

To evaluate the drug-release properties of different sodium bicarbonate dosage forms and the probable impact on therapeutic and toxicological effects, we performed comparative in-vitro studies on the two commercial products and newly developed monolithic and multiple-unit formulations.

Materials and Methods

Materials

Sodium bicarbonate (sodium monohydrogen carbonate) was purchased from Dr Paul Lohmann (Emmertal, Germany). Nephrotrans enteric-coated capsules (lots 51003 and 51004) were supplied by Medice Arzneimittel (Iserlohn, Germany). bicaNorm enteric-coated tablets (lots FBN011 and FBN012) were purchased from Fresenius Medical Care (Bad Homburg, Germany). Hydrochloric acid, potassium dihydrogenphosphate, potassium hydroxide and phosphoric acid were obtained from Merck (Darmstadt, Germany). The methacrylic acid–methyl methacrylate copolymers, Eudragit L 30 D, Eudragit L 100 and Eudragit L 30 D-55, were purchased from Röhm-Pharma (Darmstadt, Germany). Polyvinylalcohol was obtained from Colorcon (Idstein, Germany) and copovidone (vinylpyrrolidone–vinylacetate copolymer) from BASF (Ludwigshafen, Germany).

Preparation of enteric-coated sodium bicarbonate pellets

Pellets containing sodium bicarbonate (80%) were obtained by an extrusion and spheronization process using microcrystalline cellulose (20%) as a binder and purified water. The bulk was constantly extruded using the rotary ring die press PP 85 (Schlüter, Neustadt, Germany) through a 90° entry die of 1mm diameter. The cylindrical extrudates were collected in a beaker and spheronized in an RM 30 spheronizer (Schlüter, Neustadt, Germany). The obtained particles were dried for 60 min at 40°C in the fluid-bed coater Strea-1 (Aeromatic-Fiedler, Bubendorf, Switzerland). The resulting pellets were spherical with a mean diameter of 1.2 mm. The sodium bicarbonate content of the pellets was 80%, determined by atomic absorption spectroscopy. Film-coating was also performed in the Strea-1 lab coater using a top-spray setup. Each batch comprised 400 g uncoated pellet cores. Different methacrylic acid–methyl methacrylate copolymers of the Eudragit L product line and subcoating materials, like polyvinyl alcohol and copovidone, were used to obtain gastric juice resistance. Methacrylic acid–methyl methacrylate copolymer Ph. Eur. (Eudragit L 100) was used in an ethanolic solution (15% polymer mass) or as a 30% aqueous dispersion (Eudragit L 30 D). Methacrylic acid–ethylacrylate copolymer Ph. Eur. was used as a 30% aqueous dispersion (Eudragit L 30 D-55). Both polymers were used in combination with a subcoat made of either polyvinyl alcohol or copovidone and also without any subcoat. The weight gain of all produced pellets was 10–30%, which is in accordance with the recommendations of the supplier to achieve gastric resistance. Additionally, further batches were produced with extraordinary thick polymer layers obtained from up to 60% weight gain using polyvinyl alcohol as a subcoat and Eudragit L 30 D-55 as the enteric layer. The temperature of the inlet air was 32°C and the outlet air 28°C, descending to 20°C. The product temperature was relatively constant at 26–28°C.

The polymer solutions or dispersion were continuously applied to the nozzle using flow rates of 2.5–3.5 g min^{-1}.

Dissolution testing

The drug release profiles were determined using the paddle setup for tablets and capsules and the basket setup of the Ph. Eur. dissolution test for the pellet formulations. The paddle or basket was rotated at 100 rev min^{-1} and the temperature of the dissolution media was continuously kept at 37 ± 0.5°C. The dissolution fluids were 0.1 M hydrochloric acid, 0.05 M potassium dihydrogen phosphate adjusted to pH 4.5 using potassium hydroxide and phosphoric acid, and 0.05 M potassium dihydrogen phosphate adjusted to pH 6.8 by potassium hydroxide. According to the dissolution method of the Ph. Eur., the test was started at pH 1.0 using 0.1 M hydrochloric acid. In deviation from the Ph. Eur. method, the stressing acidic pH was kept constant for 180 min and not for 120 min.

In a further experimental setup, a phosphate buffer with pH 4.5 was used instead of the 0.1 M hydrochloric acid to evaluate the robustness of the various enteric formulations.

At 60, 120 and 180 min (for pH 1.0), 30, 60, 90, 120, 150, 180 and 240 min (for pH 4.5) and 15, 30, 45, 60, 120, 180, 240 and 300 min (for pH 6.8) after inserting the tested objects, a sample of 5 mL was drawn from the dissolution medium, diluted with 5 mL of the dissolution fluid and subsequently filtered through 0.45-μm cellulose acetate filters (Macherey-Nagel, Düren, Germany). Preliminary validation studies had been conducted to demonstrate that the sodium concentration is not diminished by the filtration process. The sodium cation content of the sample was determined by atomic absorption spectroscopy. All experiments were conducted with six individual samples per batch.

Atomic absorption spectroscopy

Atomic absorption spectroscopy was performed using a Spectra AA240FS from Varian (Darmstadt, Germany). The spectrometer was equipped with a SPS3 autosampler. The measurements were performed at 330.3 nm and operated at a slit width of 0.2 nm. The carrier gases used were synthetic air and acetylene, both from Air Liquid (Krefeld, Germany).

The sodium content in the samples was determined using a calibration curve obtained from dilutions of certified standard sodium solution (1000 ppm) and potassium dihydrogenphosphate ACS grade (< 0.005% Na), both from Merck (Darmstadt, Germany). The sodium standard was diluted to 5, 10, 20, 40, 60, 100, 140 and 180 ppm sodium using the dissolution medium. Pure dissolution medium was used as a blank.

Statistical methods

Statistical analysis of the effects of different formulations on the rate of drug release was performed at each time point using a one-way analysis of variance (Microsoft Excel). In all cases, post-hoc comparisons of the means of individual groups of six replicates were conducted using Tukey's Honestly Significant Difference test. $P < 0.05$ denoted significance in all cases.

Results

In preliminary investigations, the properties of two commercial products containing sodium bicarbonate as a therapeutic agent, Nephrotrans and bicaNorm, were characterized according to the European Pharmacopoeia. All the tested batches from both drugs fully met the requirements of the disintegration test (Ph. Eur.) as the tablets or capsules were stable in 0.1 M hydrochloric acid for at least 2 h and fully disintegrated in phosphate buffer at pH 6.8 within 30 min (tablets) or 1 h (capsules).

The various film-coated pellet formulations show different results both in the disintegration and the dissolution tests. Sufficient gastric fluid resistance, according to the Ph. Eur. disintegration test, was not obtained using Eudragit L 30 D dispersions, even if subcoats of copovidone or polyvinylalcohol were used. Using organic Eudragit L 100 solutions as a separation layer, gastric fluid resistance was more pronounced than for Eudragit L 30 D dispersions but not sufficient. In contrast to the other formulations, film-coated pellets with a subcoat of 5% polyvinyl alcohol and at least 40% polymethacrylate using Eudragit L 30 D-55 dispersion fully complied with the disintegration test Ph. Eur. requirements for enteric-coated solid preparations and were therefore used for the comparative studies. If less polymer mass was applied, the gastric fluid resistance decreased. The highest weight gain of a pellet batch was 60%, which is twice the highest amount of polymer for gastric juice resistance recommended by the supplier of the polymer.

As the release of sodium bicarbonate may be started without obvious damaging of the dosage forms, dissolution experiments were performed in addition. As a first step, the dosage forms were given in 0.1 M hydrochloric acid for 3 h to determine the release of sodium as a marker for sodium bicarbonate into simulated gastric fluid. Sodium bicarbonate was not released from any marketed formulation into simulated gastric fluid (pH 1.0) in a significant amount (Figure 1). The largest sodium concentration measured in the dissolution fluid was 0.4% of the dose for a single Nephrotrans soft gelatine capsule of batch 51004. The average amount of released sodium bicarbonate from capsules of the same batch was 0.33 ± 0.05% of the dose after 2 h. For batch 51003 of Nephrotrans, 0.15 ± 0.10% sodium bicarbonate was released. The drug was not released from bicaNorm enteric-coated tablets in the investigated time period.

In phosphate buffer, pH 6.8, the dissolution profiles of Nephrotrans and bicaNorm differed significantly (Figure 1). Within the first 30 min, 34.3 ± 11.8% (lot FBN011) resp. 40.9 ± 8.1% (lot FBN012) of the sodium bicarbonate dose was released from the tablets, but only 4.3 ± 0.9% (lot 51003) resp. 1.8 ± 0.6% (lot 51004) was dissolved from the soft capsules. The statistical analysis (analysis of variance/Tukey's test, $P < 0.05$) revealed significant differences between the two formulations after changing the dissolution medium, but not a significant batch-to-batch variation for the products. Even 5 h later, 14–16% of the sodium bicarbonate dose still remained inside the capsule, whereas the drug was completely released from the tablet in less than 2 h.

Both commercial products, Nephrotrans and bicaNorm, fully complied with all the quality control tests of the European Pharmacopoeia according to our studies. However, patients' complaints about adverse drug effects, mostly concerning the bicaNorm tablets, were not explained by these in-vitro methods. In contrast, the findings described above may even suggest an advantage of the tablet formulation, as the drug release into simulated intestinal fluid is faster than with the soft gelatine capsules of Nephrotrans.

An explanation for the observed differences in-vitro and in-vivo may be the varying pH values in-vivo caused by gastric

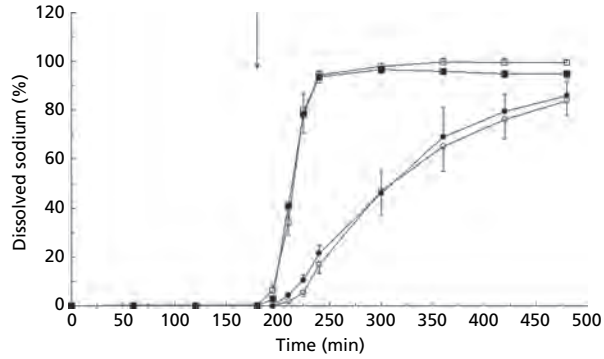

Figure 1 Dissolution of sodium bicarbonate from two different batches of commercial enteric-coated products in 0.1 M hydrochloric acid (pH 1.0) and potassium phosphate buffer pH 6.8 (paddle apparatus Ph. Eur., 37 ± 0.5°C, 100 rev min^{-1}, $x + s$ resp. $x - s$, $n = 6$). The arrow marks the switch from pH 1.0 to 6.8. Closed circles, Nephrotrans enteric-coated soft gelatine capsule, lot 51003; open circles, Nephrotrans enteric-coated soft gelatine capsule, lot 51004; closed squares, bicaNorm enteric-coated tablet, lot FBN011; open squares, bicaNorm enteric-coated tablet, lot FBN012.

and intestinal motility as well as the intake of food. The gastric pH value in the fasted state has been determined to be 1–2 using a telematical pH sensor (Heidelberger Kapsel) attached to a magnet that can be maintained in the stomach for hours by a strong external magnet (Berntgen 1997). In this experimental setup, transitory peaks up to pH 4 were measured in-vivo, which were attributed to the reflux of intestinal fluid during the rhythmical reoccurring housekeeper waves. Using a permanent nasal gastric tube with a permanent gastric pH sensor (Meditronic), pH profiles can be obtained under more realistic conditions, including food uptake and movements. In a recent study on proton pump inhibitors, the baseline pH profiles before the medication exhibited pH peaks of 4.5 and troughs of pH 1.4 (Thyroff-Friesinger 2002). The peaks could be clearly attributed to the food ingestion during the day. After lunch, the averaged gastric pH value of 21 healthy male subjects increased to 4.4, and descended within 3 h back to the fasted conditions. During proton pump inhibition therapy, the gastric pH values were significantly higher than in the baselines before starting the therapy protocol.

To simulate more realistic conditions, additional dissolution studies on sodium bicarbonate dosage forms were performed using a potassium phosphate buffer system at pH 4.5. At this pH, significant differences were observed between the Nephrotrans capsules and the bicaNorm enteric-coated tablets (Figure 2). The capsules released not more than 1.7% of one individual capsule and an average of 0.6% of the sodium bicarbonate load within 6 h. In contrast, the drug dissolution from the tablets was almost complete after 90 min and exceeded 50% before 1 h for all tested batches. The beginning of the tablet disintegration could be visually observed at 30 min (Figure 3A). At 60 min the disintegration process was approximately completed, indicated by the cloudy dissolution fluid (Figure 3B). In contrast, the Nephrotrans capsule seemed to be intact even at 6 h of the dissolution test at pH 4.5 (Figures 3C and 3D).

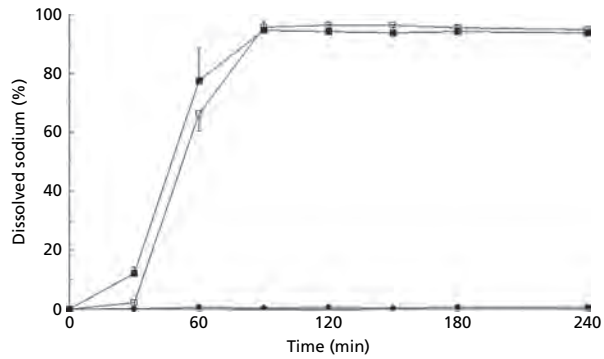

Figure 2 Dissolution of sodium bicarbonate from two different batches of commercial enteric-coated products in potassium phosphate buffer pH 4.5 (paddle apparatus Ph. Eur., 37 ± 0.5°C, 100 rev min^{-1}, x + s resp. x − s, n = 6). Closed circles, Nephrotrans enteric-coated soft gelatine capsule, lot 51003; open circles, Nephrotrans enteric-coated soft gelatine capsule, lot 51004; closed squares, bicaNorm enteric-coated tablet, lot FBN011; open squares, bicaNorm enteric-coated tablet, lot FBN012.

The developed pellet formulations showed similar dissolution profiles, but the drug release was faster and more complete at all pH conditions under investigation. The sodium bicarbonate release depended on the thickness of the external coating layer. At pH 1 almost 20% of the sodium load was released from the Eudragit L 30 D-55 coated pellets with 40% polymer after 120 min. Even with 60% polymer mass there was still 12% sodium bicarbonate released into the simulated gastric fluid after 2 h. In phosphate buffer pH 4.5, the drug release was faster and approximately completed after 180 min. Only for phosphate buffer pH 6.8 was the dissolution profile of the pellet formulation similar to those of the commercial tablets or capsules (Figure 4).

Discussion

Sodium bicarbonate is a basic agent that is unstable in an acidic environment. If it comes into contact with protons, carbonic acid is formed that separates into carbon dioxide and water. As carbon dioxide evaporates the reaction usually develops rapidly and completely. The development of oral dosage forms with sodium bicarbonate as a therapeutic agent is a special challenge for pharmaceutical technology. Due to its chemical and physicochemical properties, sodium bicarbonate must be prevented, as much as possible, from coming into contact with protons and water molecules of the gastric juice by enteric coating. If the protection is incomplete, carbon dioxide will develop due to drug degradation and will additionally stress the coating. Furthermore, dissolving sodium bicarbonate in water can diminish the protective efficiency of the acidic coatings due to the basic character of the salt. In the development of sodium-bicarbonate-containing pellet formulations the interactions became quite obvious, indicated by the failure of aqueous dispersions or organic solutions of the Eudragit L product line to form an intact enteric coating around the extrusion pellets. As the used polymers have an acidic character, they can induce the drug instability during the coating process by themselves. Recently, this contradictory phenomenon has been clearly demonstrated for the acid-sensitive drug substance omeprazole (Türkoglu et al 2004; Riedel & Leopold 2005). Furthermore, traces of water residuals may also start the drug degradation during spraying and drying the polymer dispersion. Using separation layers made of organic solutions of non-acidic polymers, like polyvinyl alcohol and vinylpyrrolidone–vinylacetate copolymer (copovidone), improved enteric-coated pellets could be obtained in these investigations. However, quite a high polymer mass had to be used for full protection of the drug-loaded core. The unwanted drug release from the pellets was still higher than from the monolithic marketed products. Therefore, the pellet formulations are not appropriate to replace the already available drugs. Comparing the tablet and the pellet formations, the tablet has the advantage that the specific surface is much lower than for the pellets. Fewer polymer masses are therefore required to ensure gastric juice resistance and this could be of importance as huge doses of 3–4.5 g of sodium bicarbonate are required per day. On the other hand, monolithic formulations with enteric coatings must stay completely intact in the stomach, as the penetration of water

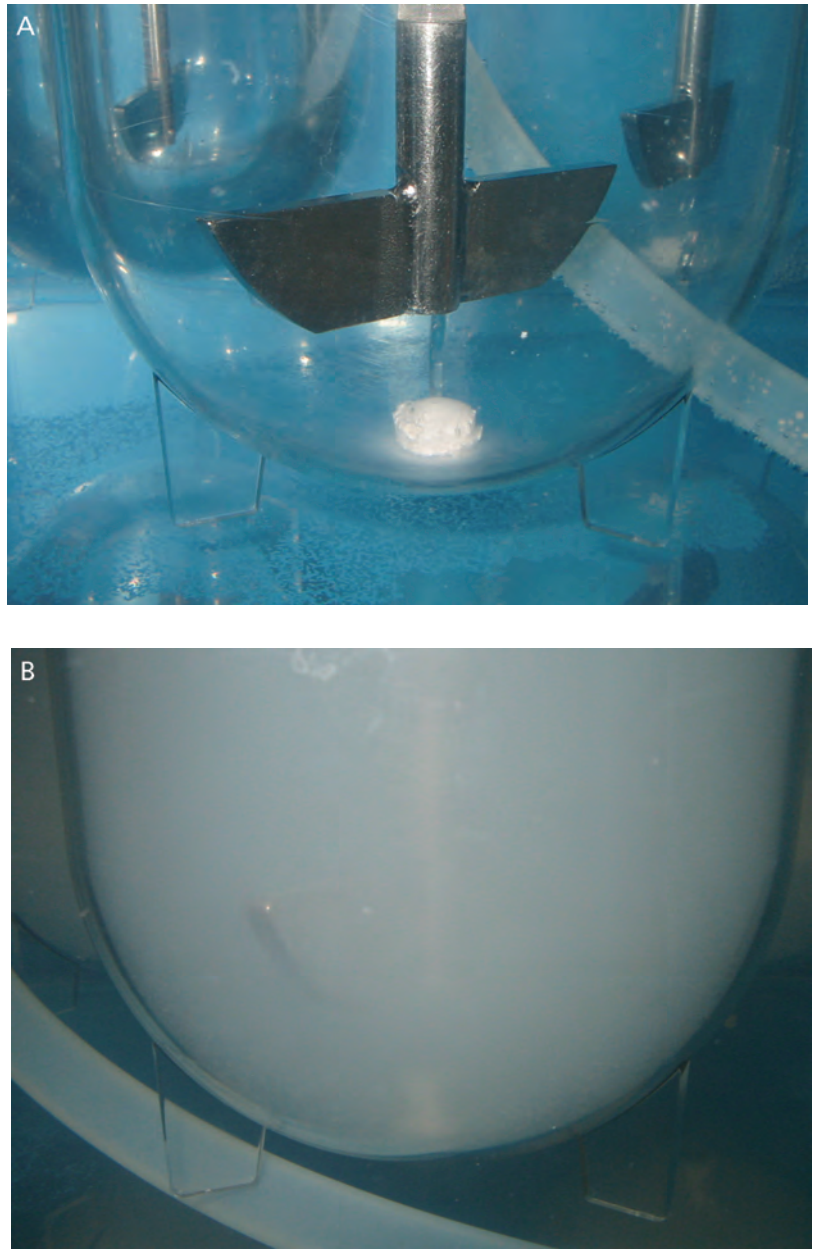

Figure 3 Photographs of the disintegration process of commercial enteric-coated dosage forms in potassium phosphate buffer pH 4.5. A. bicaNorm, lot FBN011, at 30 min, start of tablet disintegration. B. bicaNorm, lot FBN012, at 60 min, almost complete tablet disintegration. C. Nephrotrans, lot 51003, at 30 min, intact soft gelatine capsule. D. Nephrotrans, lot 51003, at 240 min, still intact soft gelatine capsule.

would cause dumping of the complete dose and, hence, adverse effects like abdominal pain. Therefore, the single-unit dosage forms containing sodium bicarbonate must overcome varying properties in the gastric environment. Both commercial formulations with sodium bicarbonate, Nephrotrans and bicaNorm, fulfil all criteria of the Ph. Eur. tests and can therefore be attributed as well-formulated and controlled drugs. However, there is a significant difference in the dissolution profiles at elevated pH values (e.g. at pH 4.5), which may be temporarily reached in the stomach. According to our results the drug is almost completely released into this moderate acidic environment from the bicaNorm tablets, but not from the Nephrotrans soft gelatine capsule. Our results may explain individual patients' reports on less occurrence of adverse effects when using Nephrotrans. The reason for the higher stability of the enteric protection is probably due to the complex composition of the capsule formulation with various protecting barriers. If water molecules or protons permeate the enteric coating based on hypromellose phthalate, they still have to pass the gelatine capsule shell. The triglyceride-based

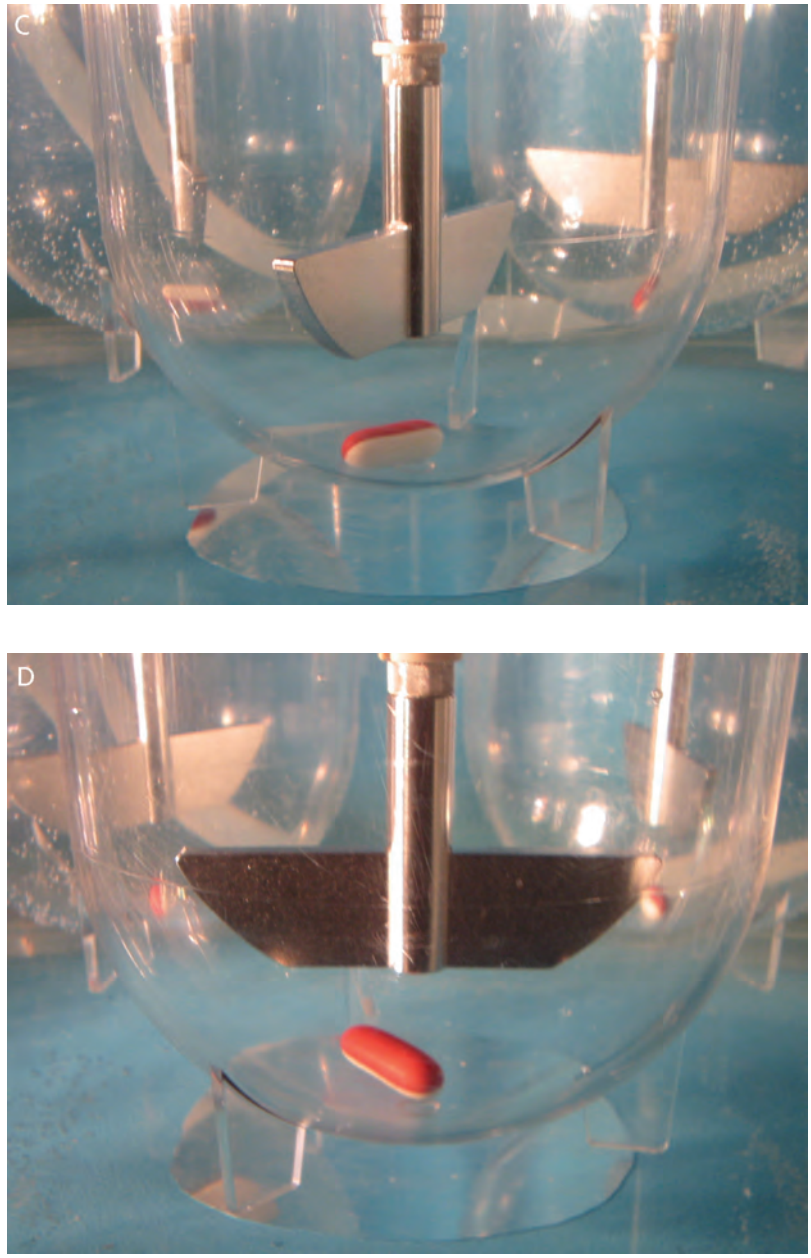

Figure 3 (Continued).

matrix inside the capsule may also hinder diffusion and direct contact to sodium bicarbonate molecules. In contrast, if water or protons pass the Eudragit L coating of the tablets or pellets they can also permeate the subcoat as it does not have a protective functionality for water or proton permeation. If water enters the tablet or pellet core, a basic milieu is formed inside that can interact with the acidic polymer film and enhance the drug release. Additionally, carbon dioxide is formed, resulting in a dramatic increase of the mechanical pressure until the film may be ruptured. Hence, dose dumping is more probable in the enteric-coated tablets (bicaNorm) or pellet formulations than in the marketed enteric-coated capsule preparation (Nephrotrans) under in-vivo conditions.

Conclusions

Both German-marketed products containing sodium bicarbonate as a drug substance, bicaNorm and Nephrotrans, are of sufficient pharmaceutical quality according to the European Pharmacopoeia. However, they and also newly developed pellet preparations show different drug release at moderately elevated pH values. This can initiate dose dumping in the stomach and may cause adverse drug effects. It appears that oral dosage formulations of sodium bicarbonate are an exception to the rule: a monolithic soft capsule, enteric-coated by a polymer film on the capsule shell, seems to be superior to an enteric-coated tablet and also to multiple-unit pellet formulations, as shown by the biopharmaceutical evaluation.

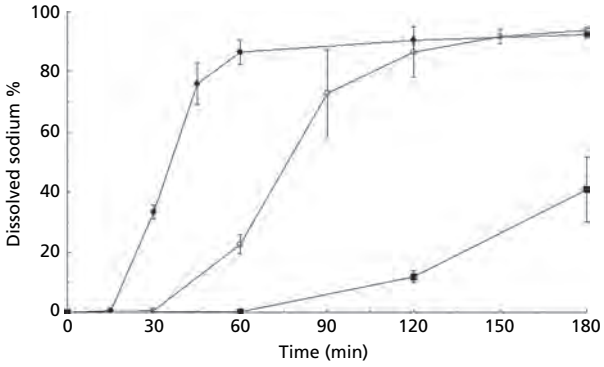

Figure 4 Dissolution of sodium bicarbonate from an enteric-coated pellet formulation with a polyvinylalcohol subcoat and a Eudragit L 30 D-55 enteric coat, batch PL4196/3, into different dissolution media (basket apparatus Ph. Eur., $37 \pm 0.5°C$, $100\ \text{rev min}^{-1}$, $x \pm s$, $n = 6$). In this batch the weight gain by coating was 60% related to the uncoated pellets. Closed circles, potassium phosphate buffer pH 6.8; open circles, potassium phosphate buffer pH 4.5; closed squares, 0.1 M hydrochloric acid, pH 1.0.

References

Adrogué, H. J., Madias, N. E. (1998) Management of life-threatening acid-base disorders – First of two parts. *N. Engl. J. Med.* **338**: 26–34

Berntgen, M. (1997) *Pharmazeutisch-technologische und pharmakokinetische Untersuchungen zur Entwicklung von Arzneiformen mit magnetisch kontrollierter Gastrointestinalpassage*. Dissertation, University of Münster, Shaker-Verlag, Aachen, Germany, ISBN 3-8265-2935-9

Breitkreutz, J. (2000) Leakage of enteric (Eudragit L)-coated dosage forms in simulated gastric juice in the presence of poly(ethylene glycol). *J. Control. Release* **67**: 79–88

Buysse, C. M. P., de Jongste, J. C., de Hoog, M. (2005) Life-threatening asthma in children. Treatment with sodium bicarbonate reduces pCO_2. *Chest* **127**: 866–870

Cuhaci, B., Lee, J., Ahmed, Z. (2000) Sodium bicarbonate controversy in lactic acidosis. *Chest* **118**: 882–883

Forsythe, S. M., Schmidt, G. A. (2000) Sodium bicarbonate for the treatment of lactic acidosis. *Chest* **117**: 260–267

Hoste, E. A., Colpaert, K., Vanholder, R. C., Lameire, N. H., De Waele, J. J., Blot, S. I., Colardyn, F. A. (2005) Sodium bicarbonate versus THAM in ICU patients with mild metabolic acidosis. *J. Nephrol*. **18**: 303–307

Kraut, J. A., Kurtz, I. (2005) Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment. *Am. J. Kidney Dis*. **45**: 978–993

Petereit, H. U., Weisbrod, W. (1999) Formulation and process considerations affecting the stability of solid dosage forms formulated with methacrylate copolymers. *Eur. J. Pharm. Biopharm*. **47**: 15–25

Raffin, F., Duru, C., Jacob, M. (1996) Permeability to hydrogen ions of an enteric coating polymer and interaction of film formulation factors. *Int. J. Pharm*. **145**: 247–252

Riedel, A., Leopold, C. S. (2005) Degradation of omeprazole induced by enteric polymer solutions and aqueous dispersions: HPLC investigations. *Drug Dev. Ind. Pharm*. **31**: 151–160

Thyroff-Friesinger, U. (2002) *Studie zum pharmakodynamischen Effekt (intragastrale pH-Messung)*. Hexal AG, Holzkirchen, Germany

Türkoglu, M., Varol, H., Celikok, M. (2004) Tableting and stability evaluation of enteric-coated omeprazole pellets. *Eur. J. Pharm. Biopharm*. **57**: 279–286