ABSTRACT SUMMARY
Aim of this work was to study multi-kinetics and site-specific delivery system for the release of gabapentin and flurbiprofen in combination employing Dome Matrix® technology. The drug combination has been proposed for the treatment of overactive bladder [1].

The in vitro dissolution behaviour of Dome Matrix® module assembled system showed a dual release of gabapentin, immediate and prolonged, and a delayed prolonged release of flurbiprofen.

INTRODUCTION
Combination products consist of two or more drugs in a single dosage form [2]. A three-layer tablet, containing gabapentin and flurbiprofen in combination for the administration of the two drugs, allowed to obtain three different release kinetics in a single unit. Moreover, an in vitro/in vivo correlation was demonstrated [3].

Dome Matrix® module assemblage technology is a new platform that allows the delivery of more than one drug in a single unit at a specific time, proper rate and duration of drug release [4]. The Dome Matrix® modules are tablets having one concave and one convex bases. Assembled systems are obtained by interlocking of drug delivery modules. When two modules (male and female shapes) are interlocked concave to concave bases a floating assembly is constructed (void assembled configuration).

Aim of this work was to study the in vitro dissolution behaviour of gabapentin and flurbiprofen modular assembled delivery system and to compare it with the dissolution profiles obtained from the three-layer tablets.

EXPERIMENTAL METHODS
The three-layer tablets were manufactured by a Manesty Layer Press (Bosch Packaging Technology Ltd., Knowsley, U.K.), equipped with oblong 9x19 mm punches.

Dome Matrix® modules were manufactured by a single-punch tableting machine (EKO Korsch, Berlin, Germany) equipped with 7.4 mm diameter punches having appropriately designated tip surface for manufacturing convex or concave faces.

In vitro dissolution tests were carried out at 37°C in Apparatus 2 with paddle rotating at 50 rpm. Simulated gastric fluid was used as dissolution medium. After 1 hour in simulated gastric fluid, the separated flurbiprofen delayed-release layer or Dome Matrix® module was transferred in phosphate buffer pH 7.2. Samples collected at prefixed time were analyzed by HPLC.

RESULTS AND DISCUSSION
The manufactured three-layer tablets are illustrated in Figure 1(a). The first layer (white layer), containing excipients such as glyceryl dibehenate, polyethylene oxide and sodium bicarbonate, was formulated as swellable hydrophilic polymeric matrix for prolonged release (PR) of 300 mg of gabapentin. The middle disintegrating layer (blue layer) was formulated for immediate release (IR) of 75 mg of gabapentin. The third layer (orange layer), containing excipients such as β-cyclodextrin, sodium alginate and hydroxypropil methylcellulose, was formulated as hydrophilic polymeric matrix insoluble in gastric fluid for delayed and prolonged release (DR) of 37.5 mg of flurbiprofen.

In vitro study of the three-layer tablets showed that in simulated gastric fluid the tablet sank in the dissolution vessel; the middle immediate release layer of gabapentin disintegrated rapidly, splitting away the prolonged release layer of gabapentin and the delayed-release layer of flurbiprofen in about five minutes. There was a development of CO2 bubbles, which entrapped in the gelified polymer of the swellable layer of gabapentin, caused its buoyancy in about two minutes. At the same time, the flurbiprofen layer remained at the bottom of the vessel without releasing significant amount of drug. The gabapentin release, after the immediate release from the middle layer, continued from the floating layer for about 7 hours during floatation. The delayed release layer of flurbiprofen, transferred in
the phosphate buffer medium, dissolved allowing drug release for about 8 hours (Figure 2). This delivery system was redesigned as Dome Matrix® module assembled system, made of five modules (Figure 1(b)): three PR modules of gabapentin (white modules: one male and two females from left to right in Figure 1(b)) containing each 100 mg of drug, a IR module of gabapentin (75 mg, pink module) and a DR module of flurbiprofen (37.5 mg, yellow module). Male and female PR modules of gabapentin were assembled in void configuration. Another PR female module of gabapentin, a IR female module of gabapentin and a DR female module of flurbiprofen were interlocked on the same face of the void system.

Male and female PR modules of gabapentin, a IR female module of gabapentin and a DR female module of flurbiprofen were interlocked on the same face of the void system. In the PR modules of gabapentin, sodium carbonate was not added to the formulation due to the floating of void configuration.

In simulated gastric fluid the Dome Matrix® assembled system sank in the vessel. The immediate release module of gabapentin disintegrated rapidly, splitting the assembled system in two portions in few seconds. The PR gabapentin modules floated in about 1 minute, due to the presence of internal empty chamber. The DR flurbiprofen module remained in the bottom of the vessel without drug release.

The release rate of gabapentin in the Dome Matrix® assembled system was faster with respect to the three-layer tablets due to a greater exposed surface area. On the contrary, the DR module of flurbiprofen, transferred in the phosphate buffer medium, dissolved at slower rate reaching the 80% in about 10 hour (Figure 3).

Figure 1. Gabapentin and flurbiprofen multi-kinetiks and site-specific delivery systems: (a) three-layer tablets and (b) Dome Matrix® modular assembled system.

Figure 2. In vitro dissolution profiles of gabapentin (pH 1.2, (○)) and flurbiprofen (pH 1.2, pH 7.2, □) (mean values, n = 6) from three-layer tablets.

Figure 3. In vitro dissolution profiles of gabapentin (pH 1.2, (○)) and flurbiprofen (pH 1.2, pH 7.2, □) (mean values, n = 6) from assembled systems.

CONCLUSION
Dome Matrix® assembled system allowed the administration of the two drugs in a single unit exhibiting three different release kinetics. A dual release of gabapentin, immediate and prolonged, and a delayed prolonged release of flurbiprofen were obtained.

Differently from the three-layer tablets, Dome Matrix® system does not required the presence of CO₂ for the floatation.

REFERENCES