Ph.D. THESIS IN PHARMACEUTICAL SCIENCES
(Summary presentation)

Floating hydrophilic matrix dosage forms for oral use:
Factors controlling their buoyancy and gastric residence capabilities

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Brussels, March 1991

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• Keywords, keyphrases

  Specific: buoyancy, clinical study, cut-off size, dimension monitoring, dosage form size, floating dosage form, floating force, gamma scintigraphy triple radiolabeling and monitoring technique, gastric emptying, gastric residence time, Hydrodynamically Balanced System (HBS), intragastric buoyancy, monolithic hydrophilic matrix, non-floating dosage form, resultant-weight measuring apparatus and method

  Non-specific: anatomical position, antral peristalsism, attrition, bioavailability, controlled release formulation, controlled drug delivery system, diffusion, digestive phase, fasted, fed, formulation optimization, fundus, gastric contents, gastrointestinal transit, gel barrier, hard gelatin capsule, human healthy volunteer, hydrophilic polymer, inlet diameter of lumen at gastroduodenal junction, non-disintegrating form, optical microscope, oral administration, post-prandial, physiological limitation, pylorus, radionuclide, scintigraphic image, swelling, standardized meal, stomach, upright vs. supine posture
• **Summary of thesis**

**Physiological limitations of oral controlled release dosage forms**

Oral administration of a medication by means of controlled drug delivery systems should ideally enable to obtain the required plasma levels and to keep them steady for a prolonged period of time. Unfortunately, this ideal therapeutic target cannot systematically be achieved; this in spite of the progresses accomplished today in formulation and control of drug release kinetics from such type of dosage forms.

The main limitations come from the inter- and intra-subject variability of gastrointestinal transit time and from the non-uniformity of drug absorption throughout the alimentary canal.

These physiological limitations could be overcome, for various judiciously selected drugs, by prolonging the gastric residence time of the pharmaceutical dosage form.

**Floating dosage forms expected to last longer in the stomach**

A number of different means have up to now been investigated to slow down the gastric emptying of a drug delivery system e.g., more particularly, the use of floating dosage forms having a bulk density lower than that of the gastric fluids.

Floating oral delivery systems are expected to remain buoyant in a lasting way upon the gastric contents and to consequently enhance the bioavailability of all drugs which are well-absorbed from the proximal gastrointestinal tract. The lasting intragastric buoyancy of a controlled release dosage form might also provide a suitable manner to constantly deliver a drug locally into the stomach and hence achieve a sustained site-specific therapeutic action. At the present time however, published results of investigations on human volunteers indicate that floating dosage forms have not in all occasions been shown to offer a prolonged gastric retention when compared to non-floating forms.

In this context, this thesis work has been dedicated to the basic study and understanding of the *in vitro* as well as *in vivo* behavior of floating dosage forms.

**Drug delivery principle from hydrophilic matrix dosage forms**

The herein-studied pharmaceutical dosage forms belong to the class of monolithic hydrophilic matrices. These polymeric matrices are essentially undigestible and non-disintegrating. The formulation powder, filled into hard gelatin capsules, is made of a homogeneous dispersion of one or more hydrophilic polymers which progressively hydrate at the outer surface upon contact with an aqueous fluid and are swelling to form an external gel barrier. Diffusion and attrition are the two main processes determining sustained drug release from the matrix.

First, an apparatus was conceived to continuously measure *in vitro*, with an appropriate readability and accuracy, the floating forces (herein defined as the resultant-weight) produced by floating dosage forms when immersed in a test fluid medium. This new approach showed that, amongst the existing floating forms named the "Hydrodynamically Balanced Systems" (HBS), several were not able to maintain floating strength values constantly high and stable. More generally speaking, the buoyancy of all classical hydrophilic matrix floating dosage forms denoted a tendency to decrease in function of the time after immersion and even sometimes appeared to reach values insufficient to keep the forms buoyant.
It was hence apparent that, to prevent inconsistent intragastric floating behaviors leading to unpredictable gastric retention results, the dosage forms had to be optimized.

An *in vitro* research phase was therefore undertaken to disclose some of the technological and experimental factors controlling the buoyancy of floating matrix capsules. For each new studied parameter, the basic set of test means comprised the resultant-weight apparatus, an optical microscope technique providing data about dimensional variation of the matrices and various other conventional measurements such as dissolution or disintegration.

Results analysis progressively enabled to understand how the buoyancy of hydrophilic matrices was dependent on their hydrodynamical evolution in immersed conditions and in which manner the formulation could be adapted to optimize the floating capabilities whilst keeping realistic sustained drug delivery profiles.

Optimized floating dosage forms fulfilling all predictable requirements for *in vivo* use were finally selected. These forms were then studied in human healthy volunteers.

The *in vivo* investigation was mainly designed to monitor the anatomical position along the gastrointestinal tract of optimized floating forms, comparatively to non-floating ones, and to evaluate their respective post-prandial gastric residence times.

Prior to clinical investigation, a gamma scintigraphic radiolabeling and monitoring technique specifically dedicated to the study objectives was developed and validated. Simultaneous utilization of three different gamma emitting radionuclides was seen to provide suitable images wherefrom the floating forms (labeled 111In) and the non-floating forms (labeled 201Tl) could be unequivocally differentiated at any time inside a well-defined gastric region of interest (labeled 99mTC). This technique allowed concurrent administration to a subject of a floating and a non-floating form under identical physiological conditions and it consequently improved the reliability of all comparative measurements made in vivo (study designed as a self-paired direct cross-over).

Floating and non-floating study capsules of three different sizes were prepared (small units : diameter 4.8mm, medium units : diameter 7.5mm, large units : diameter 9.9mm) to gather also information about the influence of the dosage form size on gastric retention time. These hydrophilic matrix capsules were administered by pairs (floating / non-floating of identical size) to each subject after a standardized breakfast. The study was performed for the three unit sizes on equivalent groups of either sitting or standing subjects (upright posture, n=27) and was repeated in the same conditions on subjects lying on their back (supine posture, n=30).

Examination of the sequential scintigraphic images acquired during the study showed that the floating forms, whatever their sizes, remained in a buoyant state upon the gastric contents for their entire gastric residence period; meanwhile the non-floating forms were seen to rapidly sink towards the bottom of the meal contents and remained in the lower part of the stomach. Hence, it was already possible to conclude that the *in vitro* measured floating or non-floating capabilities of a dosage form could be reproduced *in vivo*. 
Differences in gastric residence time between the floating and non-floating forms can be explained by their different emptying mechanisms from the stomach and by the size of the form.

This difference of intragastric residence position was used to explain how, for upright subjects, the floating forms maintained aside from the gastroduodenal junction were offered a systematic protection against gastric emptying during the digestive phase. On the contrary, non-floating forms stayed in the vicinity of the pylorus and were repeatedly submitted to the propelling and retropelling waves of the antral peristalsism. They could be readily and erratically emptied unless their size was large enough, with respect to the inlet diameter of the lumen at the gastroduodenal junction, to be retained inside the stomach. Gastric retention of non-floating forms was thus mainly dependent on their diametral size and gradually increased in duration from small to large units.

As a consequence to these distinct behaviors assignable to buoyancy and non-buoyancy, floating forms had a systematically longer gastric residence time for the small units (P<0.001) and for the medium units (P<0.05); whereas no significant difference was observed between the two types of large size matrix capsules.

For supine posture, the size of the form, but not buoyancy, is the main factor contributing to gastric residence.

For supine subjects, the surface of the gastric contents now extended horizontally towards the antrum. The intragastric residence position of the floating forms no longer remained an advantage with respect to retention and their residence period appeared to be reduced when comparing to the upright posture results. The floating forms could only resist against emptying by a size effect and their gastric residence times were slightly shorter, size for size, than these of the non-floating forms.

For the non-floating forms, however, the change of posture was seen to not significantly modify their gastric transit time.

In another study performed with a single size of floating forms alone (diameter 8.4mm) and all subjects remaining upright, a comparison was made between a group of subjects who had taken a light breakfast only (n=10) and upright subjects who had been fed with a succession of meals given at normal time intervals (n=10).

Results indicated that as often as a meal was given at the time the previous digestive phase was not yet completed, the floating form still remaining in the stomach was then carried again in the upper part of the fundus where it stayed buoyant for an additional digestive phase. Thanks to this process, the succession of meals provided a strong gastric retention enhancement to the floating forms in comparison to the effects obtained with the breakfast only (P<0.001). The here observed mean gastric residence time of about 10 hours appeared to be mostly appropriate for bioavailability purposes in the context of the use of sustained drug delivery systems.

The above described in vivo studies have thus permitted, on the one hand, to better outline some indispensable requirements for prolonging the gastric residence of a monolithic matrix oral dosage form and, on the other hand, to more clearly define the field of application, the limitations and the proper using conditions of floating dosage forms.

The present thesis work has also enabled to understand and explain, with regard to the gastric retention performances of floating matrices, why divergent results and contradictory conclusions had up to now been reported in the scientific literature.