Direct Visualization Shows that Conventional in vitro Capsule Dissolution Methods do not Reflect the in vivo Situation

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ABSTRACT SUMMARY

The most commonly employed in vitro dissolution methods were developed as quality assurance tools but are commonly assumed to be predictive of in vivo behavior. This assumption was tested by having volunteers swallow PillCams with soft or hard gelatine capsules filled with oily formulations attached to them and kept in the stomach by securing them with dental floss. The procedure was well tolerated by the subjects. The results indicate that the release was faster for the soft capsules in vivo but not for the hard ones and that capsules rupture rather than melt in the stomach. Visualization of the mechanical stress in the stomach might pave the way for better models.

INTRODUCTION

Dissolution in the stomach is a multifactorial event. Many factors, including water volume, pH, enzymatic activity, bile salts, motility, hydrodynamics, fasted or fed state and so on can and do influence the behavior of solid oral dosage forms1,2. Indirect imaging techniques such as scintigraphy and magnetic imaging have been successfully used to elucidate some parameters3 but do not provide visual informational such as the exact location of the dosage unit in the stomach, mechanical effects and so on.

EXPERIMENTAL METHODS

Three formulations were studied: Soft gelatin capsules of Evening Primrose (EP capsule) oil in were obtained from Futura, Denmark. Hard, two-piece gelatin capsules (size#2) were filled with 350 mg of sesame oil (SE capsule) and Hard,two-piece hard gelatin capsules (size#2) were filled with 350 mg of Long Chain SNEDDS (LC-S capsule) inspired by Thomas et al4. but using soy bean oil instead sesame oil (23) were prepared. The composition was: Sesame oil 27.5%, Maisine 35-1 27.5%, Chremophor RH 40 35% and Ethanol 10%. Simulated gastric media, FaSSGF was prepared according to Vertzoni et al5. (Pepsin 0.1 mg/ml, NaTaurocholate 80 μM/ml, Phospholipids 20 μM/ml and NaCl 34.2 mM/ml). The solution was stirred overnight and the pH adjusted to 1.6 with HCL. Purified water was added to volume and stored at 5°C. Another portion was prepared as described but adjusted to pH 2.9. A USP II apparatus, with 300 ml of FaSSGF, at 37°C speed of rotation 75 rpm was used for the in vitro release studies. The initial release of contents from the model formulation and the time of total disintegration of the capsules were visually detected and recorded.

The endoscopic system comprises: a digital Colon Capsule Endoscope - camera - (26 * 11 mm, Pillcam, Given Imaging Ltd. Israel), eight electrodes connected to a data recorder, and software for real-time monitoring. Sequential images are captured by the camera, transmitted through the electrodes attached to the abdominal wall and saved by the data recorder. Cameras were tied with dental floss (Colgate Total) to enable retention in the stomach and some control over the position. A drop of Histoacryl® glue was used to fix the floss securely on the camera. The tested capsule was, in turn, affixed to the front of the camera with dental floss (figure 1). The camera/capsule train (train) was swallowed with 200 ml of water. Additionally, 100–150 ml of water was available for ingestion to avoid discomfort for the healthy volunteer.
The volunteers maintained an upright position – sitting or standing and holding the dental floss with a hand to keep the train in the stomach. Rupture time was defined as the interval from swallowing of the train until the first drop of contents was observed in the lumen. Attention was paid to location, mechanical interactions, movement and so on. After total disappearance of the capsule, the recording was stopped, the floss cut and the camera allowed to travel through the gastric system until evacuation. The volunteers were asked to evaluate the discomfort with a 1-10 scale were 1 was easily tolerated and 10 extremely uncomfortable. All volunteers gave their written informed consent to the experimental procedure.

RESULTS AND DISCUSSION

Figure 2. Images of a soft capsule, EP capsule at different times in the same individual

Five of the volunteers evaluated the procedure and "1" ("easily tolerated"), three as "2" and one as "4". All would volunteer again if asked. Esophageal transit time was 35s±13.7 (n=3) for the EP capsules, 27s±14.5 for the SE capsules (n=3) and 23.7s±3.8 for the LC-S capsules (n=3). After reaching the stomach, the EC capsule was seen submerged in the gastric fluid all the time while the hard capsules floated on the fluid. The first drop of oil was seen after 112s±19 with rupture of the capsule (figure 2-c) in 2-I only the empty loop remains. The sesame oil from SE capsules was more difficult to detect as it is transparent and the SNEDDS from the LC-S capsules was seen as a bluish emulsion after 334s±162s, the last was detected at 2040s±209. In the in vitro studies the release was not affected by the presence or absence of the floss. In each capsule category, the initial release was similar at pH 1.6 or 2.9.

The initial release in vitro was faster for the soft capsules than in the in vivo, 112s±19 and 77s±6 respectively. Conversely, for the hard EP capsules, the in vitro was 540s±3 while the in vivo was334s±162s.

CONCLUSION

The method described here allowed direct visualization of capsules in the stomach, real time and recorded for subsequent examination. The first experiments indicate that our understanding of the dissolution processes might be deficient. The method might be valuable in developing better in vitro systems or in diagnosing unexpected in vivo results.

REFERENCES


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