

Short Communication

***In vivo* radio imaging studies on designed swelling gastro retentive drug delivery system**

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The objective of the study was to correlate the results of the *in vitro* release of a previously reported swelling gastro retentive drug delivery system with the *in vivo* radio imaging in rabbits. Tablets containing metformin hydrochloride evaluated for *in vitro* drug release profile showed drug release up to 14 h. Tablets containing barium sulfate was administered to rabbits after overnight fast. Radio imaging study showed that swelling matrix tablets remains in the upper small intestine of rabbit for the period of 10 h and it correlates with *ex vivo* retention time of 10 h.

Key words: Swelling matrix tablets, x-ray imaging, *ex vivo-in vivo* correlation.

INTRODUCTION

In the previous published article we reported the formulation and *in vitro* evaluation of swelling gastro retentive drug delivery system using novel polymer hypromellose (HPMC) K200M. We have reported the promising potential of HPMC K200M in the formulating swelling drug delivery system which showed *ex vivo* retention time of 10 h, depending on the *in vitro* swelling and desired *in vitro* drug release (Ige and Gattani, 2011).

Swelling devices (swelling GRDF) after being swallowed, swell to optimum size, which prevents their passage through pylorus. A dramatic swelling time frame which exists over seconds to few hours has been reported for some polymers in solid dosage form. It may swell quickly in the gastric contents and can be retained in the stomach until the size reduced, for example by erosion. Such enlarged dosage form should not block the pylorus, and size reduction should be gradual to prolong its residency in stomach (Timmermans and Moes, 1994; Munday et al., 1998; Klausner et al., 2003; Streubel et al., 2006). Swelling GRDF explores a number of applications for drugs having poor bioavailability because of narrow

absorption window and absorption in the upper part of gastro intestinal tract only. It retains the dosage form at the site of absorption and thus enhances the bio-availability (Sriamornsak et al., 2007).

Previously, we have reported that the *in vitro* retention time of 10 h can be achieved using HPMC K200M as matrix tablets for swelling gastroretentive drug delivery system. *In vitro* evaluation of swelling system was carried out by using nited States Pharmacopeia (USP) dissolution 2 apparatus (paddle method) in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) dissolution media (900 ml) at 100 rpm and the temperature was maintained at 37 ± 0.5°C (Aly and Megwa, 1989; Gohel and Panchal, 2002). We used New Zealand White strain rabbits since this strain has been used previously for an *in vivo* radio imaging study to assess the performance of the mucoadhesive gastro retentive drug delivery system.

In the present investigation, our previously reported *in vitro* data have been correlated with the *in vivo* radio imaging study conducted in rabbits. Here, we observed a 14 h sustained in *in vitro* drug release (using a type 2

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dissolution test apparatus with 100 rpm) which was then confirmed using a radio imaging technique to establish an *ex vivo-in vivo* correlation.

METHODOLOGY

Metformin hydrochloride and HPMC K200M was supplied as gift sample by Aurobindo Pharmaceuticals Ltd, Hyderabad, India. All other materials like BaSO₄ of extra pure quality for x-ray diagnosis, microcrystalline cellulose (MCC), polyvinylpyrrolidone (PVP) K30 and magnesium stearate used were of reagent grade and used without further purification.

Preparation of swelling matrix tablets of metformin hydrochloride

Sustained release swelling matrix tablets each containing metformin hydrochloride was designed using software (two factor-optimal) Design Expert version 8.0.1.0 (Stat-Ease Inc Minneapolis, MN). Swelling matrix tablets were manufactured by conventional wet granulation method. Here, the drug is replaced by BaSO₄ for x-ray diagnosis. PVP K30 10% was prepared with isopropyl alcohol (IPA) and used as binder. Talc and magnesium stearate was used as lubricants. BaSO₄ (500 mg), HPMC K100M and HPMC K200M (1:3), lubricant and binder were mixed to form a damp mass. It was passed through 20# (mesh) sieve and the granules were air dried for 30 min and compressed into matrix tablet by tablet Minipress machine (Rimek, Mumbai, India) with 5 mm diameter tooling.

In vivo radio imaging study in rabbits

The protocol for *in vivo* study was approved by the Institutional Animal Ethical Committee (IAEC) of R C Patel Institute of Pharmaceutical Education and Research, Shirpur and is in accordance with guidance of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India. In order to evaluate the *in vivo* residence time of the swelling matrix tablets the formulation batch F8 was selected for *in vivo* x-ray imaging (Sakkinen et al., 2003; Tucker et al., 1981). Six adult male New Zealand white strain rabbits of three months age and weighing approximately 2.0 to 2.5 kg were used for this study. The rabbits were fasted overnight before the start of the study. The tablets excluding drug and containing 30% BaSO₄ as well as swelling polymer HPMC K200M, HPMC K100M and PVP K30 10% binder were manufactured by method as described in the preparation using 5 mm tooling set. The tablet was administered through plastic tubing followed by flushing of 25 to 30 ml of water. During the entire study, the rabbits had free access to water only. Photomicrographs (Wipro Ge Dx300 with horizontal x-ray system, Wipro GE medical system, Pune-04, India) were taken at 0, 2, 4, 6, 8 and 10 h.

Ex vivo-in vivo correlation

As previously stated, the aim of the work described here was to correlate the results of the previously reported *in vitro* drug release study with the *in vivo* radio imaging technique to check for a difference in the retention time, if any, and to establish the findings of the *in vitro* study. The experimental results are expressed for three determinations. Statistical evaluation of the data was done using analysis of variance (ANOVA). The evaluation of data was

used to assess the significance of differences.

RESULTS AND DISCUSSION

The formulation F2 containing HPMC K100M and HPMC K200M in the ratio of 1:3 exhibits highest percent cumulative drug release. The rate of drug release from the optimized swelling matrix tablets was slower than the remaining formulations of the tablets. Percent swelling and *in vitro* drug release tend to increase together according to observed positive correlation coefficient of 0.874 and p-value less than 0.05, indicating a direct relationship between the two variables (Ige and Gattani, 2011). On the basis of *in vitro* drug release and percent swelling it may conclude that polymer swelling plays an important role in pattern and amount of drug release from the tablets. This might be due to the gel forming ability of HPMC at a high concentration which retards the rate of drug release from the tablets.

In vivo radio imaging study in rabbits

Formulations of swelling matrix tablets of formulation code F8 have shown the good *in vitro* swelling ability and *ex vivo* retention time in this study. Hence it was selected for *in vivo* x-ray imaging study to establish the product performance (residence time in stomach) in rabbits (n = 6). Photomicrographs were taken immediately after 0, 2, 4, 6, 8 and 10 h and are shown in Figure 1. The presence of tablet in the upper small intestine can be clearly noticed and it remains in the stomach not being subjected to disintegration in rabbits. *In vivo* x-ray imaging study clearly indicated that the prepared swelling matrix tablets of metformin hydrochloride retained up to 10 h in upper part of small intestine of the rabbit and hence they had good *in vivo* residence time in the stomach of rabbit. Photomicrographs was taken immediately after administration of the tablets and revealed the nature and position of the tablet up to 10 h.

Ex vivo-in vivo correlation

This novel single unit swelling gastro retentive dosage form with sufficient *in vitro* retention and *in vivo* residence time in upper small intestine up to 10 h could be fascinating for enhancement of bioavailability and the stomach specific delivery of metformin hydrochloride for the effective management of type 2 diabetes mellitus.

Conclusion

This modified swelling drug delivery system could be a

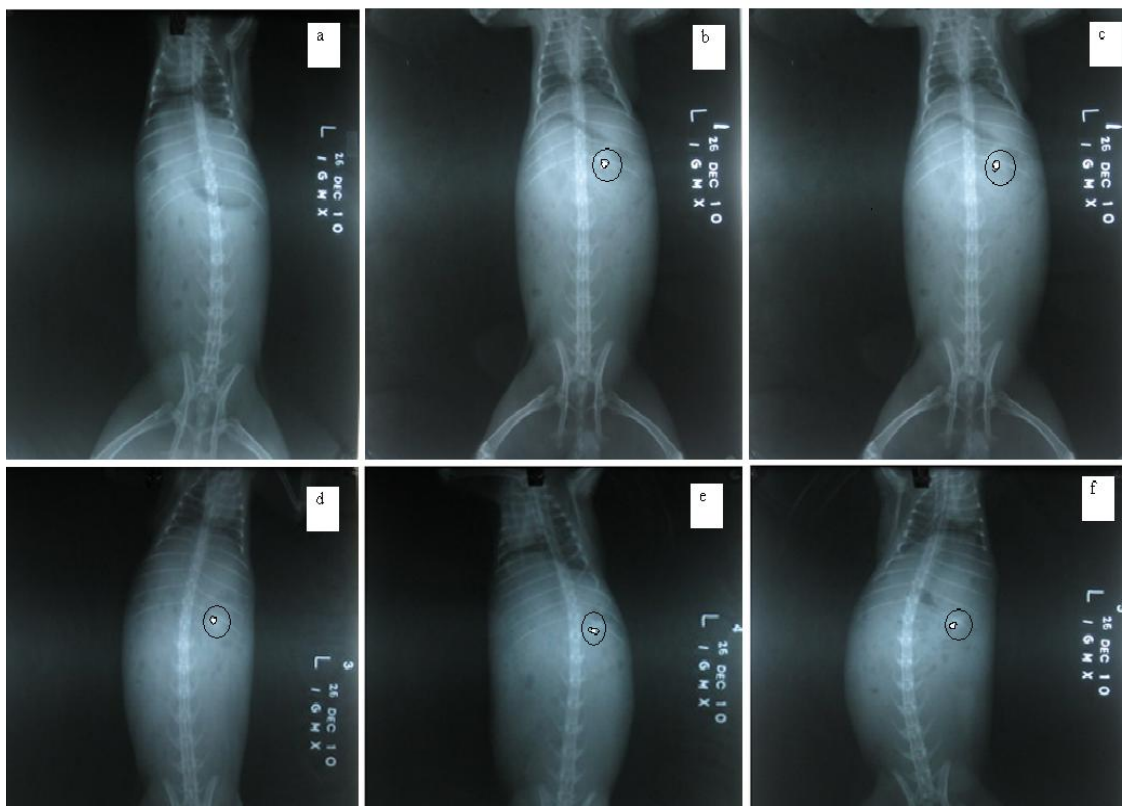


Figure 1. Photo micrographic images of swelling matrix tablet of formulation code F8 after 0 h (a) 2 h (b), 4 h (c), 6 h (d), 8 h (e) and 10 h (f) in the upper small intestinal region of the rabbit.

valuable tool for achieving the desired retention time, as a good correlation between *in vitro* studies and *in vivo* radio imaging studies was observed. The *in vitro* percent swelling, *ex vivo* mucoadhesion strength and *in vivo* radio imaging results in rabbits ($n = 6$) were consistent and reproducible. However, bioavailability studies are awaited to confirm the efficacy of the present swelling drug delivery system.

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REFERENCES

Ige PP, Gattani SG (2011). Design, development and *in vitro* evaluation of swelling gastro retentive drug delivery system for type 2 diabetic patients. *Lat. Am. J. Pharm.* 30(6):1117-1125.

- Timmermans J, Moes AJ (1994). Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy. *J. Pharm. Sci.* 83:18-24.
- Munday DL, Sujja AJ, Cox PJ, Khan KA (1998). Relationship between swelling, erosion and drug release in hydrophilic natural gum mini-matrix formulations. *Eur. J. Pharm. Sci.* 6:207-217.
- Klausner EA, Lavy E, Friedman M, Hoffman A (2003). Expandable gastroretentive dosage forms. *J. Control Rel.* 90:143-162.
- Streubel A, Siepmann J, Bodmeier R (2006). Gastroretentive drug delivery systems. *Expert Opin. Drug Deliv.* 3:217-233.
- Sriamornsak P, Thirawong N, Korkerd K (2007). Swelling, erosion and release behavior of alginate based matrix tablets. *Eur. J. Pharm. Biopharm.* 66:435-450.
- Aly SAS, Megwa SA (1989). Stability study of pyridoxine hydrochloride tablets prepared by direct compression. *Acta Pharm. Fennica* 98:21-32
- Gohel MC, Panchal MK (2002). Novel use of similarity factors f_2 and s_d for the development of diltiazem HCl modified release tablets using a 32 factorial design. *Drug Dev. Ind. Pharm.* 28:77-87
- Sakkinen M, Linna A, Ojala S, Jurjenson H, Veski P, Marvola M (2003). *In vivo* evaluation of matrix granules containing microcrystalline chitosan as a gel-forming excipients. *Int. J. Pharm.* 250(1):227-237.
- Tucker GT, Casey C, Phillips PJ (1981). Metformin kinetics in healthy subjects and in patients with diabetes mellitus. *Br. J. Clin. Pharmacol.* 12(2):235-246.