

Research Article

Formulation and evaluation of oil entrapped floating beads of Piperine for peptic ulcers

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ABSTRACT: Background: Peptic ulcers remain a challenge for identifying more effective and safer anti-ulcer therapies. Over the last few decades herbs have become the major source for the treatment of various diseases. The common spice piperine has shown a significant role in healing peptic ulcers. A fatty diet including olive oil has also proved effective for its anti ulcer activity. **Objective:** A formulation of floating piperine beads with the olive oil entrapment, to reside in the gastric environment, was tested for its therapeutic value. **Materials and Methods:** Floating beads were prepared by the ionic gellation method, followed by air drying. **Results:** The prepared beads showed entrapment efficiency in the range of 75-85% with flotation for more than 12 hours. The inclusion of HPMC prolonged the drug release up to 12 hours. **Conclusion:** From the results it can be concluded that piperine in the form of olive oil entrapped floating beads is beneficial in treating peptic ulcers because of its longer residence time at the site of action and also because of the additive anti-secretory activity of the oil.

KEYWORDS: Anti ulcer activity, floating beads, Hydroxy Propyl Methyl Cellulose, olive oil, piperine.

INTRODUCTION

Spices have become the source of therapy in most of the countries and are especially commonly used in India where herbs and spices are the indigenous part of the curing system. From previous studies, spices are known to have digestive stimulant actions and thus may be helpful in treating the digestive disorders.^[1,2] Piperine, the most common spice of Indian kitchen, has previously been shown to have the anti ulcer activity.^[3,4,5] Piperine was found to be effective for gastric ulcers in rats and mice at a dose range of 25 to 100 mg/kg.^[6] Apart from its gastro protective activity, piperine has also been investigated for other beneficial gastro intestinal effects including antileishamial activity,^[7] antidiarrheal activity,^[8] improved gastric mucosal integrity,^[9] muco-protective activity^[10] and hepato protection,^[11] along with the improved absorption^[12] and bio availability^[13] of several classes of drugs.

The present investigation focuses on the formulation of an oil entrapped gastroretentive system of piperine as a cure

the gastric ulcers as this is a simple and economic process. Gelling of hydrocolloid material such as calcium alginate by the incorporation of a vacuum filled, gas filled or oil filled flotation chamber enables it to remain on the gastric surface.^[14] In this study, the selected oil for entrapment into alginate beads is olive oil. In a previous investigation, olive oil was shown to have the capacity of lowering intra gastric acidity.^[15] Whilst the exact mechanism of action is unclear, the fatty nature of olive oil results in higher concentrations of stomatostatin in the gut mucosa and this may be responsible for the inhibition of acid secretion.^[16,17]

The use of oral sustained delivery systems for the treatment of peptic ulcers is complicated by limited gastric residence time. The combination of both piperine and olive oil together as gastro retentive beads may be an effective treatment for the ulceration. This may allow controlled delivery of the drug to its site of action and ensure the optimum bioavailability. The current study examines whether the entrapment of piperine into olive oil beads enhances the delivery and bioavailability of the drug and therefore ultimately its anti-ulcer bioactivity.

MATERIALS AND METHODS

Piperine was obtained from Alfa Aesar, Lancs, UK. hydroxy propyl methyl cellulose (HPMC) and calcium chloride were

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obtained from Universal chemicals, India. Olive oil was purchased from Yarrow chemicals, India. All chemicals and solvents used were of analytical grade.

Preparation

The oil entrapped calcium alginate beads were prepared by the ionic gelation method^[18]. Briefly, sodium alginate was dissolved in deionized water with constant stirring. Olive oil without or with HPMC at different ratios (Table 1) was added to these mixtures. Piperine (1g) was added and homogenized for 30 minutes. The homogenized mixture was extruded into 5% calcium chloride solution with gentle agitation at room temperature. The resultant beads were allowed to stand for 5 minutes in solution, were separated by filtration and dried at room temperature.^[18]

Compatibility

Compatibility studies between pure piperine and powdered beads were carried out by Fourier Transmission Infra Red spectroscopy (Schimadzu, M/S Central Analytical Department, Faculty of Technology, Osmania University, Hyderabad). The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepared were examined and the spectra of drug and other ingredients in the formulation were compared with that of original spectra.

Drug entrapment efficiency

Dried beads (100 mg) were powdered and placed in 100 mL of 0.1N HCl. The beads were stirred for 2 h and the resulting solution was filtered by vacuum filtration. The filtrate was analyzed for drug content after suitable dilution by UV Spectrophotometer (Elico SL 159) at 323nm. The drug entrapment efficiency was calculated by using following formula.

$$\% \text{ Entrapment efficiency} = \frac{\text{Theoretical content}}{\text{Practical content}} \times 100$$

Mean size

The mean diameter of dried beads was estimated by using optical microscope.

Scanning Electron Microscope

Scanning electron microscopy (M/s National Institute of Nutrition, Tarnaka, Hyderabad.) at 30KV and 5KV was used to examine the surface morphology of the beads.

Buoyancy

To determine the buoyancy of the beads, three main parameters (lag time, total floating time and % floating efficiency) were determined using 0.1N HCl as media in USP dissolution apparatus II. The initial time taken by the beads to float to the surface was noted as lag time; the total number of beads floating was noted as % floating efficiency; and the total time of floating up to 12 hours was also observed.

Drug release

The drug release studies were carried out at 37 °C at 100 rpm using 900mL of 0.1N HCl as the dissolution medium by using USP dissolution apparatus type II. At predetermined intervals, the samples were withdrawn to estimate the cumulative amount of drug release by monitoring the absorbance at 323 nm. Following each measurement the media was replaced with fresh medium.

RESULTS AND DISCUSSION

From the compatibility studies presented in the Figure 1, it is evident that the characteristic FTIR peaks for the structure of the piperine were also repeated in the FTIR spectra of powdered piperine beads. The important FTIR peaks were indicated in Figure 1 are the aromatic stretching at a wave number 3000 cm⁻¹; C=O stretching at 930 cm⁻¹; O=C-N stretching at 1635 cm⁻¹; and C-H stretching at 2800 cm⁻¹.

The results of drug entrapment efficiency, mean size and buoyancy are given in Table 2. Drug entrapment was found to be approximately 75-85% of the total drug. There is no evidence that an increase in oil content results in a significant increase in the encapsulation efficiency. However, small increases were seen with increased oil content. These

Table 1: Formulation details of oil entrapped beads.

| Formulation code | Piperine (in mg) | Sodium alginate | Olive oil (%) | Calcium chloride (5%) | HPMC (in mg) |
|------------------|------------------|-----------------|---------------|-----------------------|--------------|
| IGO1 | 100 | 1.6 % W/V | 5 | 50 mL | - |
| IGO2 | 100 | 1.6 % W/V | 10 | 50 mL | - |
| IGO3 | 100 | 1.6 % W/V | 15 | 50 mL | - |
| IGO4 | 100 | 1.6 % W/V | 20 | 50 mL | - |
| IGO5 | 100 | 1.6 % W/V | 25 | 50 mL | - |
| IGO6 | 100 | 1.6 % W/V | 20 | 50 mL | 10 |
| IGO7 | 100 | 1.6 % W/V | 20 | 50 mL | 20 |
| IGO8 | 100 | 1.6 % W/V | 20 | 50 mL | 30 |
| IGO9 | 100 | 1.6 % W/V | 20 | 50 mL | 40 |
| IGO10 | 100 | 1.6 % W/V | 20 | 50 mL | 50 |

IGO- Ionic gelled oil beads

increases may be attributed to the non-polar nature of the piperine. A comparison of piperine entrapment in the absence of HPMC, to those formed in the presence of HPMC demonstrates that the inclusion of HPMC resulted in a minor increase in the encapsulation efficiency. This increase may be due to the uniform dispersion of piperine in the extruding mixture. Increased amounts HPMC has not contributed for any improvement in the encapsulation efficiency.

The formed beads in the absence of HPMC were almost spherical in shape, with a size around 1mm. With the inclusion of HPMC there was a clear increase in the size up to 3 mm. Inclusion of HPMC generally increases the viscosity of the dispersion and the process of extrusion itself was difficult with the final 2 formulations. The increase in viscosity may responsible for the increase in the particle

size. In a previous study^[20] it was concluded that, the increase in bead size may be due to increase in droplet viscosity along with involvement of gravitational force. The surface morphology was found to be almost smooth as shown in the SEM pictures (Figure 2).

Flotation was found to be superior with 20% olive oil than lower concentrations and total flotation time was even more than 12 hours. Initial lag time was found to be higher in beads with $\leq 20\%$ olive oil and was found to decrease with an increase in the olive oil content. The reason for this trend may be the decreased density of the beads which contain more oil inside the beads. HPMC inclusion decreased the initial lag time but has less effect on the % flotation. The decrease in the initial lag time for flotation might be due to the increased water up take in presence of HPMC than in absence.

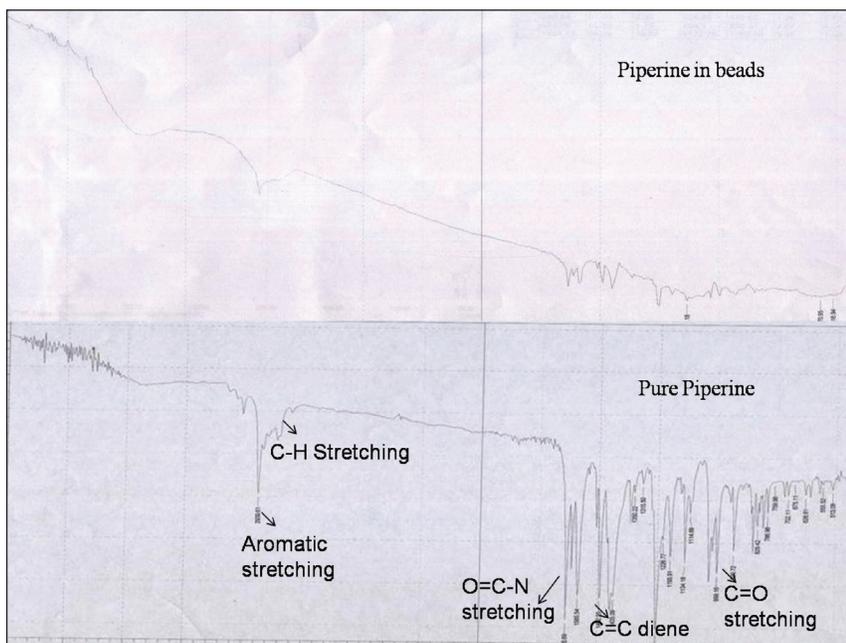


Figure 1: FTIR spectra of pure piperine and piperine present in powdered formulation of ionic gelled floating beads containing olive oil and HPMC.

Table 2: Evaluation parameters of oil entrapped beads.

| Formulation code | Mean size \pm SD (mm) [*] | Encapsulation efficiency \pm SD [*] | Total buoyancy (hours) | Lag time (minutes) \pm SD [*] | % Flotation \pm SD ^{**} |
|------------------|--------------------------------------|--|------------------------|--|------------------------------------|
| IGO1 | 0.84 \pm 0.45 | 78.4 \pm 0.52 | < 12 | 22.5 \pm 0.65 | 20 \pm 1.22 |
| IGO2 | 0.96 \pm 0.65 | 76.5 \pm 0.35 | < 12 | 29.4 \pm 0.35 | 32 \pm 0.52 |
| IGO3 | 0.99 \pm 0.56 | 78.2 \pm 0.65 | < 12 | 21.4 \pm 0.85 | 35 \pm 0.34 |
| IGO4 | 1.24 \pm 0.85 | 83.4 \pm 0.68 | >12 | 18.3 \pm 0.94 | 66 \pm 0.67 |
| IGO5 | 1.45 \pm 0.98 | 81.6 \pm 0.85 | >12 | 18.3 \pm 0.65 | 80 \pm 0.85 |
| IGO6 | 1.34 \pm 0.23 | 85.0 \pm 0.35 | >12 | 15.6 \pm 1.02 | 85 \pm 0.17 |
| IGO7 | 1.91 \pm 0.54 | 82.5 \pm 0.74 | >12 | 16.3 \pm 0.65 | 82 \pm 0.93 |
| IGO8 | 2.09 \pm 0.56 | 83.4 \pm 0.78 | >12 | 15.6 \pm 0.71 | 83 \pm 0.58 |
| IGO9 | 2.68 \pm 0.86 | 81.6 \pm 0.56 | >12 | 16.9 \pm 0.74 | 84 \pm 0.25 |
| IGO10 | 2.93 \pm 0.71 | 83.4 \pm 0.78 | >12 | 16.3 \pm 0.25 | 88 \pm 0.44 |

Average values with Standard deviation were reported where n=6, * indicates p<0.05 and ** indicates p<0.01

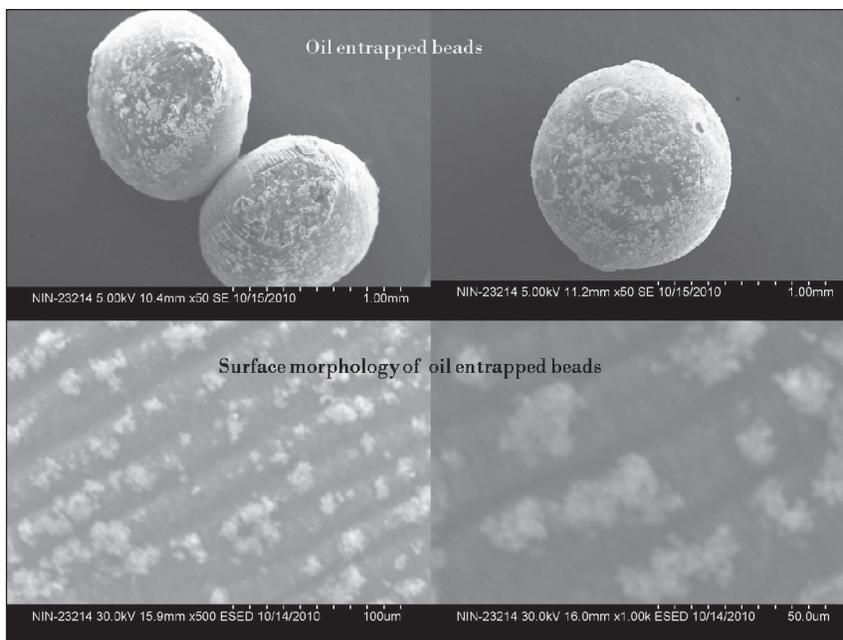


Figure 2: Scanning electron microscopic pictures of oil entrapped beads where A- Olive oil entrapped bead, B- olive oil along with HPMC entrapped bead and surface morphology of the respective beads.

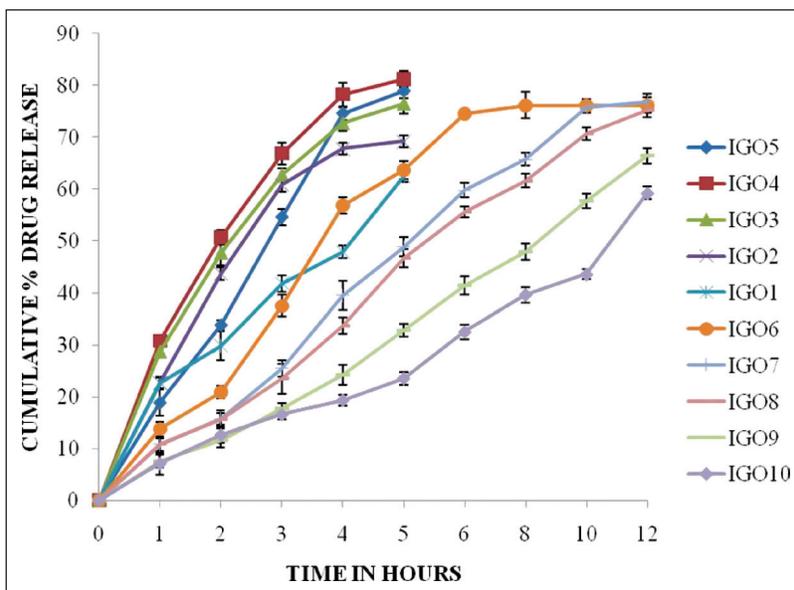


Figure 3: Cumulative % drug release with SD bars of the prepared oil entrapped beads alone with only olive oil upto 6 hours and with olive oil and HPMC up to 12 hours.

In plain olive oil entrapped beads, the cumulative % drug release (Figure 3) was up to 76% (IGO4) within 6 hours. This level was sustained with the inclusion of HPMC. The property of sustained release was further increased with the increase in the HPMC concentration. The inherent nature of HPMC to form the matrix in which the drug gets entrapped might be the reason for the sustained release of piperine from the beads. Olive oil alone is not sufficient in sustaining the release and the same is evident from the

cumulative % drug release from beads with 5% (65%) and from beads with 25% (76%).

CONCLUSION

From the obtained results it can be concluded that, the formulation of piperine having anti ulcer activity in the form of olive oil (with anti secretory activity aids in ulcer treatment)

entrapped floating beads is beneficial. Olive oil inclusion increases the buoyancy of the the beads and the further addition of HPMC makes them bouyant more quickly. As such, there was no additional effect of HPMC in total flotation except a decrease in lag time and increased sustained activity.

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