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***ORIGINAL RESEARCH ARTICLE***

# Formulation And Evaluation Of Metoclopramide Hydrochloride Microbeads By Ionotropic Gelation Method

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## ABSTRACT

Metoclopramide hydrochloride is an antiemetic and prokinetic agent used in the treatment of gastroparesis and gastroesophageal reflux disease[1, 6]. The half life of metoclopramide hydrochloride is 4-6 hours. Metoclopramide hydrochloride microbeads were prepared by ionotropic gelation method using sodium alginate in combination with guargum and HPMC as drug release modifiers in various proportions to overcome the drug related adverse effects. No significant drug-polymer interactions were observed in FT-IR studies. The drug entrapment efficiency increased progressively with increasing concentration of both sodium alginate and coating polymer resulting in the formation of larger microbeads entrapping greater amounts of the drug[2]. The drug entrapment efficiencies were obtained in the range of 50.02±1.41% to 78.21±1.03%. The size and surface characteristics were determined by an optical microscope and SEM. No significant swellings of microbeads are seen in Hcl with pH 1.2. Invitro drug release profile of metoclopramide hydrochloride from microbeads was examined in simulated gastric fluid pH 1.2 and simulated intestinal fluid pH 7.4.Microbeads coated with guargum and HPMC shows optimum level of sustained release. The drug release was found to follow non-fickian diffusion obeying zero order kinetics.

**Key words**: Microbeads, gastroparesis, Sodium alginate, Metoclopramide, non-fickian.

## INTRODUCTION:

The conventional dosage forms of Metoclopramide hydrochloride contains drawbacks like dose related side effects like chills, dizziness, convulsions, irregular heartbeat, headache, abdominal pain and loss of appetite. Its higher solubility in water results in burst effect with sudden peak levels of drug in blood. Though it is well absorbed undergoes a significant first pass metabolism which may reduce the systemic bioavailability up to 30%. It needs 3-4 times daily dosing which may leads to non-compliance [3]. We can overcome the problems by formulating as microbeads, a multiparticulate drug delivery system. It has less dose dumping property. This delivery system is independent on gastric emptying results in less inter and intra subject variability in GI transit time. Oral controlled release (CR) multiple unit dosage forms such as microparticles, beads and pellets are gaining considerable importance in recent years in view of their advantages over the conventional single unit formulations [4]. Microbeads are small solid and free flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allow a sustained release or multiple release profiles. An ionic polysaccharide, alginic acid has been used as a medicine for stomach ulcers, as well as food additive because of its protective effect on the gastric mucosa when given orally. Guargum can be used as diet for diabetic gastroparesis patients.

## MATERIALS AND METHODS

Metoclopramide hydrochloride and HPMC were the gift samples from pharmafabrikon, Tamilnadu,India. Sodium alginate and guargum were purchased from Otto Kemi,Mumbai and

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Merck chemicals,Mumbai respectively. Calcium chloride was purchased from S.B.Fine chemicals Ltd, Mumbai, India. All other reagents and solvents used were of analytical grade.

**Preparation of sodium alginate microbeads**[2]

Microbeads of metoclopramide hydrochloride were prepared by ionotropic gelation technique. In this present work three sets of microbeads were prepared by using sodium alginate alone and combination with coating polymers like Guar gum, HPMC and calcium chloride used as cross linking agent.

In the first set three batches of drug-loaded microbeads were prepared (F1, F2, and F3). A solution of sodium alginate was prepared in 100ml of deionized water. In 50ml of sodium alginate solution, weighed quantity of Metoclopramide hydrochloride (500mg-batch formula) was dispersed uniformly. Bubble free dispersion was dropped through a syringe with needle into 100 ml aqueous calcium chloride solution and stirred at 500 rpm. After stirring for 30 minutes, the gelled beads were separated by filtration, washed with distilled water and finely dried overnight. Similarly, the coating polymers like HPMC and guar gum are added in F4, F5, F6 and F7, F8, F9 respectively. The formulations are shown in (**Table 1**).

**Dose Calculation** [5]

The dose of Metoclopramide hydrochloride is 10-15mg four times a day. But the dose is reduced to 27mg for formulating sustained release microbeads.

$$\mathbf{D_t = D_i\ (1+\ 0.693 \times t_m / t_{1/2})}$$

Where, $D_t$= total dose; $D_i$= initial dose; $t_m$ = time to which the drug is sustained; $t_{1/2}$= half life of the drug. $D_t = 10(1+0.693\times12/5)$; $D_t = 27$mg

**Characterization and Evaluation of Microbeads**[2, 7, 8]**:**

The prepared metoclopramide microbeads were characterized for various characters such as particle size, surface morphology, entrapment efficiency, drug content, swelling studies, *invitro* release study.

**Particle size distribution by Particle size analyzer**

All formulations are subjected to optical microscope for particle size analysis. Then, the selected best metoclopramide microbeads formulation (F6) was subjected to laser particle counting method. It is shown in (**Fig.1**)

**Scanning electron microscopy**

The purpose of the Scanning Electron Microscopy study was to obtain a topographical characterization of beads. It is shown in the (**Fig 2 & 3**).

**Determination of Drug Content and Entrapment Efficiency**

100 mg of accurately weighed microbeads were suspended in a phosphate buffer pH 7.4 upto 24 hours. Next day, the sample was shaked using mechanical shaker for few hours. Then it was filtered and from the filtrate, few ml of aliquot was taken and made the suitable dilutions and analyzed for the drug content at 308 nm by spectrophotometry.The results are in (**Table 3**)

The drug entrapment efficiency was calculated using the formula

$$\text{Percentage entrapment efficiency} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

**Swelling Study**

The extent of swelling was measured in terms of increase in particle size using optical microscopy. The swelling ratios of formulations F1-F9 metoclopramide microbeads were studied. In this test, few mg of beads from each formulation were kept in petri dishes containing pH 1.2. Thus after 2nd hour, swelling of the bead can be determined. The results are shown in below (**Table 2**).

**Dissolution**

The dissolution studies were carried out using basket type apparatus at 75 rpm and 37±0.5°C. The beads equivalent to 27 mg of drug were filled in to colorless hard gelatin capsules and placed in basket separately. The dissolution medium was 0.1 N HCl having pH 1.2 as simulated gastric fluid (SGF) for the first 2 hour, followed by phosphate buffer pH 7.4 as simulated intestinal fluid (SIF) for the next 10 hrs. A 5 ml sample was withdrawn at specified time intervals and was replaced immediately with an equal volume of fresh medium. Samples were analyzed at 308.2 nm (Shimadzu 1700). The *In-Vitro* drug release studies results were mentioned in the (**Fig 4**)

## RESULTS AND DISCUSSION

The mean particle sizes of drug loaded microbeads were performed by Optical microscopy. The mean particle size of the various formulations (F1-F9) of microbeads was obtained in the range between 583±0.12µm and 939±0.08µm. In formulation F1-F9, the drug

entrapment efficiency ranges from 50.02±1.41% to 78.21±1.03%. The IR spectra of the drug and polymer combination were compared with the spectra of the pure drug and individual polymers in which no shifting of peaks was significantly found, indicating the stability of the drug during encapsulation process.

Metoclopramide Hydrochloride release from microbeads was studied in acidic buffer (SGF pH1.2) for initial 2 hour and phosphate buffer (SIF pH7.4) for a period of next 10 hours. The *invitro* dissolution data were analyzed by different kinetic models in order to find out the n- value, which describes the drug release mechanism. The kinetic data of F6 formulation was best fitted to Korsmeyer and Peppa's model and the value of regression co-efficient, r = 0.975 and n = 0.925 which follows non-fickian, Super case-II transport.

**Table.1- Formula for Metoclopramide Hydrochloride microbeads**

| Formulations | Sodium alginate%(w/v) | Calcium chloride%(w/v) | Guar gum %(w/v) | HPMC %(w/v) |
|---|---|---|---|---|
| F1 | 2 | 3 | - | - |
| F2 | 3 | 5 | - | - |
| F3 | 4 | 7 | - | - |
| F4 | 3 | 5 | - | 0.5 |
| F5 | 3 | 5 | - | 1.0 |
| F6 | 3 | 5 | - | 1.5 |
| F7 | 3 | 5 | 0.5 | - |
| F8 | 3 | 5 | 1.0 | - |
| F9 | 3 | 5 | 1.5 | - |

Each formulation containing 0.5 g of Metoclopramide( batch formula). Drug equivalent to 27mg is taken for single dose

**Table .2-Comparative Particle size analysis and swelling study by optical microscopy**

| S.NO | Formulation | Mean diameter* (µm) | Particle size after Swelling at 1.2 pH after 2nd hour (µm) * |
|---|---|---|---|
| 1 | F1 | 583± 0.12 | 608±0.01 |
| 2 | F2 | 612±0.13 | 632±0.02 |
| **3** | F3 | 719±0.06 | 763±0.01 |
| 4 | F4 | 826±0.04 | 876±0.01 |
| 5 | F5 | 888±0.08 | 916±0.01 |
| 6 | F6 | 931±0.08 | 963±0.02 |
| 7 | F7 | 690 ±0.08 | 709±0.02 |
| 8 | F8 | 726 ±0.05 | 762±0.02 |
| 9 | F9 | 781±0.03 | 797±0.02 |

* Values are mean± SD, n=3.

**Fig.1-Particle size analysis for formulation F6**

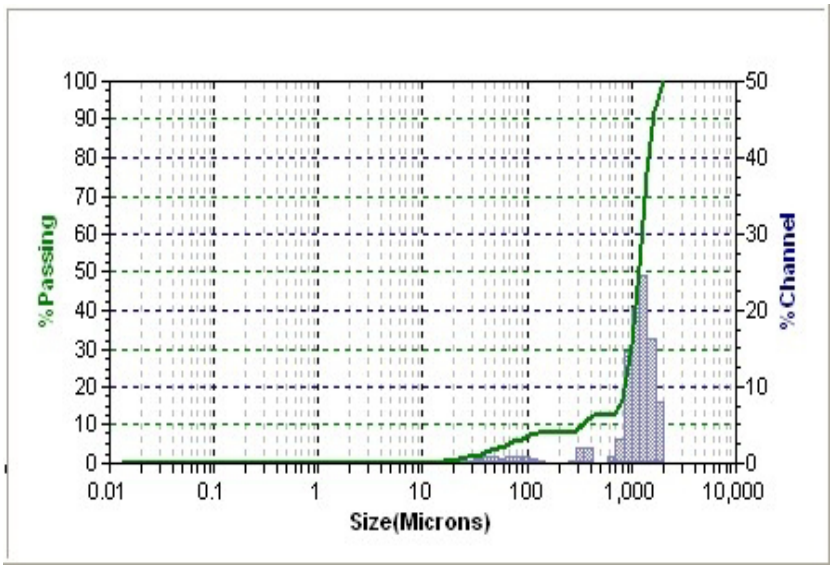


**FIG.2- SEM Photomicrograph of HPMC Microbeads (F6)**

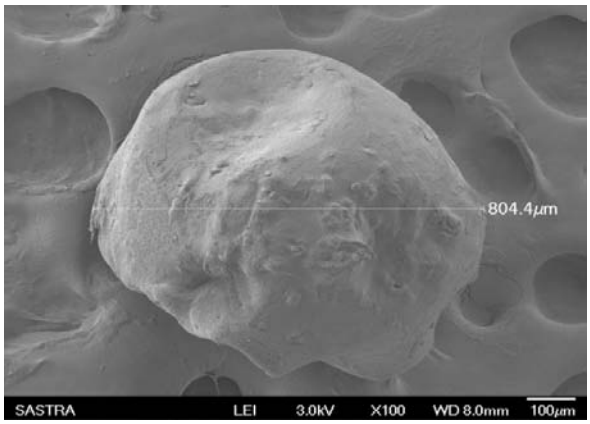



**FIG.3-SEM Photomicrograph of Guargum Microbeads (F9)**

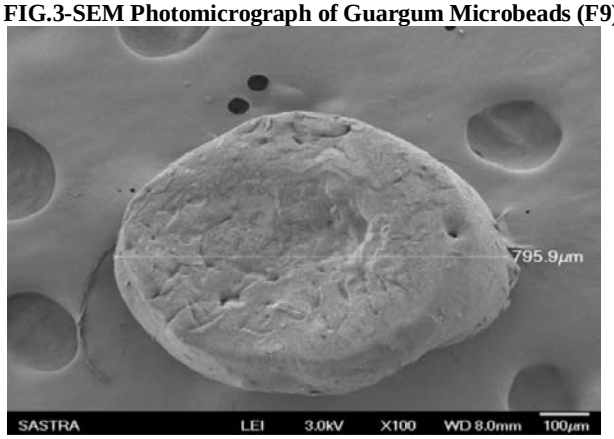
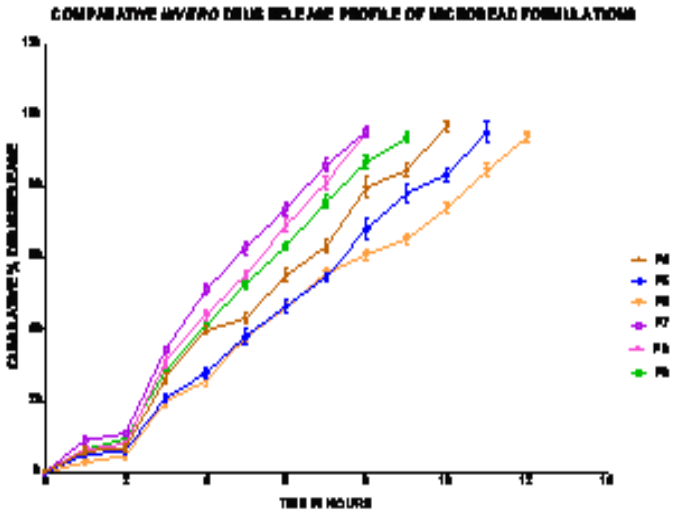



**Table.3 -Comparative Entrapment efficiency and drug content of formulations**

| S. N | Formulation | Drug content mg/100 mg beads* | % Entrapment efficiency* |
|---|---|---|---|
| 1 | F1 | 10±0.28 | 50.02±1.41 |
| 2 | F2 | 11.27±0.13 | 56.05±0.55 |
| 3 | F3 | 11.59±0.15 | 60.01±0.77 |
| 4 | F4 | 13±0.18 | 67.04±0.9 |
| 5 | F5 | 13.93±0.2 | 72.17±1.05 |
| 6 | F6 | 15.04±0.2 | 78.21±1.03 |
| 7 | F7 | 11.93±0.22 | 62.78±1.51 |
| 8 | F8 | 12.73±0.29 | 67.46±1.56 |
| 9 | F9 | 13.35±0.12 | 71.29±0.64 |

* Values are mean± SD, n=3.

**Fig.4: Comparative *Invitro* drug release of microbead formulations**



## CONCLUSION

Ionotropic gelation technique can be successfully used for preparation of Metoclopramide Hydrochloride microbeads using sodium alginate and with other coating polymers like guar gum, HPMC as drug release modifiers. Among the different formulations, microbeads containing Sodium alginate with HPMC F-6 was found to be the best formulation because it has higher drug entrapment efficiency of 78.21±1.03% and it releases the drug of 99.05±0.91% at 12$^{th}$ hour. So the formulation F6 showed sustained release for the treatment of gastroparesis and gastrosophageal reflux disease by decreasing the dose and frequency of administration and thereby reducing the side effects and improving the patient compliance.

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