*Available online www.jocpr.com*

**Journal of Chemical and Pharmaceutical Research, 2020, 12(7): 40-49**

**Research Article**

**ISSN: 0975-7384**
**CODEN(USA): JCPRC5**

# Formulation and Evaluation of Floating Microsphere of Muscle Relaxant Drug Thiocolchicoside

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**ABSTRACT**

*The main objective of this work was to design, synthesized and evaluates the Floating microsphere of muscle relaxant drug Thiocolchicoside. Thiocolchicoside (THC) is used clinically for its muscle relaxant, anti-inflammatory, and analgesic properties. Microspheres are solid spherical particles ranging in size from 1-1000 μm. They are spherical free flowing particles consisting of proteins or synthetic polymers. They are biodegradable in nature. The work investigated the design and evaluation of microspheres by Ionotropic gelation technique method. The surface morphology study by SEM indicated that microspheres were spherical with smooth surface. There was no interaction between the drug and polymers, as studied by FTIR study. The prepared microspheres were characterized by entrapment efficiency, particle size, and micromeritics properties. The drug must be delivered for a prolonged period and many medicines must be taken simultaneously in case of chronic patients. The Floating microspheres were shown to be effective for increasing the bioavailability. Among all formulations, F5 showed better drug release rate and buoyancy, which is considered as the best formulation. Stability studies shows about less than 0.5 % of drug degrade in 60 days indicating relatively good stability study of the formulation. The Floating microspheres were shown to be effective for increasing the bioavailability of Thiocolchicoside in gastric region. From the current study it can be concluded that the increase in bioavailability due to the floating microsphere drug delivery system.*

**Keywords:** Thiocolchicoside; Floating microspheres; Ionotropic gelation method; Bioavailability

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## INTRODUCTION

Microspheres are defined as “Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. It has a particle size of (1-1000 μm) [1]. Microspheres as carriers of drug become an approach of controlled release dosage form in novel drug delivery system. Further, currently available slow release oral dosage forms, such as enteric coated or double-

layer tablets which release the drug for 12-24 hours still result in inefficient systemic delivery of the drug and potential gastrointestinal irritation [2]. Microspheres are solid spherical particles ranging in size from 1-1000 μm [3]. They are spherical free flowing particles consisting of proteins or synthetic polymers which are biodegradable in nature. Glass microspheres polymer and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and therefore, are used for different applications [4]. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are. In contrast to drug delivery system, the word novel is searching something out of necessity [5]. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period thereby causing little toxicity and minimal side effects [6].

## MATERIALS AND METHODS

The muscle relaxant drug Thiocolchicoside was obtained from Associated Biotech Pvt. Ltd. H.P. India (India Glycols Limited), HPMC was obtained from (LOBA Chemical Pvt. Ltd.), Ethyl Cellulose obtained from (SD Fine Chem Ltd.), Sodium alginate were obtained from (SD Fine Chem Ltd.), Sodium bi carbonate (Merk India Limited), Ethanol obtained from (SD Fine Chem Ltd.), Calcium Chloride obtained from (SD Fine Chem Ltd.), Glacial acetic acid obtained from (SD Fine Chem Ltd.), All the other chemicals were of analytical grade [7].

### Preparation of thiocolchicoside microspheres

Microspheres of Thiocolchicoside were prepared by ionotropic gelation method using different proportion of polymers as shown in Table 1. Sodium alginate solution was added to weighed amount of ethyl cellulose dissolved in required quantity of ethanol. Weighed quantity of drug and polymer was triturated to form fine powder then added to above solution. Sodium Bicarbonate, a gas forming agent was added to this mixture and the resulting solution was stirred uniformly using a 26 gauge syringe needle the above solution was dropped into 100 ml of gently agitated calcium chloride 4% w/v solution to obtain microspheres. The solution containing microspheres was stirred slowly using magnetic bead for 10 min. the microspheres were further allowed to remain in the same solution for 20 minutes to improve mechanical strength. The formed microspheres were filtered, washed with distilled water air dried at room temperature and stored in desiccators [8,9].

### Evaluation of prepared microspheres

There are following preformulation parameter which is evaluated before the preparation of microsphere like Micromeritic property such as Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of repose. Particle Size Analysis, Percentage drug entrapment and Floating behavior [10].

### Surface morphology

**Scanning electron microscopy:** The shape and surface of morphology of drug loaded microspheres were investigated by using scanning electron microscope. The sample was spread on stub and coated with a layer of gold using spur coater. Afterwards, the stub containing the sample was placed in the scanning electron microscope chamber at the acceleration voltage of 20 kV chamber pressures of 0.6 mm/Hg then photomicrographs were taken at different magnification [11].

**Table 1. Formulation chart of microspheres [9].**

| Formulation Code | HPMC (gm) | EC (gm) | $NaHCO_3$ (mg) | Na-Alg (gm) | Thiocolchicoside (gm) | $CaCl_2$ (%) |
|---|---|---|---|---|---|---|
| $F_1$ | 0.750 | 0.500 | 150 | 1.75 | 0.500 | 4 |
| $F_2$ | 1 .00 | 1.00 | 50 | 1.75 | 0.500 | 4 |
| $F_3$ | 0.500 | 0.750 | 200 | 1.75 | 0.500 | 4 |
| $F_4$ | 1.00 | 1.50 | 100 | 1.75 | 0.500 | 4 |
| $F_5$ | 0.750 | 0.500 | 250 | 1.75 | 0.500 | 4 |
| $F_6$ | 0.750 | 1.00 | 250 | 1.75 | 0.500 | 4 |
| $F_7$ | 1.00 | 0.750 | 500 | 1.75 | 0.500 | 4 |
| $F_8$ | 1.50 | 0.500 | 125 | 1.75 | 0.500 | 4 |
| $F_9$ | 1.00 | 1.500 | 50 | 1.75 | 0.500 | 4 |
| $F_{10}$ | 2.25 | 0.750 | 100 | 1.75 | 0.500 | 4 |

**Scanning electron microscopy of prepared microsphere:** The floating microspheres of Thiocolchicoside prepared by the ionotropic gelation method were found to be discrete, spherical, free flowing, and the monolithic matrix type. The microcapsules were uniform in size, with size range of 300 µm. The SEM photographs indicated that microcapsules were spherical and completely covered the coat polymer [12] (Figures 1-3).

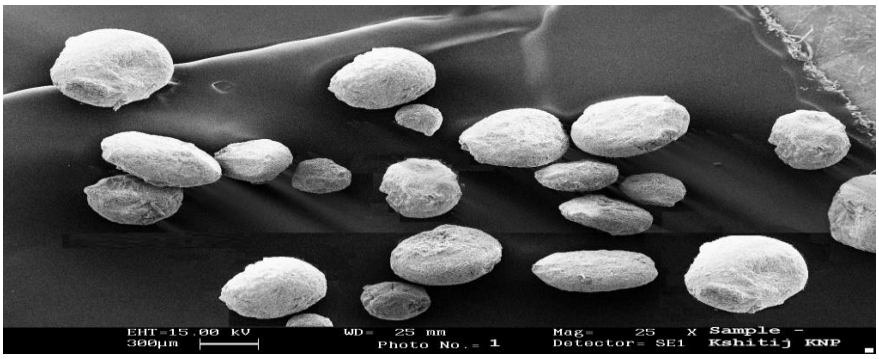


**Figure 1. Microspheres with size ranging approximately from 300 to 900 µm.**

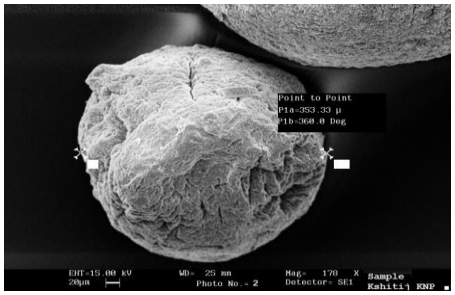


**Figure 2. Size of an individual Microsphere.**

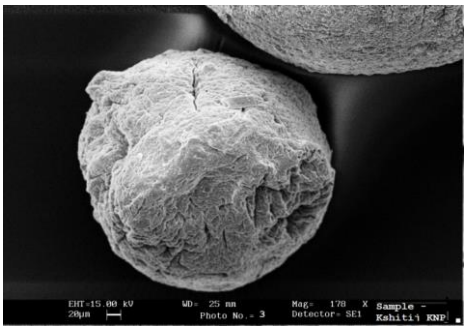


**Figure 3. Shape of an individual microsphere.**

## Differential scanning calorimetry

The DSC curve of Thiocolchicoside showed single endothermic peak at 194°C. The DSC profile of optimize formulation shows low intensity peak at about 165°C. By this it is clear that in formulation crystallinity is decrease and no interaction takes place between drug and polymer [13] (Figures 4 and 5).

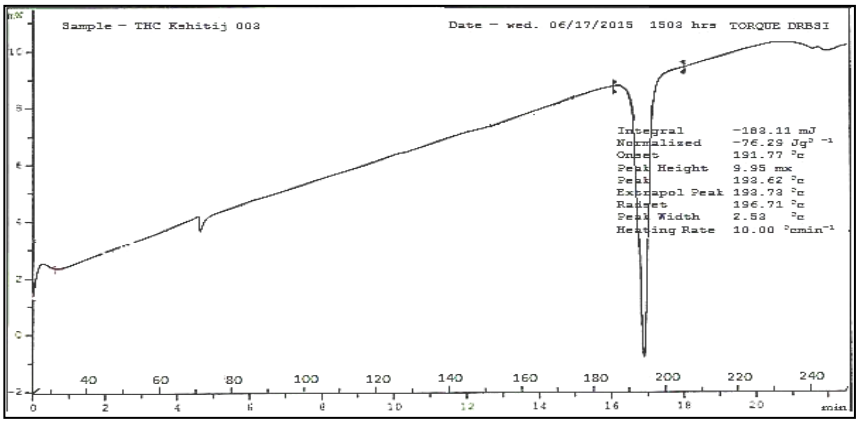


**Figure 4. Differential Scanning Calorimetry (DSC) of pure drug.**

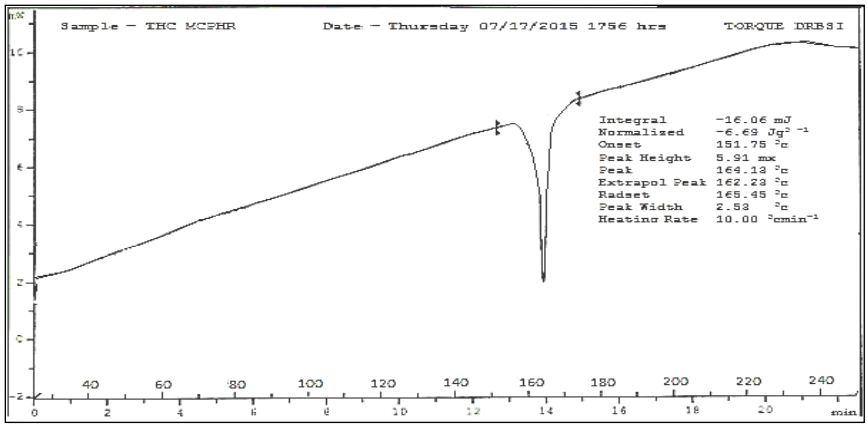


**Figure 5. Differential Scanning Calorimetry (DSC) of Thiocolchicoside microsphere.**

## *In-vitro* buoyancy

Five hundred milligrams of the floating microspheres were placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0) containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 hours, the layer of buoyant microspheres was pipetted and separated by filtration [14]. Particles in the sinking particulate layer

were separated by filtration. Particles of both types were dried in a desiccator until constant weight was achieved. Both the fractions of microspheres were weighed, and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\textbf{Buoyancy (\%)} = \{W_f / (W_f + W_s)\} \times 100$$

Where, $W_f$ and $W_s$ are the weights of the floating and settled micro particles [15].

***In-vitro* dissolution studies**

The release rate of floating microspheres was determined in a United States Pharmacopoeia Standard basket type dissolution apparatus. A weighed amount of floating microspheres equivalent to required amount of drug was filled into a hard gelatin capsule size '0' number and placed in the basket of dissolution rate apparatus containing dissolution medium. The dissolution fluid was maintained at 37 ± 1°C and rotation speed at a 50 rpm. Perfect sink conditions prevailed during the drug release study. 5 ml samples were withdrawn at each time interval, passed through a 0.25 µm membrane filter (Millipore), and analyzed using UV Spectrophotometer to determine the concentration present in the dissolution medium. The initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal [16].

**Stability studies of microspheres**

Stability studies were performed according to ICH guidelines. Optimized formulation was packed in a glass vial sealed with aluminum foil and rubber cap and kept for three months at 25 ± 5°C and 75% RH & 40 ± 5°C and 75% RH in stability chamber [17]. At the end of studies microsphere were evaluated for *in-vitro* % drug release and % Buoyancy.

**Drug identification test**

**FTIR spectra of pure drug:** FTIR spectra of pure Thiocolchicoside sample recorded by FTIR spectrum is shown in below Figure 6, which was compared with standard functional group [18-20] (Table 2).

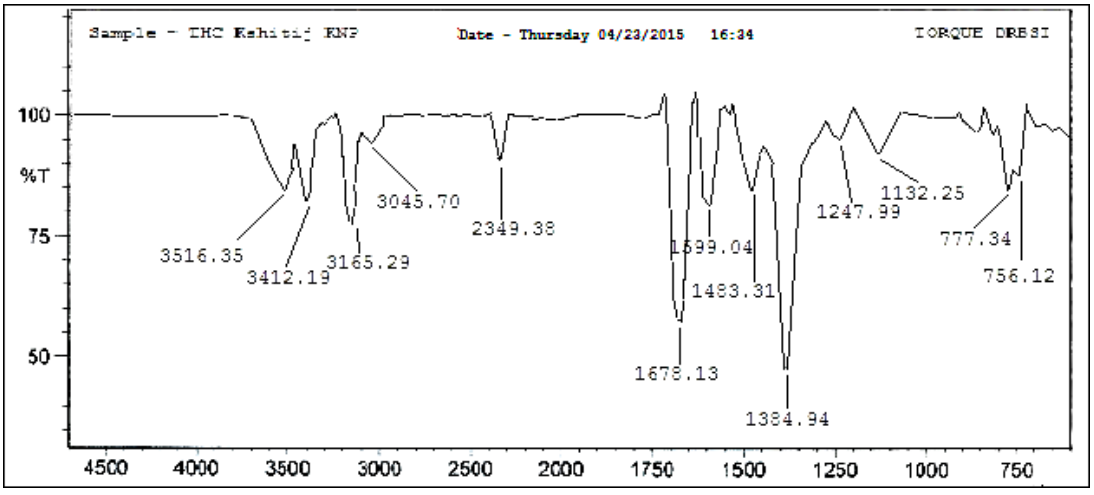


**Figure 6. FTIR Spectra of Thiocolchicoside**

**Table 2. IR Frequencies of Drug and excipients [20].**

| S.No. | Functional Groups | Observed frequencies ($cm^{-1}$) |
|---|---|---|
| 1 | NH- stretching | 3350 |
| 2 | OH-stretching | 2919 |
| 3 | CH-stretching | 2839 |
| 4 | C=O stretching | 1613 |
| 5 | $-COO^-$ stretching vibration | 1411 |
| 6 | C-C stretch | 1082 |
| 7 | C-H roking | 800 |

**Loss on drying**

Loss on drying is measured by taking weighed amount (500 mg) of drug in petri dish and kept in hot air oven at 105°C until the weight reduction stopped in definite time interval (Table 3 and Figure 7) [19].

**Table 3. Loss on drying reading**

| S.No. | Time interval | Wt. of Drug | Wt. of Petridish | Total Wt. |
|---|---|---|---|---|
| 1 | 0 min | 500 mg | 51.561 gm | 52.061 gm |
| 2 | 30 min | 481 mg | 51.561 gm | 52.042 gm |
| 3 | 60 min | 474 mg | 51.561 gm | 52.035 gm |
| 4 | 90 min | 470 mg | 51.561 gm | 52.031 gm |
| 5 | 150 min | 470 mg | 51.561 gm | 52.031 gm |

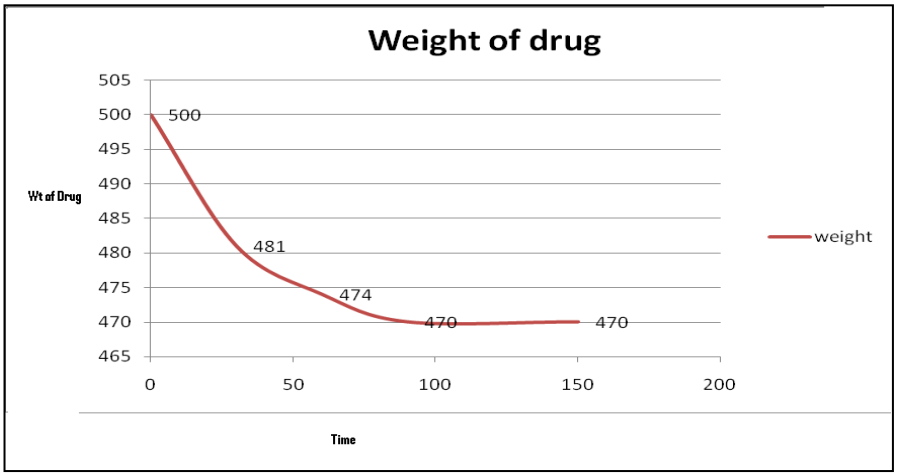


**Figure 7. Loss on Drying Curve of Thiocolchicoside.**

## RESULT AND DISCUSSION

The particle size was determined by optical micrometer and average particle size was found to be in range of 379 ± 2.63 to 400 ± 2.14. From Scanning Electron microscopy (SEM) it was observed that, microspheres were found to be spherical in shape with smooth surface texture with a hollow space within. Among all formulations, F5 showed

better drug release rate & buoyancy, which is considered as the best formulation. Various Micromeritic properties of prepared microspheres are following (Tables 4 and 5).

**Table 4. Micromeritics study of formulated microspheres [18].**

| Formulation Code | Bulk Density ± SD | Tapped Density ± SD | Carr's Index ± SD | Hausner's Ratio ± SD | Angle of Repose ± SD |
|---|---|---|---|---|---|
| F1 | 0.530 ± 0.032 | 0.591 ± 0.036 | 10.264 ± 0.430 | 1.080 ± 0.065 | 23.941 ± 0.019 |
| F2 | 0.495 ± 0.006 | 0.557 ± 0.007 | 11.183 ± 0.307 | 1.123 ± 0.004 | 24.750 ± 0.011 |
| F3 | 0.501 ± 0.018 | 0.572 ± 0.015 | 12.307 ± 1.651 | 1.168 ± 0.028 | 26.748 ± 0.024 |
| F4 | 0.505 ± 0.028 | 0.562 ± 0.022 | 10.179 ± 1.604 | 1.151 ± 0.064 | 25.734 ± 0.127 |
| F5 | 0.570 ± 0.153 | 0.633 ± 0.171 | 9.994 ± 0.847 | 1.191 ± 0.129 | 20.254 ± 0.088 |
| F6 | 0.484 ± 0.029 | 0.542 ± 0.040 | 10.574 ± 1.376 | 1.159 ± 0.075 | 27.022 ± 0.099 |
| F7 | 0.534 ± 0.046 | 0.598 ± 0.048 | 10.622 ± 0.699 | 1.182 ± 0.103 | 24.560 ± 0.034 |
| F8 | 0.547 ± 0.076 | 0.633 ± 0.095 | 13.456 ± 0.867 | 1.151 ± 0.018 | 28.413 ± 0.126 |
| F9 | 0.633 ± 0.071 | 0.677 ± 0.078 | 6.482 ± 0.636 | 1.087 ± 0.037 | 18.778 ± 0.112 |
| F10 | 0.498 ± 0.022 | 0.544 ± 0.025 | 8.377 ± 1.930 | 1.122 ± 0.072 | 21.949 ± 0.019 |

**Table 5. Percent Yield, %Buoyancy, Drug Content & Drug entrapment efficiency of microspheres.**

| Formulation Code | % Yield | % Buoyancy | Theoretical drug Content(gm) | Actual drug Content (gm) | % Drug entrapment efficiency |
|---|---|---|---|---|---|
| F1 | 58.47 | 67.5 | 0.5 | 0.3978 | 62.56 |
| F2 | 59.88 | 69 | 0.5 | 0.3177 | 59.54 |
| F3 | 63.8 | 78 | 0.5 | 0.3582 | 65.64 |
| F4 | 56.7 | 71.2 | 0.5 | 0.3665 | 55.3 |
| F5 | 60 | 80.1 | 0.5 | 0.3398 | 57.56 |
| F6 | 56.04 | 69.3 | 0.5 | 0.36925 | 56.85 |
| F7 | 61.48 | 71.9 | 0.5 | 0.3665 | 64.3 |
| F8 | 68.33 | 73.9 | 0.5 | 0.35635 | 68.27 |
| F9 | 62.21 | 72.7 | 0.5 | 0.36005 | 66.01 |
| F10 | 58.54 | 78.1 | 0.5 | 0.28545 | 59.09 |

***In-vitro* dissolution studies**

*In-vitro* drug release of prepared microsphere were carried out in 900 ml of HCl buffer pH 1.2 using USP Standard eight stage basket type (VEEGO) dissolution rate test apparatus. Temprature of the dissolution medium was maintained at 37 ± 0.5°C a rotating speed of 50 rpm the further information shows as following [21] (Table 6 and Figure 8).

**Table 6. *In-vitro* release profile of Thiocolchicoside microspheres.**

| Time (hr) | F1 % Drug Release F1 | F2 % Drug Release F2 | F3 % Drug Release F3 | F4 % Drug Release F4 | F5 % Drug Release F5 | F6 % Drug Release F6 | F7 % Drug Release F7 | F8 % Drug Release F8 | F9 % Drug Release F9 | F10 % Drug Release F10 |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1.5 | 21.63 | 15.14 | 25.52 | 19.47 | 22.71 | 16.44 | 20.55 | 24.66 | 17.74 | 22.5 |
| 3 | 27.69 | 24.87 | 31.37 | 28.55 | 30.28 | 24.87 | 29.85 | 30.28 | 26.61 | 29.85 |
| 4.5 | 35.91 | 36.34 | 38.5 | 36.34 | 38.5 | 33.53 | 41.32 | 37.21 | 35.91 | 36.77 |
| 6 | 46.94 | 47.59 | 49.32 | 44.35 | 49.75 | 39.8 | 51.49 | 46.73 | 44.56 | 42.18 |
| 7.5 | 53.65 | 53.22 | 59.9 | 56.46 | 54.95 | 49.11 | 59.49 | 55.6 | 51.27 | 52.35 |
| 9 | 67.28 | 64.25 | 64.25 | 63.17 | 64.25 | 58.84 | 63.6 | 63.17 | 59.49 | 61.87 |
| 10.5 | 72.25 | 69.87 | 70.31 | 69.44 | 72.25 | 65.58 | 67.5 | 71.39 | 66.63 | 68.58 |
| 12 | 80.26 | 77.01 | 82.21 | 79.18 | 81.77 | 74.85 | 78.31 | 81.34 | 76.58 | 79.39 |

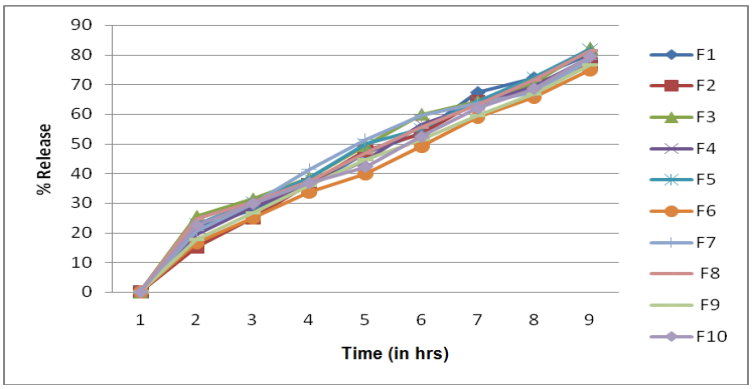


**Figure 8. % Drug Release of optimized formulation.**

### Accelerated stability studies

Stability of preparation is an important factor to estimate the quality of the dosage forms. Thus, accelerating testing was carried out to study on stability of Thiocolchicoside loaded microspheres. The results showed no marked change in physical properties (color, surface morphology and particle flow) and no significant difference in floating ratio and drug loading was observed in comparison with the Thiocolchicoside loaded microspheres before storage in stability chamber (Table 7) [22].

**Table 7. Accelerated stability study for optimized formulation.**

| Temprature & Humidity | Items | | Days 0 | 30 | 60 | Colour |
|---|---|---|---|---|---|---|
| 25 ± 5°C & 75% RH | %Buoyancy | F5 | 72.24 | 69.78 | 66.69 | Light Brown Yellow |
| | %Drug release | F5 | 81.23 | 80.61 | 79.82 | Light Brown Yellow |
| 40 ± 5°C & 75% RH | %Buoyancy | F5 | 71.81 | 70.78 | 68.56 | Light Brown Yellow |
| | %Drug release | F5 | 80.77 | 80.32 | 79.44 | Light Brown Yellow |

## CONCLUSION

The floating hollow microspheres (microspheres) of Thiocolchicoside by inotropic gelatin method for sustained delivery by using polymers like Hydroxy Propyl Methyl Cellulose (HPMC) and Ethyl cellulose in order to extend the drug release for about 8 hour in the upper GIT, which may result in enhanced absorption and there by improved bioavailability. The particle size was determined by optical micrometer and average particle size was found to be in range of 379 ± 2.63 to 400 ± 2.14. From Scanning Electron microscopy (SEM) it was observed that, microspheres were found to be spherical in shape with smooth surface texture with a hollow space within. Among all formulations, F5 showed better drug release rate & buoyancy, which is considered as the best formulation. Stability studies shows about less than 0.5 % of drug degrade in 60 days indicating relatively good stability study of the formulation.

The Floating microspheres were shown to be effective for increasing the bioavailability of Thiocolchicoside in gastric region. From the current study it can be concluded that the increase in bioavailability due to the floating microsphere drug delivery system. Floating Drug Delivery Systems have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations.

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