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# DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF FLOATING MICROSPHERES BEARING TRAMADOL HCl

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**Keywords:** tramadol HCl, floating drug delivery system, microspheres, non-aqueous solvent evaporation

The gastrointestinal transit time is one of several physiological limitations that must be controlled in the development of oral sustained release dosage forms. Various attempts have been made to prolong the retention time of the dosage form in the stomach (1, 2). One such technique is based on the preparation of floating microspheres that remain buoyant in the stomach content due to its lower density than that of the gastric fluid (3). A floating system made of multiple units has relative advantage compared to a single unit preparation. In a multi particulate system the risk of dose dumping is relatively lower (4).

The concept of floating microsphere can also be utilized to minimize the irritant effect of drug in the stomach by avoiding direct contact with the mucosa and providing means of getting low dose for prolonged period of time (5).

In the present study the prime objective is to develop a newer floating drug delivery system of tramadol HCl as a model drug to prolong gastric retention with low frequency of administration for better patient compliance. The other object is to investigate the performance of hydrophobic polymer system in controlling the release of this freely water soluble drugs (6, 7).

Tramadol is a synthetic opiod of the aminocyclohexanal group, it is a centrally acting analgesic with weak opioid agonist properties. Tramadol has been proved to be effective in both experimental and clinical pain without causing serious cardiovascular and respiratory side effects. Its oral dosage regimen is 50 to 100 mg every 4 to 6 h and maximum dosage of 400 mg/day (8). A sustained release formulation of tramadol HCl is desirable due to its shorter half life time (i.e., 4.5 to 5.5 h) (9).

## MATERIALS AND METHODS

Tramadol HCl was obtained as a gift sample from Rantus Pharmaceutical Ltd., Pashamylaram, Medak district. Ethyl cellulose was purchased from Hi-media Laboratories Ltd., Mumbai and Eudragit S100 was received as a gift sample from Rohm Pharma GmbH, Germany. All other chemicals and reagents were of analytical grade and were used as obtained.

### Preparation of floating microspheres

Microspheres containing drug as a core material were prepared by non-aqueous solvent evaporation method (10). First, drug and polymer were mixed in acetone in various ratios. The formed slurry was slowly introduced to 35 mL of liquid paraffin while being stirred at 1000 to 1500 rpm by a mechanical stirrer equipped with three blade propeller at room temperature. The system was stirred for 2 h to allow the solvent to evaporate completely and the microspheres were collected by filtration. The microspheres were washed repeatedly using petroleum ether (40–60$^{o}$C) until being free from oil. The collected microspheres were dried at room temperature and subsequently stored in a dessicator for 24 h.

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Table 1. Batch specification of the prepared floating microspheres for group A.

| No. | Batch code | Variables | | |
|---|---|---|---|---|
| | | Drug : polymer TDM : ES-100 (mg : mg) | Stirring rate (rpm) | Vol. of internal phase (acetone, mL) |
| 1. | FMEU-1 | 1 : 1 | 1000 | 15 |
| 2. | FMEU-2 | 1 : 2 | 1000 | 15 |
| 3. | FMEU-3 | 1 : 3 | 1000 | 15 |
| 4. | FMEU-4 | 1: 4 | 1000 | 15 |
| 5. | FMEU-5 | 1 : 1 | 1000 | 10 |
| 6. | FMEU-6 | 1 : 2 | 1000 | 10 |
| 7. | FMEU-7 | 1 : 1 | 1000 | 20 |
| 8. | FMEU-8 | 1 : 2 | 1000 | 20 |
| 9. | FMEU-9 | 1 : 1 | 1500 | 15 |
| 10. | FMEU-10 | 1 : 2 | 1500 | 15 |

TDM = tramadol HCl, EC = ethyl cellulose, ES 100 = Eudragit S-100.

Table 2. Batch specification of the prepared floating microspheres for group B.

| No. | Batch code | Variables | | |
|---|---|---|---|---|
| | | Drug : polymer TDM : ES-100 (mg : mg) | Stirring rate (rpm) | Vol. of internal phase (acetone, mL) |
| 1. | FMEC-1 | 1 : 1 | 1000 | 15 |
| 2. | FMEC-2 | 1 : 2 | 1000 | 15 |
| 3. | FMEC-3 | 1 : 3 | 1000 | 15 |
| 4. | FMEC-4 | 1 : 4 | 1000 | 15 |
| 5. | FMEC-5 | 1 : 1 | 1000 | 10 |
| 6. | FMEC-6 | 1 : 2 | 1000 | 10 |
| 7. | FMEC-7 | 1 : 1 | 1000 | 20 |
| 8. | FMEC-8 | 1 : 2 | 1000 | 20 |
| 9. | FMEC-9 | 1 : 1 | 1500 | 15 |
| 10. | FMEC-10 | 1 : 2 | 1500 | 15 |

TDM = tramadol HCl, EC = ethyl cellulose, ES 100 = Eudragit S-100.

## Characterization of floating microspheres

### Micromeritic study

The prepared microspheres were characterized for their micromeritic properties such as particle size, tapped density and % compressibility index.

The size of microspheres was determined using an optical microscope (Magnus MLX-DX, Olympus, India) fitted with an ocular micrometer and stage micrometer. The mean particle size was calculated by measuring 200–300 particles (11).

The tapping method was used to calculate tapped densities and % compressibility index as follows (equations 1 and 2):

$$\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}} \quad (1)$$

$$\% \text{ Compressibility index} = (1 - V/V_0) \times 100 \quad (2)$$

where, V and $V_0$ are the volumes of the sample after and before the standard tapping, respectively.

### Morphology

Scanning electron microscopy (SEM) was applied to study morphology of microspheres. The samples for SEM were prepared by sprinkling the powder on a both side adhesive tape suck to a stub. Gold palladium coating on the prepared stub was

Table 3. Micromeritic properties of different floating microspheres for group A.

| Batch code | Mean particle size [a] (μm) | Tapped density [b] (g/cm$^3$) | Compressibility index [b] (%) |
|---|---|---|---|
| FMEU-1 | 127.87 ± 14.31 | 0.134 ± 0.015 | 36.65 ± 5.36 |
| FMEU-2 | 136.11 ± 09.39 | 0.162 ± 0.009 | 30.58 ± 7.59 |
| FMEU-3 | 148.54 ± 15.74 | 0.202 ± 0.021 | 24.43 ± 3.87 |
| FMEU-4 | 160.44 ± 11.43 | 0.235 ± 0.017 | 19.68 ± 2.11 |
| FMEU-5 | 133.76 ± 12.56 | 0.140 ± 0.002 | 38.23 ± 2.14 |
| FMEU-6 | 143.98 ± 11.64 | 0.170 ± 0.008 | 33.05 ± 3.05 |
| FMEU-7 | 118.69 ± 15.51 | 0.121 ± 0.011 | 35.69 ± 2.33 |
| FMEU-8 | 130.39 ± 21.48 | 0.143 ± 0.013 | 30.24 ± 1.83 |
| FMEU-9 | 114.45 ± 17.39 | 0.120 ± 0.021 | 34.78 ± 2.11 |
| FMEU-10 | 122.5.0 ± 19.04 | 0.157 ± 0.034 | 27.95 ± 3.11 |

[a] The mean ± SD, n = 200–300. [b]the mean ± SD, n = 3.

Table 4. Micromeritic properties of different floating microspheres for group B.

| Batch code | Mean particle size [a] (μm) | Tapped density [b] (g/cm$^3$) | Compressibility index [b] (%) |
|---|---|---|---|
| FMEC-1 | 119.56 ± 16.31 | 0.140 ± 0.010 | 37.61 ± 4.34 |
| FMEC-2 | 134.51 ± 10.79 | 0.169 ± 0.019 | 30.23 ± 6.50 |
| FMEC-3 | 150.64 ± 15.54 | 0.209 ± 0.031 | 25.45 ± 3.98 |
| FMEC-4 | 169.44 ± 10.48 | 0.245 ± 0.012 | 20.67 ± 1.17 |
| FMEC-5 | 140.56 ± 10.46 | 0.149 ± 0.002 | 39.33 ± 3.44 |
| FMEC-6 | 148.21 ± 10.66 | 0.170 ± 0.011 | 35.05 ± 3.15 |
| FMEC-7 | 128.40 ± 14.00 | 0.129 ± 0.017 | 37.69 ± 2.43 |
| FMEC-8 | 135.32 ± 22.40 | 0.146 ± 0.019 | 31.24 ± 1.86 |
| FMEC-9 | 119.65 ± 17.99 | 0.129 ± 0.031 | 35.80 ± 2.10 |
| FMEC-10 | 132.5.0 ± 19.14 | 0.166 ± 0.029 | 28.09 ± 3.12 |

[a] The mean ± SD, n = 200–300. [b]the mean ± SD, n = 3.

carried out by using sputter coater (POLARON model SC-76430). The thickness of coating was about 200 Å. The coated stubs were randomly scanned under electron microscope (LEO-430,UK) (12).

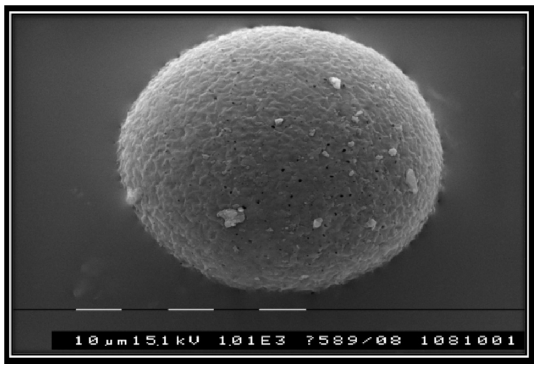


Figure 1. Scanning electron micrograph showing sphericity of floating microspheres

**Yield of microspheres**

The prepared microspheres were collected and weighted. The actual weight of obtained microspheres divided by the total amount of all non-volatile material that was used for the prepration of the microsphere and multiplied by 100, gives the % yield of microspheres (equation 3):

$$\% \text{ yield} = \frac{\text{Actual weight of product}}{\text{Total weight of non-volatile material}} \times 100 \qquad (3)$$

**Determination of drug entrapment efficiency and yield of floating microspheres** (13)

To determine the entrapment efficiency, 10 mg of floating microspheres were weighed and crushed in pestle mortar, then dissolved in 10 mL of SGF (simulated gastric fluid). Then, the solution was filtered to separate shell fragments. The filtrate samples were analyzed for drug content using UV-Spectrophotometer (Shimadzu UV- 1700 Series, Japan) at the $\lambda_{max}$ 271.5 nm after suitable dilution.

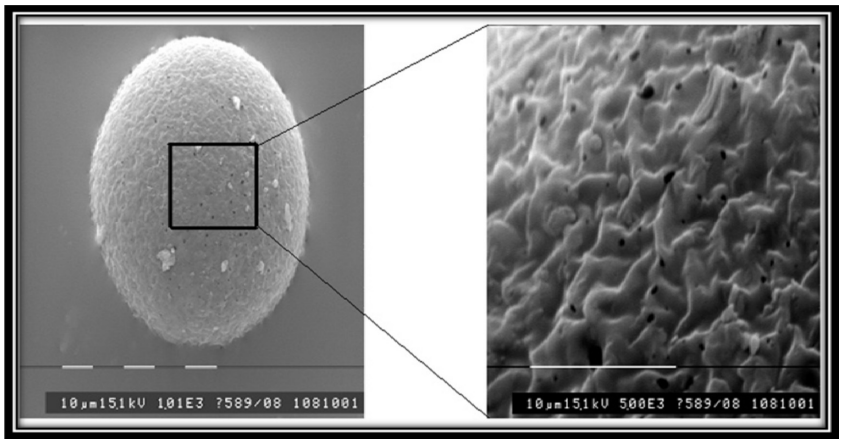


Figure 2. Scanning electron micrograph showing enlarged view of perforated surface

Table 5. Various formulation parameters for microspheres for group A.

| Batch code | Yield [a] (%) | Incorporation efficiency [a] (%) | Buoyancy [a] (%) |
|---|---|---|---|
| FMEU-1 | 54.68 ± 08.28 | 60.10 ± 04.23 | 59.43 ± 02.01 |
| FMEU-2 | 65.74 ± 05.26 | 69.55 ± 02.60 | 67.52 ± 06.77 |
| FMEU-3 | 71.82 ± 06.88 | 75.59 ± 06.28 | 74.98 ± 10.23 |
| FMEU-4 | 76.79 ± 10.06 | 80.19 ± 04.26 | 85.72 ± 09.58 |
| FMEU-5 | 47.23 ± 04.85 | 59.12 ± 10.00 | 58.23 ± 01.11 |
| FMEU-6 | 59.53 ± 07.22 | 67.44 ± 05.94 | 64.59 ± 02.35 |
| FMEU-7 | 65.85 ± 10.21 | 65.59 ± 08.09 | 60.23 ± 03.56 |
| FMEU-8 | 79.89 ± 15.08 | 76.12 ± 09.02 | 70.55 ± 05.09 |
| FMEU-9 | 56.38 ± 09.21 | 61.19 ± 01.95 | 60.45 ± 05.54 |
| FMEU-10 | 66.85 ± 04.56 | 71.05 ± 06.27 | 69.79 ± 08.23 |

[a] The mean ± SD, n = 200–300.

Table 6. Various formulation parameters for microspheres for group B.

| Batch code | Yield [a] (%) | Incorporation efficiency [a] (%) | Buoyancy [a] (%) |
|---|---|---|---|
| FMEC-1 | 56.58 ± 09.39 | 58.10 ± 05.23 | 57.26 ± 05.01 |
| FMEC-2 | 67.79 ± 05.36 | 71.65 ± 01.62 | 60.42 ± 06.56 |
| FMEC-3 | 73.82 ± 07.98 | 77.50 ± 04.29 | 70.38 ± 11.23 |
| FMEC-4 | 77.79 ± 10.16 | 82.19 ± 03.27 | 82.22 ± 08.28 |
| FMEC-5 | 49.33 ± 04.55 | 60.11 ± 11.12 | 56.22 ± 03.31 |
| FMEC-6 | 60.43 ± 08.22 | 68.54 ± 06.00 | 59.69 ± 02.33 |
| FMEC-7 | 67.85 ± 11.23 | 66.48 ± 08.01 | 60.59 ± 08.52 |
| FMEC-8 | 80.09 ± 13.10 | 76.11 ± 08.11 | 68.55 ± 06.10 |
| FMEC-9 | 58.15 ± 02.31 | 59.71 ± 01.61 | 60.12 ± 9.38 |
| FMEC-10 | 70.08 ± 05.24 | 72.57 ± 04.53 | 62.57 ± 03.51 |

[a] The mean ± SD, n = 200–300.

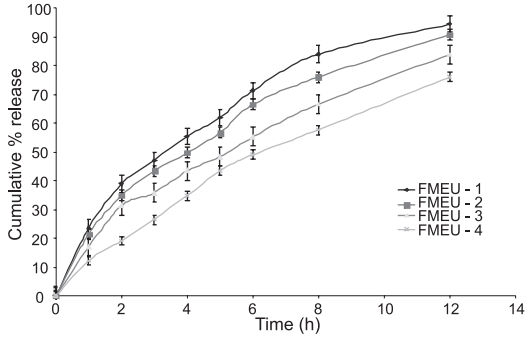


Figure 3. Release profile of tramadol HCl in SGF (pH 1.2) for group A showing effect of polymer ratio

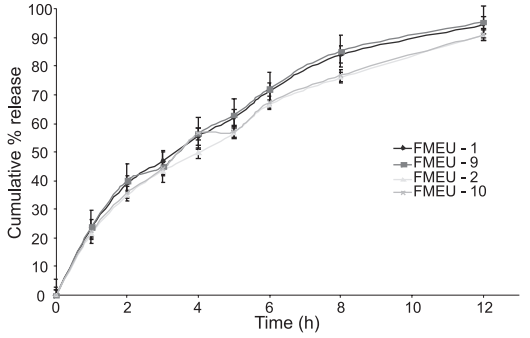


Figure 4. Release profile of tramadol HCl in SGF (pH 1.2) for group A showing effect of revolutions

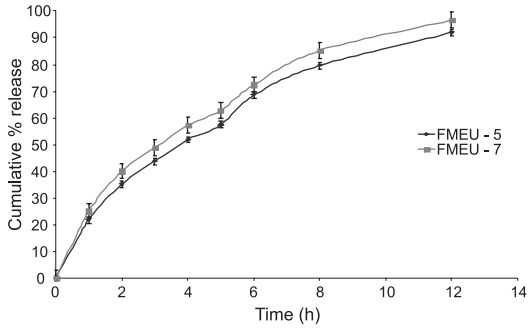


Figure 5. Release profile of tramadol HCl in SGF (pH 1.2) for group A showing effect of internal phase

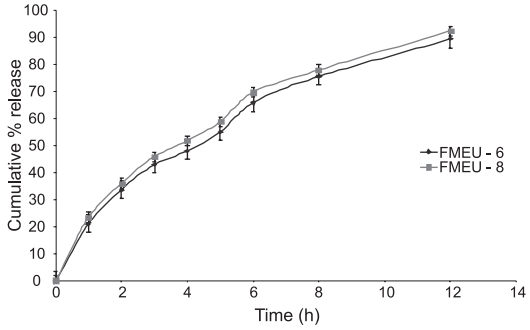


Figure 6. Release profile of tramadol HCl in SGF (pH 1.2) for group A showing effect of internal phase

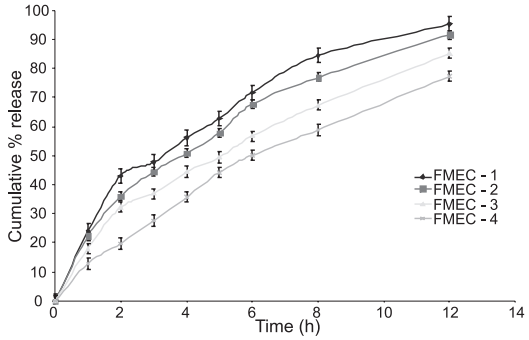


Figure 7. *In vitro* release profile of tramadol HCl in SGF (pH 1.2) for group B showing effect of polymer ratio

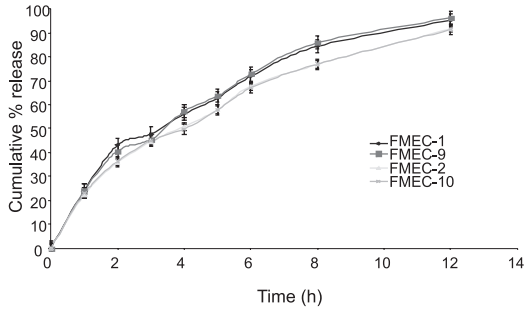


Figure 8. *In vitro* release profile of tramadol HCl in SGF (pH 1.2) for group B showing effect of revolutions

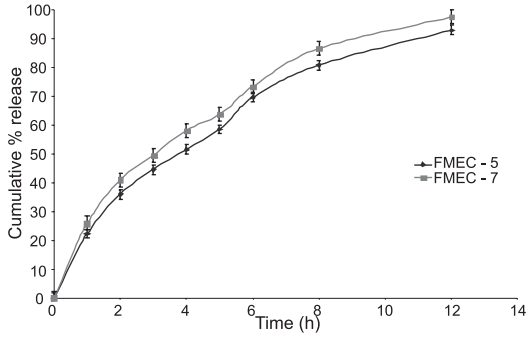


Figure 9. *In vitro* release profile of tramadol HCl in SGF (pH 1.2) for group B showing effect of internal phase

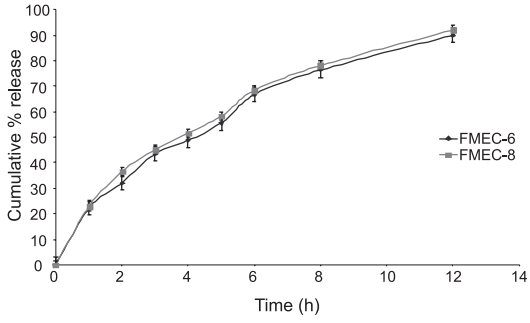


Figure 10. *In vitro* release profile of tramadol HCl in SGF (pH 1.2) for group B showing effect of internal phase

The entrapment efficiency was calculated as follows (equation 4):

$$\text{Incorporation efficiency} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content}} \times 100 \quad (4)$$

***In- vitro* floating ability**

An *in vitro* floating ability test was carried out using SGF at pH 1.2 containing 0.02% w/v Tween 20 without enzyme as a dispersing medium. Microspheres were spread over the surface of 500 mL dispersing medium at 37 ± 0.1°C. The medium was agitated by a paddle rotating at 100 rpm for 12 h. The floating and settled portions of microspheres were collected separately. The separated microspheres were dried till constant weight (14). The percentage of floating ability of microspheres was calculated as (equation 5):

$$\% \text{ floating ability} = \frac{\text{Weight of floating microspheres}}{\text{Initial weight of microsphere}} \times 100 \quad (5)$$

***In vitro* drug release**

The drug release rate from floating microspheres was determined by using standard USP paddle type dissolution apparatus (15). A weighed amount of floating microspheres equivalent to 100 mg of drug was placed in a non reacting muslin cloth that had a smaller mesh size than the microspheres. The mesh was tied with a nylon thread to avoid the escape of any microspheres and a glass bead was placed in the mesh to induce the sinking of microspheres. The dissolution test was performed in 900 mL SGF (pH 1.2). The temperature and rotation were maintained at 37 ± 05°C and 100 rpm, respectively. At specified time interval, 5 mL samples were withdrawn, filtered, diluted with the same medium and analyzed spectrometrically at 271.5 nm. The volume of samples withdrawn was replaced with an equal volume of the same dissolution medium.

**Statistical analysis**

In this study, the results are given as the mean ± standard deviation (SD). Student's *t*-test and one way analysis of variance (ANOVA) were applied to find out the significant difference in drug release from different batches using Graph Pad Instant software program. The considered statistically significant difference was at $p < 0.05$.

## RESULTS AND DISCUSSION

The formulation of tramadol HCl loaded floating microspheres were developed in two groups A and B by non-aqueous solvent evaporation technique. In group A, acrylic polymer i.e., Eudragit S100 was used in different ratios and acetone was used as solvent system. Ten formulations were developed for this group. (Table 1)

In group B, varying ratio of ethyl cellulose was used as a polymer and solvent system was the same as in group A. Ten formulation batches were also developed for this group. (Table 2) and three variables were taken into account: polymer ratio, stirring rate and volume of internal phase.

**Micromeritic study**

The mean particle size of the floating microspheres was found to be ranging from 114.45 ± 17.39 µm to 160.44 ± 11.4 3 µm (for group A) and 119.56 ± 16.31 µm to 169.44 ± 10.48 µm (for group B). It was observed that on increasing the polymer amount, the average particle size increased but on increasing the stirring rate the mean particle size was reduced. Similarly, on increasing solvent volume (acetone) the particle size was also reduced. The measured tapped densities values ranged from 0.120 ± 0.021 to 0.235 ± 0.017 g/cm$^3$ for group A and from 0.129 ± 0.017 to 0.245 ± 0.012 g/cm$^3$ for group B. The % compressibility index ranged from 19.68 ± 2.11 to 38.23 ± 2.14 for group A and from 25.45 ± 3.98 to 39.33 ± 3.44 for group B. (Tables 3 and 4, respectively).

**% Yield**

The maximum and minimum percentage yield of floating microspheres was 79.89 ± 15.08 and 47.23 ± 04.85 in batches FMEU-8 and FMEU-5, respectively, for group A and 80.09 ± 13.10 and 49.33 ± 04.55 in batches FMEC-8 and FMEC-5, respectively, for group B. (Tables 5 and 6, respectively).

**Morphology**

SEM photo micrograph showed spherical shape of microspheres with perforated surface. (Figs. 1 and 2). The perforation may be due to evaporation of acetone from embryonic microspheres.

**Drug entrapment efficiency**

The drug entrapment efficiency of microspheres was found to be good (59.12 ± 10.00 to 80.19 ± 04.26% for group A and 58.10 ± 5.23 to 82.19 ± 3.27% for group B). It was found that on increasing the solvent volumes the entrapment efficiency increased (Tables 5 and 6).

***In vitro* floating ability**

The floating microspheres floated on SGF containing 0.02% w/v Tween 20 due to insolubility of

the polymer in the gastric fluid. Microspheres showed good floating ability (58.23 ± 01.11 to 85.72 ± 09.58% for group A and 56.22 ± 03.31 to 82.22 ± 08.28% for group B) for 12 h. It was observed that the floating ability increased with an increase of average particle size (Tables 5 and 6).

***In vitro* drug release**

It was observed that on increasing polymer concentration, the cumulative percent release decreased significantly ($p < 0.05$) in both groups (Fig. 3 for group A and Fig. 7 for group B). There was not any significant effect of rpm on cumulative drug release. (Fig. 4 and Fig. 8).

There was significant increase observed in cumulative drug release on increasing the volume of internal phase. (Figs. 5, 6 for group A and 9, 10 for group B).

## CONCLUSION

The tramadol HCl floating microspheres were successfully prepared by non-aqueous solvent evaporation method for prolonged as well as controlled action of drug. Due to their low density, these multi particulate drug delivery systems showed good floating ability (> 12 h). From *in-vitro* drug release studies, it may be concluded that by changing the ratio of polymers and solvent, tramadol release can be controlled. This system could be useful for narrow absorption window and/or gastric site specific delivery. Therefore, it may be concluded that drug loaded floating microspheres are suitable delivery system for tramadol.

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