Formulation and In Vitro Evaluation of Cimetidine Microsphere as Gastro Retentive Floating Drug Delivery System

Mokale Vinod*, Naik Jitendra, Shirude Priyanka, and Shimpi Navin

***Abstract*—**Context: The purpose of this work was preparation and evaluation of floating microsphere using cimetidine (CM) as a model drug by solvent evaporation method (O/O).

Objective is to achieve an extended retention of floating microsphere using cimetidine (CM) microspherein the upper GIT followed by enhanced absorption and improved bioavailability.

Methods: The microspheres were prepared by the solvent evaporation method using different ratios of polymers like hydroxy propyl methyl cellulose and ethyl cellulose.

Results: The prepared Cimetidine microspheres were evaluated for FTIR and XRD study and found no interaction between drug and excipients, entrapment efficiency was found to be 91.12%, microspheres was spherical in shape with smooth surface in micro size it reveals by surface morphology (FE-SEM) and in vitro drug release study shown 79.6% drug release within 12 hrs.

Conclusion: In vitro study of polymer encapsulated Cimetidine shown good buoyancy and entrapment efficiency along with decrease in dosing frequency.

***Keywords*—** Floating microsphere, Hydroxypropyl methyl cellulose, ethyl cellulose, solvent evaporation (O/O).

I. Introduction

THE main objective in the development of oral controlled dosage forms is to prolong the retention of the dosage forms in the stomach or upper gastrointestinal (GI) tract until all the drug is released for the desired period of time (Arora, 2005).Rapid GI transit could result in incomplete drug release from the drug delivery device in the absorption zone leading to diminished efficacy of the administered dose (Baccarin, 2006;Barhate, 2009).Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms (Fartyal, 2011).

Recently, gastro retentive drug delivery systems are used for increasing gastric residence time. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients (Struebel, 2003;Jain, 2005).

Cimetidine is a Histamine H2 receptor antagonist, which is widely prescribed in gastric ulcers, duodenal ulcers and gastroesophageal reflux disease. It is poorly absorbed from the lower gastrointestinal tract and has a short elimination half-life (~ 2 hr) (Jayswal,2011;Ma, 2008). The purpose of the work was to prepare cimetidine (CM) microspheres in order to achieve an extended retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability (Senthilkumar, 2011;Singh, 2010).

Floating drug delivery system (FDDS) promises potential approaches for gastric retention. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying (Mayavanshi, 2008;Thomas, 2011).

II. Materials and Methods

A. Materials

Cimetidine (CM) from Ruskin Chemipharm, Mumbai, India; Hydroxypropylmethyl cellulose (HPMC) K100Mfrom Colorcon, Goa and Ethyl cellulose from Lobachemie, India were received as gift samples. Tween 80, Dichloromethane and Methanol were purchased from Merck Specialities Pvt. Ltd. (Mumbai, India). All other solvents and reagents were used as analytical grade.

B. Methods

Cimetidine microspheres were prepared by solvent evaporation (oil-in-oil emulsion) technique(O'Donnell, 1997). Drug and polymer in different proportions (1:1, 1:2, 1:3) were weighed & dissolved at room temperature in to a mixture of methanol-dichloromethane mixture (1:1v/v) with vigorous agitation to form uniform drug-polymer solution. Formulated solution was then slowly poured in to the dispersion medium

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consisting of 100 ml of light liquid paraffin containing 0.02% Tween 80 maintained at temperature 30-400c. After 60 min, n-hexane was added into the solution for hardening of the microspheres. Stirring was continued using lab stirrers at 800 rpm until the complete evaporation of the organic solvent from solid microspheres. Microspheres were collected by filtration through a whattmann filter paper no. 2, washed with n-hexane, air dried for 24 hours and was used for further studies.

C. Characterization Techniques

Encapsulation efficiency (% EE): To determine the encapsulation efficiency, accurately weighed microspheres equivalents to 5 mg of drug were stirred with dichloromethane and 0.01N HCL for 30 min at room temperature until the evaporation of organic solvent. The solution was filtered and diluted with gastric fluid and drug concentration was determined by using a UV-visible spectrophotometer (Hitachi U-2900) at the wavelength of 218nm. The encapsulation efficiency of CM using the following equations:

$$\% \text{ Encapsulation Efficiency} = \frac{\text{Actual Quantity}}{\text{Theoretical Quantity}} \times 100$$

D. Morphology

The size of microspheres was determined using a microscope fitted with an ocular micrometer and stage micrometer. The surface morphology of microspheres made of HPMC and ethyl cellulose contents was investigated by using field emission scanning electron microscopy (FE-SEM-Hitachi S 4800). The particles were examined for shape, size and surface characteristics.

E. Fourier Transform Infrared (FTIR) spectroscopy study

The possible interactions between drug and polymers were analysed using an FTIR Spectrophotometer (Shimadzu; FTIR-8400) by KBr pellet method. For that about 2 mg of the pure drug, polymers and optimized formulations were selected separately. Pure drug, polymers and formulation were dispersed in KBr powder and the pellets were made by applying 6000 kg/cm2 pressure. Spectra were recorded in the scan range of 4000-500 cm-1.

F. X-ray diffraction analysis (XRD)

The wide angle X-ray diffraction (WAXD) patterns of the samples were collected from an X-ray generator (Bruker D8 Advance, Serial Number: 204795) with Cu Kα radiation (λ = 1.5418 A°) source at voltage 40 kV and 30 mA current in the 2θ range 5-40°.

G. Buoyancy percentage

Microspheres (100mg) were spread over the surface of a USP XXIV dissolution apparatus (type II) (Electrolab TDT-08L) filled with 900 ml 0.01N HCl containing 0.02% Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hrs. The floating and the settled portion of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

$$\% \text{ Buoyancy} = \frac{\text{Microsphere remained floating}}{\text{Total mass of microsphere}} \times 100$$

H. In vitro drug release studies

The percent cumulative release of cimetidine microsphere was determined by using the dissolution test apparatus (Paddle type dissolution tester- Electrolab TDT-08L). Amounts of microsphere equivalent to 100 mg of drug was introduced into the 900ml of dissolution medium, were maintained at 37±0.50C throughout the study with stirring speed of 100 rpm. Aliquots of the dissolution medium were withdrawn at predetermined intervals and replenished with fresh dissolution media to maintain the sink condition. The Cimetidine content of each sample after suitable dilutions was assayed by using UV-vis spectrophotometer (Hitachi U-2900) at λmax of 218 nm. The mean values were plotted as percentage cumulative drug release against time. The mechanism of release was determined by fitting the release data to the various kinetic equations, and finding the R2 values of the release profile corresponding to each model.

III. Results

A. % Drug Entrapment efficiency (DEE)

The %DEE of cimetidine microsphere was within the range between 78.21%(Batch C3) and 91.12% (Batch C7) (Table 2). The variation in the concentration of hydroxy propyl methyl cellulose and Ethyl cellulose had a significant effect on the entrapment of Cimetidine Microsphere. Drug Entrapment Efficiency was increased with increasing polymer concentration in the microsphere. Among the different drug to polymer ratios investigated, 1:3 drug- polymer ratios had the significant capacity for drug encapsulation.

B. Morphology

Shape, size and surface morphology of the cimetidine microspheres were examined by using FE-SEM (Figure 3). Dried microspheres were mounted on metal stubs with double side tape. Metal stub was examined under FE-SEM(HITACHI S4800). The results we found by FE-SEM photographs that the microspheres were spherical in shape with a smooth surface.

C. Fourier Transform Infrared (FTIR) spectroscopy study

Pure form of Polymers, drug and optimized formulations were characterized by FTIR spectroscopy and results found that there were no possible interaction between drug and polymer (Figure-1).The FTIR spectrum of Cimetidine [Figure-1(B)] showed peaks corresponding to (C-H) bending at 1346.36 cm-1 and aromatic group (C=C) at 1501.63 cm-1, alkane group (C-C) at 1202.66 cm-1,Amine group (C-N) at 1281.74 cm-1, Imines (C=N) at 1630.90 cm-1, and (N-H) stretching at 3141.18 cm-1.

In the FTIR spectrum of microsphere containing cimetidine

[Figure-1(D)] various characteristic peaks of ethyl cellulose, HPMC and cimetidine were appeared without any significant shifting of these peaks. In short, the cimetidine microspheres had significant characters of cimetidine drug in the FTIR spectrum, suggesting, there were no interaction between the cimetidine drug and the polymers (HPMC and Ethyl Cellulose) which is used in formulation.

D. X-ray diffraction (XRD)

XRD was done for pure drug, polymers and optimized formulations. XRD patterns of pure cimetidine have given sharp peaks at 2θ-scattered angles of 7, 15, 18, 20 and 23.5; these peaks were indicating the crystalline nature of drug [Figure-2(B)]. These drug crystalline peaks were decreased in the Cimetidine microsphere [Figure-2(D)]. This indicates that the drug was not in crystalline form after entrapment. Intensities of drug peaks were also decreased in the microsphere formulation. This reduced intensity indicates the decreased crystallinity of drug.

E. Buoyancy %

The buoyancy percentage for all batches showed more than 70%, which was studied for 12 hr. Average buoyancy in the percentage, was found to be 70.8 % to 83.5 %. The highest percentage was obtained with formulation C9. There was increase in the buoyancy % with increasing the polymer concentration.

F. In Vitro dissolution Study

The CM Microspheres formulated as per Table 1 and they have been investigated for the % cumulative release of drug in 0.01N HCl. The CM Microspheres were incorporated into the 0.01N HCl for 12 hrs. The release of CM from microspheres in Batch (C1) was about 94.34% within 12hr (Figure-4). The Batch C1 contains low concentration of the polymers. The rate and extent of drug release from prepared microspheres significantly decreased with an increase in polymer concentration. In case of Batch C8 &C9, they show very slow release of CM (75.3% & 71.2% within 12 hr. respectively).The in vitro drug release data from all batches of CM Microsphere were evaluated kinetically using various mathematical models like zero-order, first-order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell, models. The interpretation of data was based on the value of the regression coefficients. The drug release showed the highest regression coefficient values for higuchi model.

IV. Discussion

Different formulation of cimetidine microspheres were carried out by using solvent evaporation technique (O/O emulsion) for Gastro retentive drug delivery system. FTIR study proved that there were no interaction between the drug (CM) and thepolymers used (HPMC and Ethyl Cellulose). XRD study revealed the crystallinity of drugand formulation. FE-SEM study revealsthat, the morphology of microsphere formulation shows more spherical and smooth surface with increase in polymer concentration. The mean particle size of the microspheres increased with increasing polymer concentration and was in the range 82 ± 1.41µm to 122 ± 1.87 µm. Cimetidine microspheres floated more than 70% for 12 hours.

The drug entrapment efficiency (DEE) of microsphere increases (from 78.21% to 91.12%)with increase in polymer concentration. In vitro study obtained from formulated floating microspheres of Cimetidine shown excellent floatability, good buoyancy and prolonged drug release pattern with highest regression coefficient values for higuchi model.

V. Conclusions

This work shows that it is possible to encapsulate Cimetidine in rate controlling polymers like HPMC and Ethyl cellulose, by using solvent evaporation technique. In vitrostudy shown good buoyancy, entrapment efficiency as well as decrease in dosing frequency.The release kinetics followed the Higuchi Model.

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TABLE I
EXPERIMENTAL BATCHES OF CIMETIDINE MICROSPHERE

Sr.No.	Formulation code	Drug (mg)	Polymer		Stirring rate
			HPMC	Ethyl Cellulose	
1	C_1	200	100	100	700
2	C_2	200	100	100	800
3	C_3	200	100	100	1000
4	C_4	200	200	200	700
5	C_5	200	200	200	800
6	C_6	200	200	200	1000
7	C_7	200	300	300	700
8	C_8	200	300	300	800
9	C_9	200	300	300	1000

TABLE II
PARTICLE SIZE, ENCAPSULATION EFFICIENCY AND IN VITRO BUOYANCY OF MICROSPHERE

Sr. No.	Formulation code	Particle size	Encapsulation Efficiency (%)	Buoyancy (%)
1	C_1	113 ± 1.87	84.12 ± 0.70	70.8 ± 0.70
2	C_2	91 ± 1.87	81 ± 1.41	72.1 ± 0.70
3	C_3	82 ± 1.41	78.21±0.70	74.5 ± 0.70
4	C_4	116 ± 1.87	88.13 ± 1.41	75.5 ± 0.35
5	C_5	102 ± 0.70	85 ± 1.41	78.4 ± 0.70
6	C_6	87 ± 2.12	80.56 ± 1.41	80.5 ± 0.70
7	C_7	122 ± 1.87	91.12 ± 1.87	76.5 ± 0.70
8	C_8	108 ± 0.70	87 ± 1.87	79.7 ± 0.35
9	C_9	95 ± 1.41	85.45 ± 0.70	83.5 ± 0.70

TABLE III
CUMULATIVE PERCENTAGE DRUG RELEASE PROFILE OF CIMETIDINE FROM FORMULATION C1-C9

Sr.No.	Time (hours)	Cumulative Percentage drug Release								
		C1	C2	C3	C4	C5	C6	C7	C8	C9
0	0	0	0	0	0	0	0	0	0	0
1	1	25.4	24.3	21.3	20.5	20.06	18.2	18.4	14.2	9.5
2	2	39.91	38.3	35.4	32.5	29.3	25.8	24.7	20.5	15.3
3	3	49.87	47.6	44.3	41.2	39.5	36.4	32.9	26.7	21.4
4	4	54.35	52.3	49.6	46.5	44.3	41.2	38.6	34.5	28.7
5	5	63.21	61.21	58.3	55.3	52.4	49.2	45.3	41.2	36.5
6	6	69.81	66.76	63.4	60.2	57.6	54.1	50.4	46.9	42.6
7	7	76.51	74.41	71.2	68.4	65.4	62.4	59.4	54.3	49.7
8	8	81.48	79.52	76.51	73.5	70.3	67.9	63.5	58.5	54.5
9	9	84.21	82.3	80.23	78.91	75.3	72.3	68.5	64.7	59.6
10	10	87.41	85.43	83.41	81.23	78.5	75.4	72.3	68.8	64.3
11	11	92.56	89.5	87.61	84.41	82.24	79.6	75.2	71.7	69.2
12	12	94.34	91.24	89.67	87.23	85.34	83.45	79.6	75.3	72.1

TABLE IV
IN VITRO DRUG RELEASE KINETICS FROM FORMULATION C1-C9

Sr. No.	Formulation Code	Drug Release Kinetic models (R^2Values)				
		Zero Order	First Order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas
1	C1	0.922	0.981	0.996	0.971	0.897
2	C2	0.923	0.984	0.996	0.970	0.898
3	C3	0.936	0.987	0.994	0.975	0.916
4	C4	0.943	0.987	0.993	0.977	0.915
5	C5	0.948	0.988	0.992	0.978	0.913
6	C6	0.958	0.989	0.987	0.982	0.920
7	C7	0.953	0.985	0.991	0.977	0.903
8	C8	0.981	0.994	0.969	0.992	0.924
9	C9	0.996	0.992	0.927	0.995	0.936

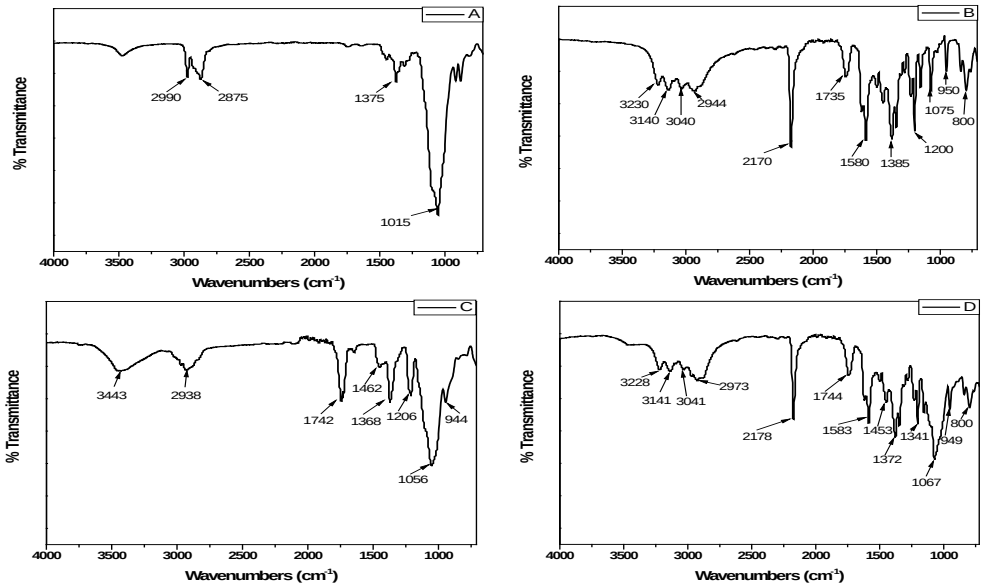

Fig. 1 FTIR spectra of Ethyl Cellulose (A), Cimetidine (B), Hydroxy propyl methyl Cellulose(C) and Cimetidine Microsphere (D).

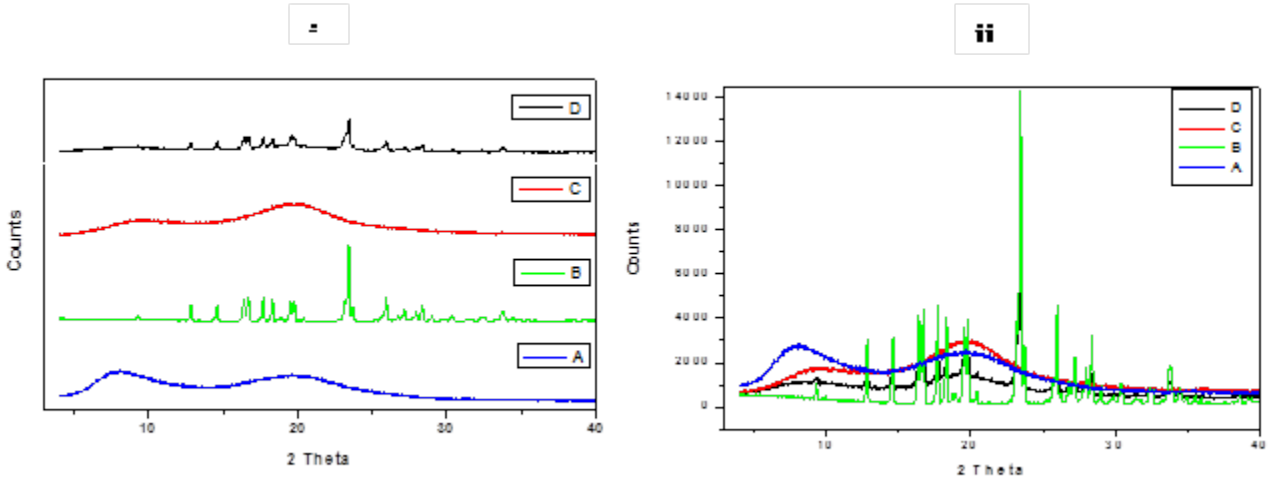

Fig. 2: i) X-Ray Powder Diffraction patterns. A) Ethyl Cellulose, B) Cimetidine, C) Hydroxy propyl methyl cellulose, D) CM Microsphere. ii) Overlay graph of Figure 2 (i).

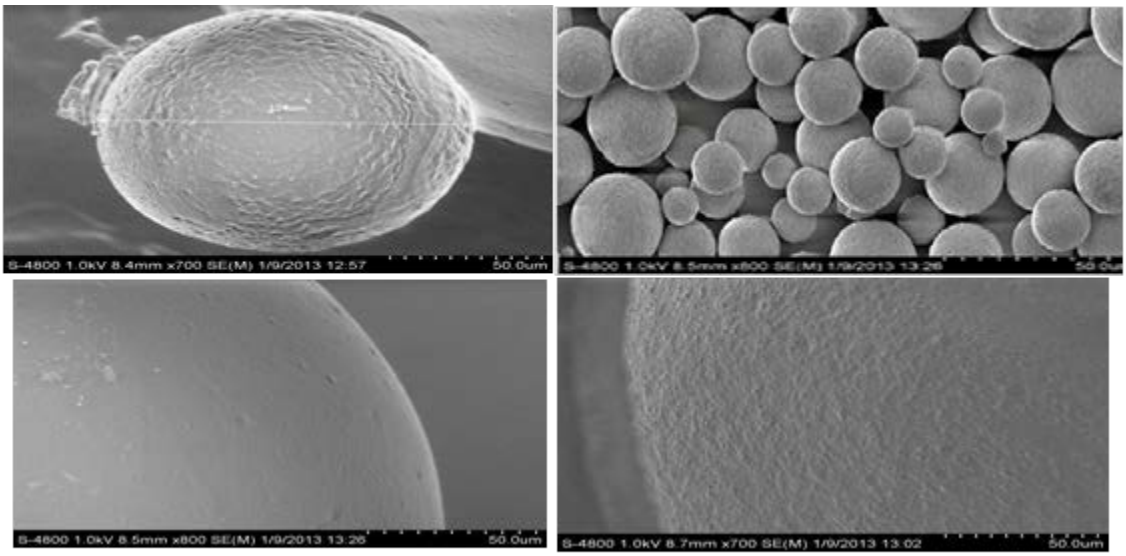

Fig. 3 FE-SEM images of CM Microsphere A) and B) while C) and D) are surface morphology of the same sample

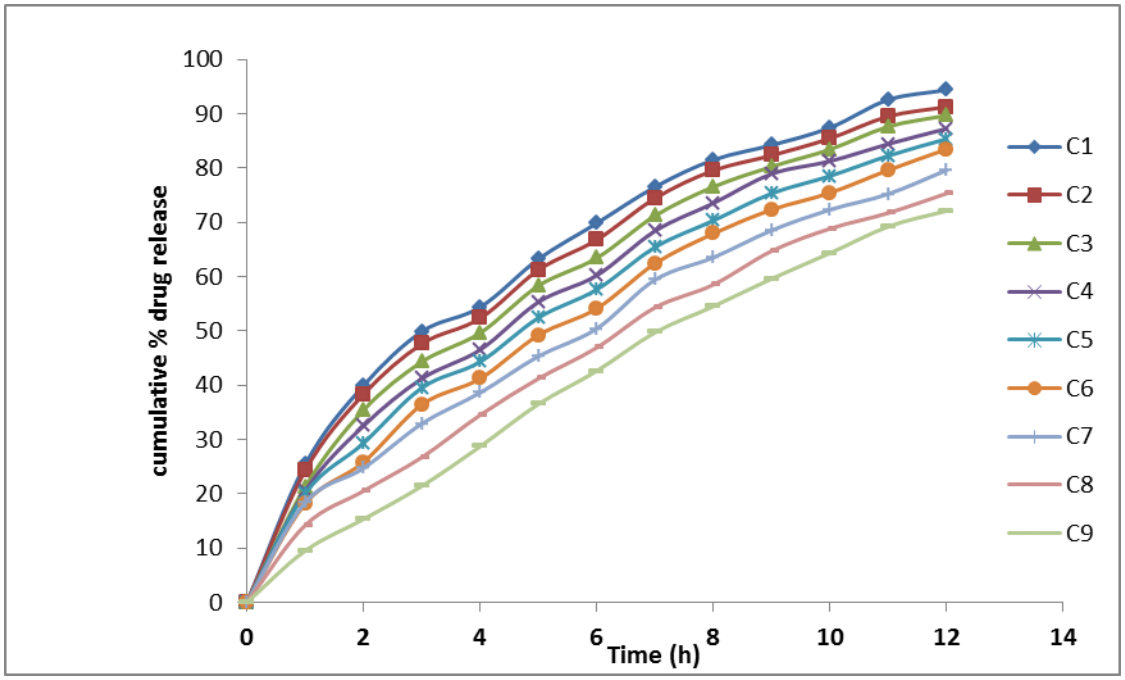

Fig. 4 In vitro drug release of different CM Microsphere Formulation