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# Floating Microcarriers of an Antidiabetic Drug : Preparation and its *In-Vitro* Evaluation

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**Abstract**

The purpose of present research work was to prepare floating microcarriers of Metformin hydrochloride. A multiple-unit-type oral floating dosage form of Metformin hydrochloride was developed to prolong gastric residence time and increase drug bioavailability with decreased GI side effects. The floating microcarriers were prepared by ionotropic gelation method dispersing Metformin hydrochloride with calcium carbonate and sodium bicarbonate separately into a mixture of anionic sodium alginate, as primary polymer with oppositely charged counter ion polymer namely HPMCK4M, EC and mixture of both the polymer into a solution of calcium chloride containing acetic acid. The prepared microcarriers were evaluated for micromeritic properties, % yield, drug loading, drug entrapment efficiency, particle size and shape, buoyancy and *in vitro* drug release studies. The formulations were optimized for different weight ratios of gas-forming agent and combination of polymer. The prepared microcarriers were in range of 447.1 to 801.8 µm. The results of these studies indicate that $CaCO_3$ is superior to $NaHCO_3$ as a gas forming agent in polymer combination microcarriers.

**Keywords:** Metformin hydrochloride, Floating dosage form, Calcium alginate, Microcarriers, Gastric residence time, Bioavailability, Gas forming agent

## 1. Introduction:

Despite tremendous advancement in the drug delivery system, oral route remains the preferred route for the administration of therapeutic agents and because of low cost therapy and ease of administration leads to higher levels of patient compliance. Conventional oral dosage forms such as tablets and capsules, provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. The design of oral controlled drug delivery system should be primarily aimed to achieve more predictable and increased bioavailability. An incomplete release of the drug and shorter residence time of the dosage forms in the upper GIT, which is a prominent site for the absorption of many drugs, leads to decreased bioavailability [1, 2].

Metformin hydrochloride is an Antihyperglycemic agent widely used in the management of NIDDM. Absolute oral bioavailability of Metformin hydrochloride is 50-60% due to its site-specific absorption limitations. It is safe drug and it has a half-life of 2 hrs. It is not absorbed completely and gives low bioavailability problem. Almost 80-100% of the drug is excreted unchanged. The total daily requirement of Metformin hydrochloride is 1.5-3g/day. Henceforth, there being high incidence of GI side effects and toxicity [3]. Therefore, there are continued efforts to improve the pharmaceutical formulation of metformin hydrochloride in order to achieve an optimal therapy. Bioavailability of the drug has been found to be reduced further with sustained release dosage forms, probably due to the fact that passage of the sustained release single unit dosage forms from absorption region of the drug is faster than its release and most of the drug released at the colon where metformin hydrochloride is poorly absorbed[4]. Sustained release formulation suitable for metformin hydrochloride, therefore, should be a gastro-retentive by using effervescent agent in the combination of different permeability polymers [5].

In this paper the floating drug delivery system employed separate formulations for $CaCO_3$ and $NaHCO_3$ as a gas-forming agent dispersed separately in an alginate matrix. Alginate is a polysaccharide which contains varying amounts of 1, 4-linked -D-mannuronic acid, Lguluronic acid residues. As biocompatible and biodegradable biopolymer, it forms a bio-adhesive and stable gel with divalent cations such as $Ca^{2+}$, $Sr^{2+}$, and $Ba^{2+}$. These properties have enabled widespread use for sustained release of drugs. Since alginate microcarriers are stable in acidic media and easily depredated in alkaline media [6].

The objective of present investigation is to prepare a sustained release floating microcarriers of Metformin hydrochloride using polymers of different permeability

characteristics. Anionic Sodium alginate, as primary polymer with oppositely charged counter ion polymer namely Hydroxy propyl methyl cellulose, Ethyl cellulose (10 cps) together with gas forming agent $CaCO_3$ and $NaHCO_3$ in separate batches. The effects of $CO_2$ gas-formation on the physical properties, morphology, micromeritic properties, floating ability, drug loading, drug entrapment and release rate of alginate microcarriers were examined. The comparative efficacy of $CaCO_3$ and $NaHCO_3$ as gas forming agents and polymer for FDDS was also evaluated.

## 2. Materials and methods:

### 2.1 Material

Metformin hydrochloride was a gift sample from Arti drugs, Baroda. Hydroxy propyl methyl cellulose K4M gifted from Unichem laboratories, Mumbai, Ethyl cellulose (10 cps) gifted from JCPL, Jalgaon, Sodium alginate, calcium carbonate and sodium bicarbonate were purchased from S.D fine laboratories. All other reagents used were analytical grade.

### 2.2 Method

A solution was prepared by dissolving 0.5 g drug in 5 ml distilled water. The solution was dispersed in 30 ml alginate solution (2%w/v) containing polymer (alginate: polymer=6:1, w/w). Then, gas-forming agent $NaHCO_3$ and $CaCO_3$ was separately added to the solution with levels from 0:1 to 1:1 (gas-forming agent/alginate, w/w). The resulting solution was dropped through a syringe into 5% (w/v) $CaCl_2$ solution containing 10% (v/v) acetic acid. The solution containing suspended microcarriers was kept for 1.5hr, to improves the mechanical strength and allowed to produce gas. Since the carbonate salts are insoluble at neutral pH, the divalent ions were only released in the presence of acid, thereby preventing premature gelation.The fully formed microcarriers were collected, washed with ethanol and distilled water, and subsequently air dried [7, 8]. Composition of formulations are shown in table no. 1.

$CaCl_2$ acted as a counter ion. The droplets instantaneously formed gelled spherical microcarriers due to cross linking of calcium ions with sodium ions of alginates.

Sodium alginate and $CaCl_2$ react to form calcium alginate gel, which in presence of acetic acid forms divalent ions of gas forming agent. Acetic acid provides spherical shape to the formulation.

### 2.3 Characterization of floating microcarriers

#### 2.3.1 Compatibility study of drug and polymer

**A. Fourier Transform- Infrared spectroscopic analysis (FT-IR)**

Drug polymer interactions were studied by FT-IR spectroscopy. IR spectrum of drug, physical mixture and drug loaded microcarriers were recorded in the stretching frequency range 450-4000 $cm^{-1}$. The samples were prepared by KBr pellet technique.

**B. Differential Scanning Calorimetry (DSC)**

Differential Scanning Calorimetry (DSC) was performed using Mettler Toledo DSC 822e, India, to study the thermal behavior of drug, blank and drug loaded microcarriers. The samples were heated in sealed aluminium pans under nitrogen flow (10 ml/min) at scanning rate 10 $^0$C/min.

#### 2.3.2. Micromeritic properties [9]

The flow properties were investigated by measuring angle of repose of drug loaded microcarriers using fixed base cone method. The bulk and tapped densities were measured to its packability. Carr's index and Hausner's ratio were calculated. Each experiment carried out in triplicate

#### 2.3.3. Particle size analysis

The particle size of drug loaded formulations were measured by an optical microscope fitted with calibrated ocular and stage micrometer and particle size distribution was calculated. 50 particles in five different fields were examined. Each experiment carried out in triplicate [10].

#### 2.3.4. Scanning electron microscopy analysis (SEM)

Morphological examination of the surface and internal structure of the dried microcarriers was performed by using a Scanning electron microscope (model-6360 $A^0$, Jeol, Japan) using platinum sputter technique. The working distance is 50 micrometer. Photographs were taken with in a range of 30 -300 magnifications.

**Table 1:** Composition of Microcarriers

| Formulation No. | Drug (mg) | Sodium Alginate (%) | HPMC K4M* (%) | EC* (%) | $CaCO_3$** (w/w) | $NaHCO_3$*** (w/w) |
|---|---|---|---|---|---|---|
| H1 | 500 | 6 | 1 | - | 0:1 | - |
| H2 | 500 | 6 | 1 | - | 0.25:1 | - |
| H3 | 500 | 6 | 1 | - | 0.50:1 | - |
| H4 | 500 | 6 | 1 | - | 0.75:1 | - |
| H5 | 500 | 6 | 1 | - | 1:1 | - |
| H6 | 500 | 6 | 1 | - | - | 0.25:1 |
| H7 | 500 | 6 | 1 | - | - | 0.50:1 |
| H8 | 500 | 6 | 1 | - | - | 0.75:1 |
| H9 | 500 | 6 | 1 | - | - | 1:1 |
| E1 | 500 | 6 | - | 1 | 0:1 | - |
| E2 | 500 | 6 | - | 1 | 0.25:1 | - |
| E3 | 500 | 6 | - | 1 | 0.50:1 | - |
| E4 | 500 | 6 | - | 1 | 0.75:1 | - |
| E5 | 500 | 6 | - | 1 | 1:1 | - |
| E6 | 500 | 6 | - | 1 | - | 0.25:1 |
| E7 | 500 | 6 | - | 1 | - | 0.50:1 |
| E8 | 500 | 6 | - | 1 | - | 0.75:1 |
| E9 | 500 | 6 | - | 1 | - | 1:1 |
| M1 | 500 | 6 | 0.5 | 0.5 | 0:1 | - |
| M2 | 500 | 6 | 0.5 | 0.5 | 0.25:1 | - |
| M3 | 500 | 6 | 0.5 | 0.5 | 0.50:1 | - |
| M4 | 500 | 6 | 0.5 | 0.5 | 0.75:1 | - |
| M5 | 500 | 6 | 0.5 | 0.5 | 1:1 | - |

HPMC K4M-Hydroxyl Propyl methyl Cellulose, *EC-Ethyl Cellulose, *$CaCO_3$ – Calcium carbonate, *$NaHCO_3$ - Sodium bicarbonate, ** ($CaCO_3$: alginate) (w/w) , *** ($NaHCO_3$:alginte) (w/w).

**2.3.5. Percentage Yield**

Percentage yield depends on the ratio of polymer and gas forming agent, can be calculated by the following formula:

$$\text{Production Yield} = \frac{\text{Practical Yield (Microcarriers)}}{\text{Theoretical Yield (Polymer + Drug)}} \times 100 \quad (1)$$

**2.3.6. Drug loading and entrapment efficiency**

Drug loading increases as the concentration of polymer concentration can be calculated from the equation no. 2.For entrapment efficiency microcarriers (50 mg) were crushed in a glass mortar-pestle and the powdered microcarriers were suspended in 50 ml of distilled water and sonicated for one hr. The solution was filtered to separate shell fragments and make suitable dilutions and the filtrate was analyzed spectrophotometrically for the drug content[11]. Entrapment efficiency can be calculated by equation no. 3

$$\text{Drug loading \%} = \frac{\text{Weight of drug added (mg)} \times 100}{\text{Weighed of quantity of Microcarriers}} \quad (2)$$

$$\text{\% Incorporating Efficiency} = \frac{\text{Actual wt.}}{\text{Theoretical wt.}} \times 100$$

**2.3.7. Percentage of floating behavior**

50 mg of the floating microcarriers were placed in 50 ml beaker. 30 ml of 0.1 N HCl were added. The beakers were shaken horizontally in a water bath at 37±0.1°C by rotary shaker at 100 rpm. Floated particles were collected at 1, 2, 4 and 6 h and dried in a desiccators till constant weight.

**Table 2:** Micromeritic properties of floating microcarriers

| Formulation code | Angle of repose (θ) | Bulk Density (g/ml) | Tapped Density (g/ml) | Carr's Index (%) | Hausner's ratio |
|---|---|---|---|---|---|
| H1 | 22.41±0.98 | 0.463±0.02 | 0.588±0.03 | 14.46±0.91 | 1.17±0.03 |
| H2 | 20.56±0.92 | 0.562±0.01 | 0.649±0.02 | 16.42±0.97 | 1.18±0.05 |
| H3 | 21.42±0.74 | 0.653±0.03 | 0.735±0.04 | 17.72±1.55 | 1.14±0.03 |
| H4 | 21.42±0.7 | 0.693±0.01 | 0.851±0.04 | 18.31±0.80 | 1.21±0.03 |
| H5 | 21.64±1.04 | 0.749±0.04 | 0.864±0.04 | 15.58±1.29 | 1.2±0.01 |
| H6 | 22.41±0.98 | 0.463±0.02 | 0.588±0.03 | 14.46±0.91 | 1.17±0.03 |
| H7 | 20.56±0.92 | 0.562±0.01 | 0.649±0.02 | 16.42±0.97 | 1.18±0.05 |
| H8 | 21.42±0.74 | 0.653±0.03 | 0.735±0.04 | 17.72±1.55 | 1.14±0.03 |
| H9 | 21.42±0.7 | 0.693±0.01 | 0.851±0.04 | 18.31±0.80 | 1.21±0.03 |
| E1 | 22.50±1.04 | 0.669±0.03 | 0.598±0.06 | 20.45±0.69 | 1.18±0.03 |
| E2 | 21.98±0.86 | 0.543±0.03 | 0.758±0.03 | 18.60±0.88 | 1.14±0.02 |
| E3 | 21.54±1.25 | 0.571±0.05 | 0.802±0.04 | 20.61±0.91 | 1.17±0.02 |
| E4 | 22.83±1.56 | 0.744±0.04 | 0.652±0.04 | 14.51±1.30 | 1.13±0.02 |
| E5 | 23.43±1.09 | 0.755±0.02 | 0.581±0.05 | 13.67±1.05 | 1.22±0.02 |
| E6 | 25.68±0.38 | 0.555±0.03 | 0.464±0.17 | 13.08±0.29 | 1.30±0.17 |
| E7 | 23.12±0.28 | 0.657±0.01 | 0.647±0.02 | 13.29±0.73 | 1.17±0.03 |
| E8 | 27.37±0.38 | 0.749±0.03 | 0.656±0.03 | 14.98±0.78 | 1.13±0.01 |
| E9 | 24.13±0.59 | 0.642±0.02 | 0.674±0.05 | 17.26±0.58 | 1.15±0.01 |
| M1 | 22.61±0.54 | 0.718±0.06 | 0.632±0.04 | 14.33±1.30 | 1.16±0.02 |
| M2 | 20.85±0.66 | 0.850±0.03 | 0.752±0.03 | 13.31±0.35 | 1.16±0.03 |
| M3 | 21.81±1.52 | 0.624±0.06 | 0.593±0.05 | 12.55±0.39 | 1.15±0.04 |
| M4 | 20.66±1.11 | 0.587±0.02 | 0.750±0.04 | 15.66±0.40 | 1.19±0.05 |
| M5 | 21.81±0.68 | 0.842±0.03 | 0.771±0.05 | 16.50±0.38 | 1.16±0.02 |

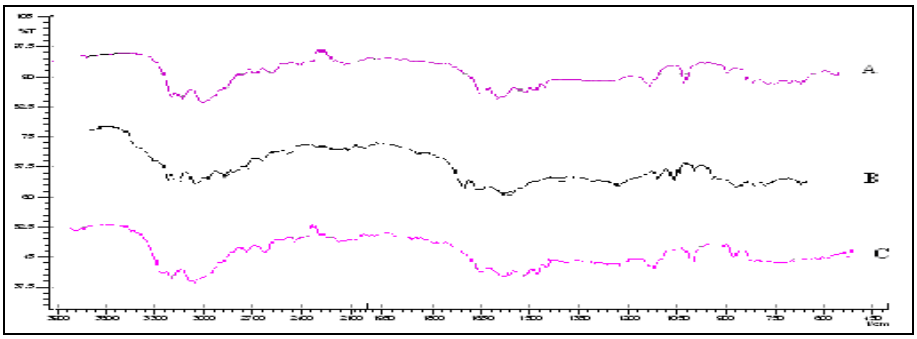


**Figure 1:** Comparative study of FTIR spectra (A) pure drug, (B) physical mixture of optimized formulation, (C) formulation (M5).

The percentage of floating microcarriers was calculated [12].

**2.3.8. *In-Vitro* drug release studies**

The drug release was studied using USP XXVII paddle apparatus (Electrolab, TDT-08L, India) at 37 ± 0.5$^0$C and at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. 10 ml of the sample solution was withdrawn at pre determined time intervals, filtered, diluted suitably and analyzed spectrophotometrically at 232nm. Equal amount of the fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug dissolved at different time intervals was calculated using the Lambert-Beer's equation. The result was obtained in triplicate and the average value reported [13].

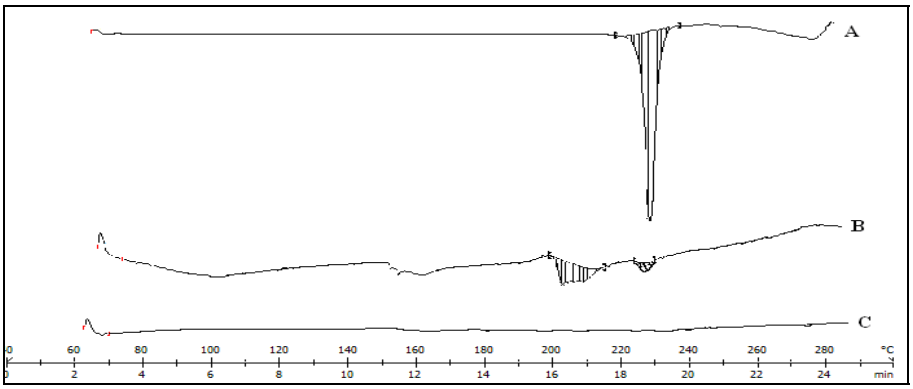


**Figure 2:** Comparative study of DSC spectra (A) pure drug, (B) physical mixture of optimized formulation, (C) formulation (M5).

**2.3.9. Kinetics of drug release mechanism**

In order to understand the mechanism and kinetics of drug release, the drug release data of the *in-vitro* dissolution study was analyzed with various kinetic equations like zero order (% release v/s time), first order (Log% retained v/s time), Hixon crowell, Matrix and Peppas equation. Coefficient of correlation (r) values were calculated for the linear curves obtained by regression analysis of the above plots [14].

## 3. Result and discussion

The present study was aimed not only to improve the buoyancy of microcarriers, but also to release the drug in acidic pH in sustained fashion by making a density of formulation lower than the gastric contents, using mixture different permeability polymers in addition to gas forming agent.

### 3.1 Characterization of floating microcarriers

### 3.1.1Interaction studies of drug and polymer

**FTIR spectroscopy**

IR spectra were recorded for metformin hydrochloride, physical mixture and drug loaded microcarriers. Pure metformin hydrochloride spectra showed sharp characteristic peaks at 3367.34, 3298.05, 3169.04, 2977.89,1627,1222, 1064.63, 636.47$cm^{-1.}$ Comparative study of FTIR graph was shown in figure no.1. FTIR characteristic peaks of drug appear in the spectra of physical mixture at the same wave number indicating no modification or interaction between the drug and the polymer while disappears of some peaks in drug loaded microspheres which confirms encapsulation of drug into the polymer.

**Differential scanning calorimetry**

The thermogram of metformin hydrochloride exhibited sharp endothermic peak at $230^0$C indicated melting point which was reported in literature. DSC studies shows there was no interaction between drug and polymer. Further, the decrease in sharpness of Metformin HCl endothermic peak in physical mixture may be due to the conversion of crystalline to amorphous form. The peak of drug didn't appear in the thermogram of formulation indicate that the drug was uniformly dispersed at molecular level. The DSC thermograms were shown in figure no.2.

### 3.1.2Micromeritic properties

Micromeritic properties like angle of repose, bulk density and tapped density, Carr's index and Hausner's ratio of all microcarriers confirms better flow and packaging properties ,represented in Table no. 2.

### 3.1.3 Particle size analysis

Average particle size of microcarriers depend on both gas-forming agents, significantly increased the size of the beads over the control (no gas-forming agent). In the particle size observed that when $NaHCO_3$ was added to the alginate solution at a 1:1 ratio, spherical microcarriers could not be formed because released $CO_2$ gas burst the microcarriers before the wall was sufficiently hardened.

### 3.1.4 Scanning electron microscopy (SEM)

The optimized formulation loaded microcarriers were analyzed by SEM for

**Table 3:** Evaluation parameters of formulations

| Formulation Code | % Yield* | % Loading | % Entrapment | Average particle size(µm) | Shape of particle |
|---|---|---|---|---|---|
| H1 | 70.03±1.56 | 59.33±1.33 | 95.87±1.44 | 447.1±6.75 | Spherical |
| H2 | 54.63±1.16 | 67.79±1.45 | 92.03±2.19 | 486.5±8.71 | Spherical |
| H3 | 52.10±0.69 | 63.97±0.85 | 85.79±1.44 | 533.3±10.3 | Spherical |
| H4 | 64.01±0.91 | 47.33±0.68 | 72.84±2.88 | 556.0±6.93 | Slightly irregular |
| H5 | 58.36±1.71 | 47.61±1.38 | 64.88±1.66 | 562.9±5.75 | Slightly irregular |
| H6 | 80.34±1.93 | 46.10±1.11 | 65.83±1.59 | 588.9±3.63 | Slightly irregular |
| H7 | 68.81±2.76 | 48.48±1.92 | 60.98±1.53 | 604.5±7.22 | Slightly irregular |
| H8 | 68.11±5.35 | 44.66±3.61 | 50.76±1.17 | 612.4±2.49 | Irregular |
| H9 | 64.44±3.26 | 43.17±2.20 | 41.06±1.53 | 618.6±2.90 | irregular |
| E1 | 86.75±2.19 | 44.76±1.20 | 86.75±2.19 | 693.4±8.39 | Spherical |
| E2 | 80.51±2.19 | 45.48±0.56 | 80.51±2.19 | 708.5±2.49 | Spherical |
| E3 | 66.60±2.19 | 44.43±1.63 | 66.6±2.19 | 718.4±2.58 | Slightly irregular |
| E4 | 52.67±2.57 | 38.45±1.41 | 52.67±2.57 | 731.4±4.46 | Irregular |
| E5 | 48.36±2.87 | 35.55±1.77 | 48.36±2.87 | 741.2±4.97 | Irregular |
| E6 | 84.81±3.45 | 43.71±1.79 | 60.72±1.17 | 779.1±3.40 | Slightly irregular |
| E7 | 79.93±3.80 | 41.76±1.99 | 51.28±1.17 | 783.8±3.67 | Slightly irregular |
| E8 | 82.21±4.19 | 36.91±1.89 | 43.10±1.17 | 790.3±5.02 | Irregular |
| E9 | 81.05±3.48 | 34.30±1.5 | 37.75±1.94 | 801.8±5.05 | irregular |
| M1 | 98.59±0.63 | 42.26±0.27 | 94.91±0.83 | 626.4±5.99 | Spherical |
| M2 | 76.56±1.28 | 48.39±0.80 | 82.43±2.19 | 638.2±5.10 | Spherical |
| M3 | 84.18±1.60 | 39.61±0.76 | 77.64±2.19 | 650.2±5.33 | Spherical |
| M4 | 77.78±1.85 | 40.02±1.38 | 68.52±1.44 | 662.5±8.80 | Spherical |
| M5 | 77.95±0.91 | 35.78±0.41 | 64.20±1.44 | 687.0±7.89 | Slightly irregular |

**Table 4. :** *In vitro* release kinetic parameter of drug loaded microcarriers

| Sr.No. | Zero Order ($r^2$) | 1st Order ($r^2$) | Matrix ($r^2$) | Peppas | | Hix-Crowel ($r^2$) |
|---|---|---|---|---|---|---|
| | | | | ($r^2$) | ( n) | |
| M1 | 0.9125 | 0.9715 | 0.9819 | 0.9644 | 0.4782 | 0.9578 |
| M2 | 0.4956 | 0.8517 | 0.9551 | 0.9763 | 0.3112 | 0.7759 |
| M3 | 0.6891 | 0.9372 | 0.9676 | 0.9443 | 0.3295 | 0.8920 |
| M4 | 0.8711 | 0.9692 | 0.9920 | 0.9925 | 0.4855 | 0.9724 |
| M5 | 0.8093 | 0.9147 | 0.9667 | 0.9332 | 0.3641 | 0.9422 |

studying particle shape and surface structure as shown in figure 3.

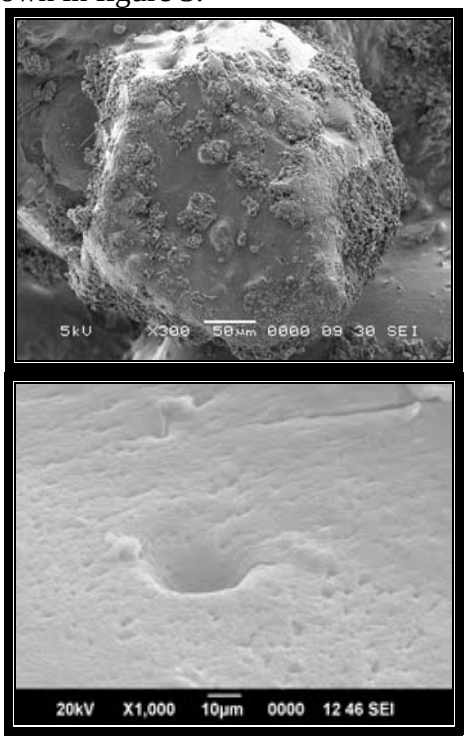


**Figure 3:** Scanning Electron Micrographs of metformin hydrochloride microcarriers.

Scanning electron microscopy revealed that due to presence of $Ca^{2+}$ ions homogeneous microcarriers were formed. Small projection were occurs due to ionotropic gelation method. It shows the pore formation on the surface due to gas forming agent. Surface morphology shows rough surface area due to presence of drug.

**3.1.5 Percentage yield**

Yield of production was found in the range between 48.36 to 98.59 % (Table No.3). It is observed that increasing the polymer and gas forming agent in formulation significantly lowers the production yield, due to production of high viscous polymer dispersion which may lost during manufacturing process. The formulation H1, E1 and M1 (without gas forming agent) showed the high production yield as compare to formulation code H5, H9, E5, E9 and M5.

**3.1.6 Drug loading and incorporation efficiency**

Drug loading was in the range of 34.30 to 48.48%. Incorporation efficiency was high since it always exceeded 37.75 to 95.85% the drug entrapment efficiency was initially very low for metformin hydrochloride because it, being highly water soluble, diffuses out to calcium chloride solution at the time of encapsulation .A change in solvent system to acetic acid improved drug encapsulation. HPMCK4M shows better entrapment efficiency as compared to EC also $CaCO_3$ and $NaHCO_3$ affect on drug entrapment efficiency. Formulation M1 to M5 shows better entrapment efficiency .The formulations without gas forming agent shows the high entrapment efficiency as compared to with gas forming agent this is given table no. 3

**3.1.7 Floating behavior**

Without gas- forming agent microcarriers sink uniformly in medium. H3 to H5 shows floating behavior in the range of 9.70 to 34.96%. Floating behavior is directly related to the gas content in polymer matrix as shown in figure no.4. The formulation H6 to H9 shows the floating behavior in the range of 28.56 to 75.37% due to $NaHCO_3$.

Formulation E1 presence of low viscosity hydrophobic polymer it shows 21.36 % floating ability upto 24 hrs. Formulations E2 to E5 contain $CaCO_3$ shows floating behavior 33.65 to 70.16% upto 24 hrs. The formulation E6 to E9 shows the floating ability in the range of 47.08 to 85.59%. The formulation containing ethyl cellulose and $NaHCO_3$, low pore formation occur on the surface of the formulation so may remain floated for several hours given in figure 5.

The formulation M1 to M5 containing hydrophilic and hydrophobic polymer along with the $CaCO_3$ shows the excellent floating ability in the range of 11.44 to 94.72%.shown in figure no. 6.

**3.1.8. *In- vitro* drug release studies**

In order to investigate the release rate with hydrophilic polymer in presence of $CaCO_3$, the formulation H1 shows less drug release than other formulations. The formulation H6 to H9 could not control drug release rate due to $NaHCO_3$ and showed near about 100% drug release within a 9 to 14 hrs. Formulation H9 shows 100.71% drug release within 9 hr.while H6 shows 99.35 % drug release up to 14 hrs.

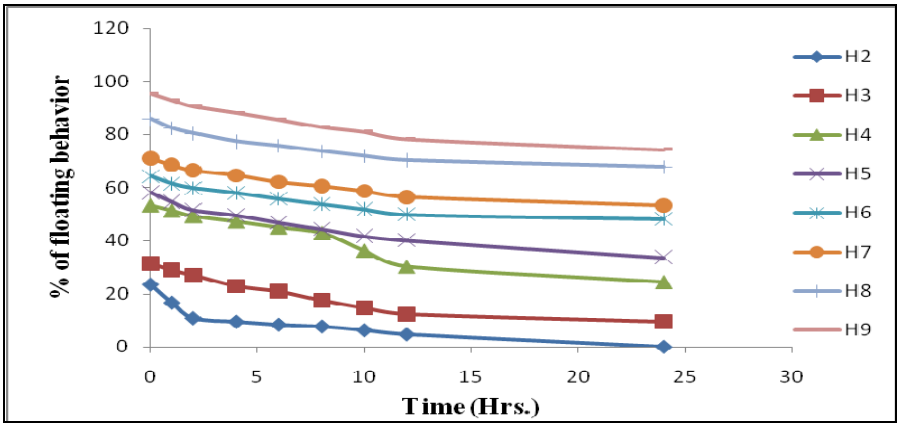


**Figure 4:** Floating behavior of H1 to H9

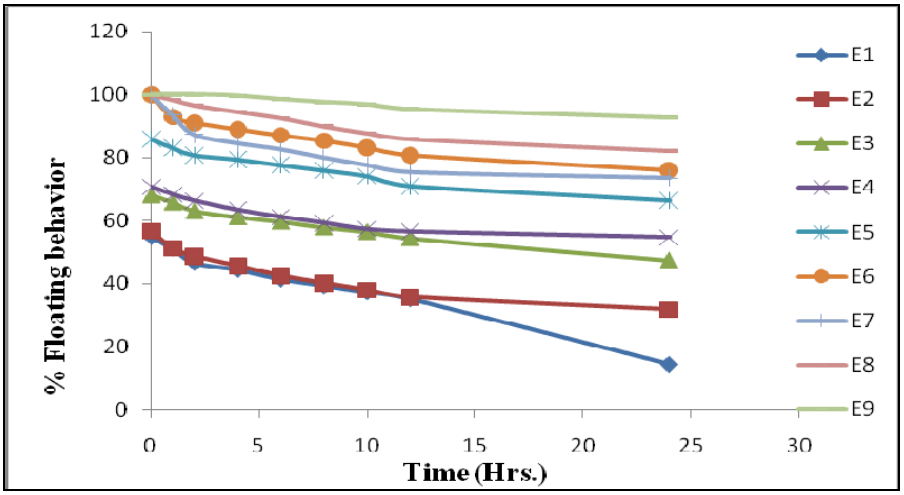


**Figure 5:** Floating behavior of formulation E1 to E9

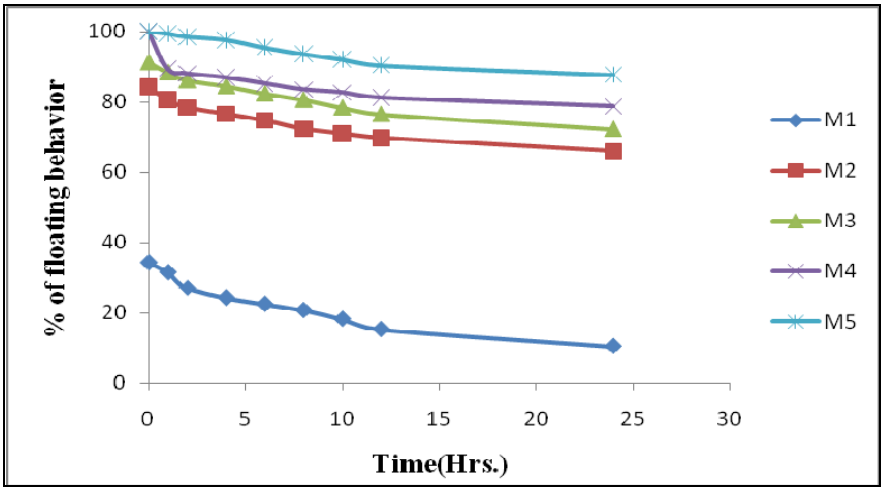


**Figure 6:** Floating behavior of formulation M1 to M6

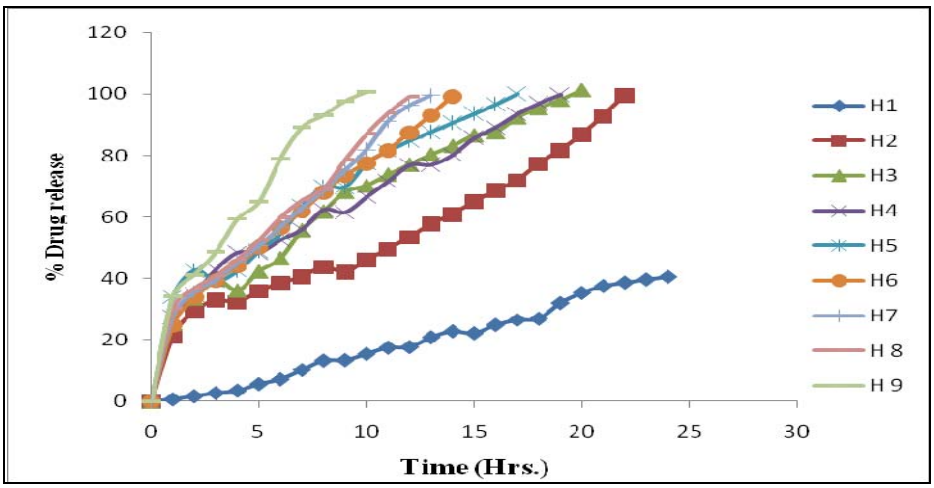


**Figure 7:** In- Vitro Release Data of formulation H1 to H9

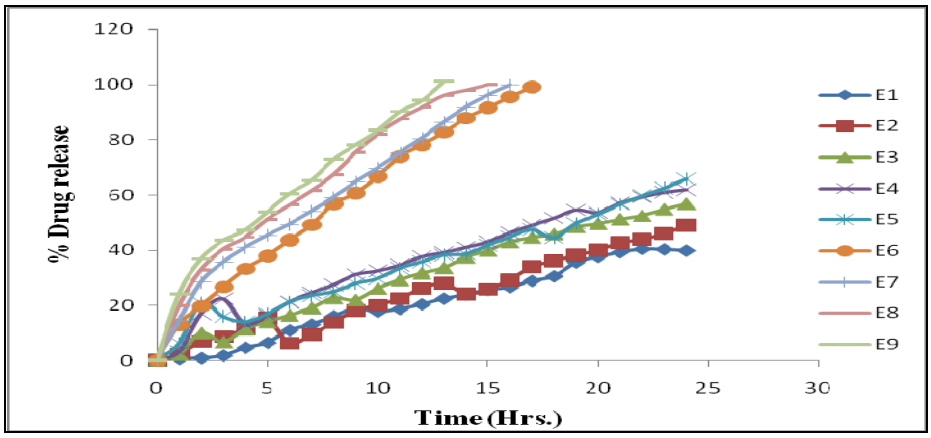


**Figure 8:** *In- Vitro* Release Data of formulation E1 to E9

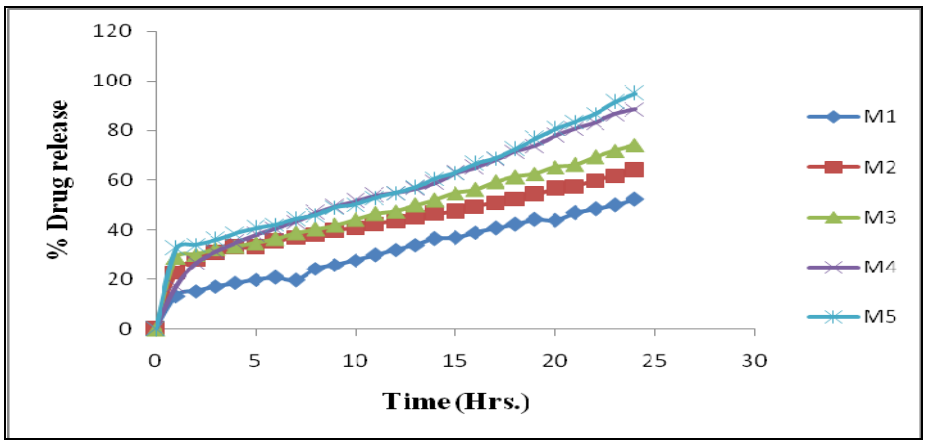


**Figure 9:** In -Vitro Release Data of formulation M1 to M5

Ethyl cellulose is hydrophobic in nature should lower water penetration in presence of $CaCO_3$ and provide effective drug release retardation when used in combination with hydrophilic polymer such as sodium alginate. The dissolution study of formulation E1 to E5 shows very slow release of drug within 24 hrs. in presence of $CaCO_3$. Formulation E2 to E5 shows increased drug release with increase concentration of the gas forming agent. It give drug concentration within 24 hrs was 49.07 to 65.89 %. This is in order to investigate the release rate with $NaHCO_3$, The formulation E6 releases drug upto 99.13 % within 17 hrs.

while formulation E9 release drug upto 99.17% within 13 hrs. It means no one formulation will give drug release upto 24 hrs. in the presence of high gas forming agent. Above all the batches does not gave satisfactory results. So combinations of both the polymers, hydrophilic and hydrophobic in presence of $CaCO_3$ were prepared. $NaHCO_3$ was not used because it releases the drug faster than the $CaCO_3$ with disturbing the structure of formulation.

Formulation M1 is without gas forming agent so it shows only 42.43% drug release within24 hrs.while M2 to M5 shows drug release in between 63.47 to 94.71% which is desirable for sustained release formulation. This is shown in figure no. 9

From dissolution it is conclude that CaCO3 is effective in sustained drug delivery system. HPMCK4M and sodium alginate shows more burst release effect in presence of gas forming agent while EC shows acts as a release retardant. The combination of polymers shows little burst effect occurred due to presence of drug on the microcarries gives drug release upto 24 hrs

### 3.1.9. Drug release kinetics

The *in vitro* dissolution data were analyzed by different kinetic models in order to find out the n- value, which describes the drug release mechanism. Table no.4 describes n values of each model.

The value of 'n' gives an indication of the release mechanism; when n = 1, the release rate is independent of time (zero-order) (case II transport), n = 0.5 for Fickian diffusion and when $0.5 < n < 1.0$, non-Fickian transport are implicated and when $n > 1.0$ in case II transport (relaxation controlled) was apparent. According to results obtained, the 'n' value Peppas equation was in range of 0.3112 to 0.3641 which suggest the drug release from mixture of polymers containing microcarriers were non fickian diffusion controlled.

## 4. Conclusion

Ionotropic gelation technique can successfully used for preparation of metformin hydrochloride microcarriers using different permeability polymer and gas forming agent. Various formulation variables such as concentration of gas forming agent, combination of polymer, calcium chloride concentration, cross linking time were used, which are influenced to the drug entrapment efficiency, particle size and shape, floating behavior, and *in-vitro* drug release. The FTIR and DSC studies did not reveal any significant drug interactions. From above all results we conclude that $CaCO_3$ is more suitable for sustained drug delivery system as compared to $NaHCO_3$. The formulation M5 shows the satisfactory results of evaluation parameters, it remains floated up to 24 hrs. shows 94% drug release within 24 hrs. it means this formulation is suitable for floating sustained drug delivery system.

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