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Preparation and Evaluation of Bioadhesive Microspheres Prepared by Ion Gelation Method and Effect of Variables on Quality of Microspheres

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ABSTRACT

Gastroretention is advisable for metformin hydrochloride due to its site specific absorption and low bioavailability (60%). Therefore, the attempts have been carried out in present study to formulate bioadhesive microspheres of metformin hydrochloride. Microspheres provide precise control on drug release and bioadhesion is useful to obtain gastroretention for improvement in bioavailability. Drug loaded microspheres of bioadhesive polymers were prepared by ionic gelation method. Hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC) and methyl cellulose (MC) were used as bioadhesive polymers. Microspheres were prepared by using various ratios of sodium alginate to respective polymer(s). One gram of drug was added in 50ml solution of polymers separately. Microspheres were collected in 10% w/v calcium chloride solution with constant stirring. Formulation MS2 (sodium alginate: HPC; 1:1) was found to be the best among all. For MS2, percent yield (65.5%), drug entrapment efficiency (72±0.56%), particle size (851 µm), in vitro wash off test (63.9 %), in vitro drug release (80.77 %) etc. Some process parameters viz orifice diameter of needle used to pass polymer solution, dropping height and stirring speed were studied. It was observed that as the orifice diameter of needle decreased from needle no. 18 to 23, the microspheres were more spherical with retention in their shape and needle no. 20 was found to be optimum. More spherical microspheres were observed with decrease in dropping height and optimum was found to be 6 cm. With increase in stirring speed from 250 to 750 RPM, drug entrapment efficiency decreased.

Keywords: bioadhesive, gastroretention, metformin hydrochloride, microspheres

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INTRODUCTION

As per the reports of World Health Organization (WHO), diabetes is one of the major causes of death and disability in the world. WHO estimated the number of people with diabetes worldwide is 171 million in 2000 which is likely to reach to at least 366 million by 2030. This is the evident that diabetes has become a major health problem worldwide. This indicate the need of much research in this area. [1]

Drugs that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life require frequent dosing. Therefore oral sustained/controlled release formulations have been developed to release the drug slowly into the GIT and to maintain an effective drug concentration in the blood for longer period of time. However, such oral drug delivery has a limitation of gastric retention time in the absorption zone, stomach or upper part of small intestine, therefore possibility of diminished efficacy of the administered dose. To overcome this limitation, gastro-retentive delivery systems are recommended. [2]

Metformin hydrochloride is a very widely accepted drug as it does not induce hypoglycemia at any reasonable dose. In type II diabetes, metformin is drug of choice alone or in combination with other hypoglycaemic agents.[3] In spite of its favourable clinical response and lack of significant drawbacks, chronic therapy with metformin hydrochloride suffers from certain specific problems of which, the most prominent being the high dose (1.5-2.0 g/day), low bioavailability (60%) and high incidence of GI side effects (30% cases). The low bioavailability and short half-life of metformin hydrochloride make the development of sustained-release forms desirable.[4, 5]

Bioavailability of the drug has been found to be reduced with dosage forms, probably due to the fact that passage of the controlled 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. Therefore, controlled release formulation suitable for metformin hydrochloride should be a gastroretentive dosage form which releases the drug slowly in the stomach. [6]

Microsphere carrier systems have attracted considerable attention due to release of drug at a controlled rate and less chance of dose dumping.[7] Use of microspheres as gstroretentive carrier systems is achieved by overcoming short residence time at the site of absorption. This is provided by intimate contact of drug delivery system with mucous membrane. This is in turn, achieved by providing bioadhesive nature to microspheres.[8] Bioadhesive microspheres have

advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site.[9] Bioadhesion is successfully obtained by using certain natural polymers. Natural polymers are preferred due to their bioadhesive nature and biodegradation. Alginates are naturally occurring substances. They are nontoxic if taken orally and also have protective effect on the mucous membrane of upper GIT. These are block polymers consist of mannuronic acid, guluronic acid and mannuronic -guluronic blocks.[10] The dried microspheres swell in presence of aqueous medium and thus act as controlled/sustained release system. It has been widely used in drug delivery. Spherical gel formation takes place after dropwise addition of aqueous alginate solution into aqueous solution of calcium ions. [11]

The present work was aimed to develop bioadhesive microspheres of metformin hydrochloride and to study effect of variables on quality of microspheres.

MATERIALS AND METHODS

Materials

Metformin hydrochloride was kindly gifted by Emcure Pharmaceuticals Ltd., Pune, India. Sodium alginate, hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), methyl cellulose (MC), calcium chloride, sodium carbonate were procured from Loba chemicals, Mumbai, India.

Methods

Preparation of calibration curve

A calibration curve for metformin hydrochloride was established by using hydrochloric acid buffer of pH 2.2. [12] A plot of absorbance vs. concentration was obtained. Dilutions were prepared from stock solution to contain 4, 8,12,16,20, 24, 32 µg/ml.

Preparation of drug loaded bioadhesive microspheres of HPC, HPMC and MC

Microspheres were prepared by ion gelation method which involved reaction between sodium alginate and calcium to produce calcium alginate.[13,14] Sodium alginate and HPC were taken in the ratio of 1:0.5, 1:1 & 1:2 w/w and dissolved in distilled water in three separate beakers. Metformin hydrochloride of 1 g was dissolved in each polymer solution. Sodium carbonate 0.25 g was added in each. Solutions of these polymers was passed drop wise through syringe with a needle no 20 in 100 ml of 10% w/v solution of calcium chloride with continuous stirring on mechanical stirrer. The contents in beaker were kept aside for 15 minutes. Microspheres were collected by decantation and washed several times with distilled water to remove excess calcium

impurity deposited on the surface of microspheres and then dried in hot air oven at about 45 ^{0}C for sufficient time. Drug loaded microspheres were obtained by same procedure for HPMC and MC for the same three ratios with sodium alginate as shown in table 1.

Table 1: Composition of metformin hydrochloride microspheres formulation

Formulation	Polymer ratio	Drug (g)
MS1	Sodium alginate: HPC (1:0.5)	1 g
MS2	Sodium alginate: HPC (1:1)	1 g
MS3	Sodium alginate: HPC (1:2)	1 g
MS4	Sodium alginate: HPMC (1:0.5)	1 g
MS5	Sodium alginate: HPMC (1:1)	1 g
MS6	Sodium alginate: HPMC (1:2)	1 g
MS7	Sodium alginate: MC (1:0.5)	1 g
MS8	Sodium alginate: MC (1:1)	1 g
MS9	Sodium alginate: MC (1:2)	1 g

Characterization of drug loaded bioadhesive microspheres

1) **Size of microspheres[15]:**

Microsphere size was determined by using an optical microscope. The mean microsphere size was calculated by measuring 300 microspheres with the help of a calibrated ocular micrometer.

2) **Morphological Study[15]**

Morphological study was carried out by using Scanning electron microscope (SEM). A scanning electron micrograph of drug loaded microspheres was obtained. A small amount of microspheres was spread on glass stub. Afterwords, the stub containing the sample was placed in scanning electron microscope (JEOL JSM-6360A) chamber. The photomicrograph was taken at 5.0 KV. These photographs are depicted in figure 3 and figure 4.

3) **Micromeritics Study[16]**

a) Angle of repose: Angle of repose of each batch was carried out by glass funnel method. Angle of repose was calculated by the formula, $\theta = \tan^{-1}(h/r)$.

b) Bulk density: Bulk density of known mass of microspheres in graduated measuring cylinder. The bulk density was calculated by taking ratio of weight of microspheres in gram to bulk volume of microspheres in cm^3

c) Tapped density: Tapped density is the volume of powder determined by tapping using measuring cylinder containing pre-weighed amount of sample. Tapped density of microspheres was calculated by the ratio of weight of microspheres in gram to volume of microspheres after tapping in cm^3

d) Carr's compressibility index

Carr's compressibility index= (Tapped density-Bulk density)/Tapped density x100

4) Percentage yield[17]

Prepared microspheres of all batches were accurately weighed. Percent yield was calculated by using following formula.

Percent yield= (Actual weight of product/ Total weight of excipients and drug)x100

5) Drug entrapment efficiency[17]

Microspheres equivalent to 50 mg of drug were taken for evaluation. Drug entrapment efficiency was estimated by crushing the microspheres and extracting with aliquots of hydrochloric acid buffer of pH 2.2 repeatedly. The extract was diluted to 100 ml in a volumetric flask using hydrochloric acid buffer of pH 2.2. The solution was filtered and amount of metformin hydrochloride was estimated against appropriate blank.

6) In vitro wash off test[11,15]

In-vitro bioadhesive properties of microspheres were evaluated by in –vitro wash off test. A 1cm x 2 cm piece of stomach mucosa of goat was tied on glass slide using thread. A fixed number of microspheres were spread on this mucosa and allowed to wet by mucus for 5 min. This glass slide was hanged in grove of USP disintegration test apparatus containing hydrochloric acid buffer of pH 2.2 and operated for regular up and down movements as shown in figure 1. After 15 minutes number of microspheres remain adhered on the mucus membrane were counted and further percentage was calculated.

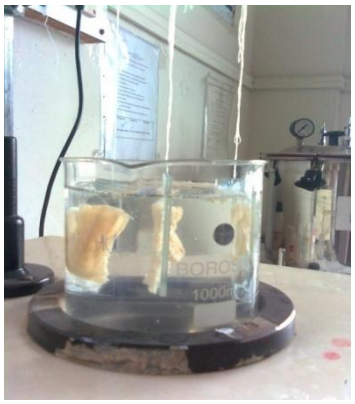

Figure 1: Bioadhesion testing by in vitro wash off test

7) In vitro drug release study[17]

In vitro dissolution studies were carried out by using USP paddle type dissolution apparatus. Weighed amount of drug loaded microspheres were introduced into 900 ml dissolution medium of hydrochloric acid buffer of pH 2.2 maintained at 37^0C at 50 RPM.

Five ml of aliquots were withdrawn at predetermined time intervals and equal volume of fresh dissolution medium was replaced to maintain sink condition. The samples were analyzed spectroscopically at 222.5 nm to determine the concentration of drug present.

Study of effect of various factors

Effect of orifice diameter of needle:

It was observed that diameter of needle plays important role in the quality of microspheres. Therefore, three different needles viz needle no. 18, 20 and 23 were selected. Orifice diameter decreases with increase in needle no. Thus, needle no. 18 has larger diameter and 23 has smaller orifice diameter. Solutions of polymers were passed through all three different needles and formation of microspheres was observed. Needle diameter decides volume of each drop of polymer solution passing through the needle and probably size and shape of microspheres.

Dropping height

Dropping height, that is, distance between tip of needle and level of contents in container affects on size and shape of microspheres. This distance decides mainly the shape of microspheres. Three different distances were selected viz 6 cm, 15 cm, and 22 cm.

Stirring speed

Optimized batch was used to check effect of stirring speed on drug entrapment efficiency. Therefore, microspheres of optimised batch were prepared at different stirring speed viz 250, 500 and 750 RPM keeping all other variables constant.

RESULTS AND DISCUSSION

Calibration curve

Calibration curve was prepared in hydrochloric acid buffer pH 2.2. Within stated concentration range linearity was observed and Beer Lambart law was obeyed as shown in figure 2. λ_{max} was found to be 222.5 nm and correlation coefficient 0.9997.

Preparation of drug loaded bioadhesive microspheres of HPC, HPMC and MC

Bioadhesive microspheres were prepared by ionic gelation method. Sodium alginate was fixed polymer in all combinations with other polymers. Three polymers viz HPC, HPMC and MC were used in combination with sodium alginate. The viscosity of same concentration of these three polymers has order of MC>HPMC>HPC at room temperature. When these polymers were combined with sodium alginate, there was increase in resultant viscosity of solution which was sufficient for drop formation and further to convert into microspheres. The microspheres were formed in calcium chloride solution (10%w/v in distilled water). The solution of polymers of

stated concentrations were added dropwise into calcium chloride solution while the contents were stirred with mechanical stirrer at constant RPM. Mechanical stirring avoids aggregation of microspheres in the solution and also accelerates curing reaction which ultimately leads to formation of more rigid microspheres. The attempts have been made to maintain flow rate constant for all polymer solutions. Time of 15 minutes was allowed for microspheres to remain in calcium chloride solution after its formation in order to carryout complete curing reaction. Various numbers of needles viz 16, 18, 20 and 23 were tried for microsphere preparation. But needle no.20 was found to be satisfactory as far as size, shape and overall appearance of microspheres is concerned.

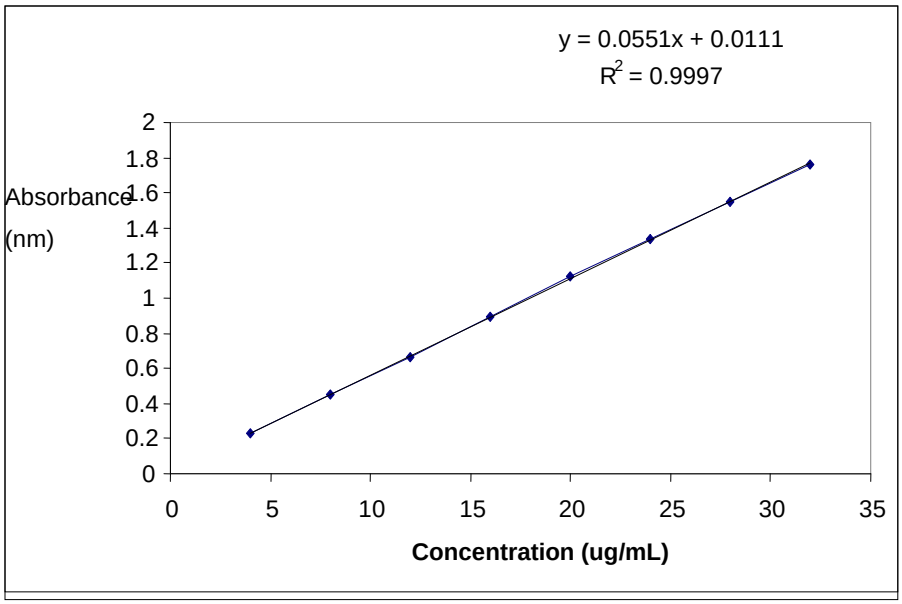

Figure 2: Calibration curve of metformin hydrochloride

It was thought that metformin hydrochloride can produce adverse effects in the form of gastric irritation to the mucosa of upper gastrointestinal tract. Therefore, bioadhesive microspheres should reduce the local pH at the site where they are adhered to mucosa. Therefore, in the process 0.25 g of sodium carbonate was added as alkalizing agent. In practice, it was simultaneously observed that this was also helpful to avoid sinking of microspheres in the hemispherical bowl of dissolution apparatus due to partial buoyancy contributed by sodium carbonate for first few minutes.

Characterization of drug loaded bioadhesive microspheres:

Size of microspheres

Micromeritics study revealed that dried microspheres were faint brown in colour, discrete and spherical. The particle size range for microspheres was 800 µm to 920 µm shown in table 2. The

particle size was found to be increased with the polymer concentration due to increase in viscosity of the polymer solution which increased droplet size. The microspheres when formed in solution were large in size due to entrapment of large volume of solution. However, sufficient size reduction was observed after drying due to evaporation of solvent and shrinkage of polymer coat.

Morphological Study

Morphology of microspheres was studied by scanning electron microscope (SEM) at Dept. of Physics, University of Pune. Images were obtained and that illustrated spherical shape of microspheres and incomplete coat on surface. Porous structure was observed on the surface as shown in figure 3 and figure 4.

Figure 3: SEM: Spherical shape

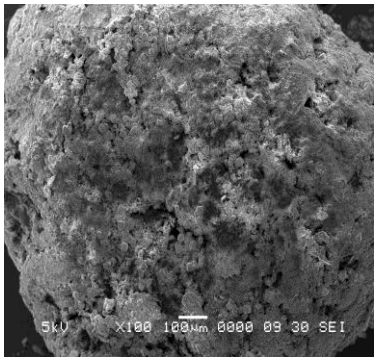

Figure 4: SEM: Porous surface of microspheres

Micromeritics Study

The bulk density and tapped density was found to be in the range of 0.549±0.04 to 0.621±0.04 and 0.655±0.02 to 0.710±0.05. Formulation MS2 showed compressibility index of 11.80±1.3 and angle of repose $26^0$41’ (table 2). The values of angle of repose of all samples indicated that microspheres were free flowing. These properties are suitable for conversion into solid dosage form.

Table 2: Micromeritics properties of metformin hydrochloride microspheres

Formulation	Average particle size	Angle of Repose	Bulk density	Tapped density	Carr’s Index
MS1	825.23	$28^0$65’	0.590±0.03	0.667±0.04	13.54±1.2
MS2	851.65	$26^0$41’	0.621±0.04	0.720±0.05	11.80±1.3
MS3	898.98	$29^0$32’	0.612±0.02	0.719±0.04	14.88±1.1
MS4	910.24	$27^0$12’	0.589±0.03	0.742±0.04	20.61±0.9
MS5	905.23	$27^0$64’	0.549±0.04	0.678±0.03	19.02±0.9
MS6	895.21	$29^0$87’	0.550±0.05	0.655±0.02	16.03±1.2
MS7	871.64	$26^0$97’	0.590±0.04	0.660±0.03	11.70±1.1
MS8	869.64	$29^0$97’	0.589±0.04	0.679±0.04	13.25±1.3
MS9	896.65	$28^0$99’	0.599±0.04	0.710±0.05	15.63±1.2

Percentage yield

Percent yield was varied from 58.4 % to 65.5%. Increase in ratio of polymer concentration, yield was increased but not significant.(table 3)

In vitro wash off test

In vitro wash off test was carried out to observe the bioadhesion of microspheres. Percent microspheres retained on the mucosa were found to be in the range of 59.1 % to 66.0 % (table 3). It was observed that as the viscosity of polymers increased, there was increase in the percentage of retention of microspheres on mucosa. This was attributed to formation of highly viscous gel around microspheres which showed greater extent of bioadhesion. For in vitro wash off test, MC has shown highest microspheres retention on mucus membrane due to high viscosity and high extent of polymer chain entanglements with mucus and also due to stickiness of polymer.

Drug entrapment efficiency

Entrapment efficiency was found in the range of 65% to 72% (table 3). Overall, drug entrapment was found increasing with increase in polymer concentration due to its higher viscosity.

Table 3: Characterization of microspheres

Formulation	Percent yield	Entrapment Efficiency%	In-vitro wash off test (% microspheres retained on mucosa)
MS1	60.0±0.96	69±0.49	55.4±1.10
MS2	65.5±1.0	72±0.56	63.9±0.98
MS3	64.3±1.1	71±0.36	64.3±1.12
MS4	58.4±0.95	65±0.48	56.2±1.15
MS5	58.6±1.2	70±0.49	62.7±1.20
MS6	60.2±1.12	69±0.52	59.2±1.11
MS7	61.4±1.2	66±0.66	59.1±1.20
MS8	62.4±1.0	67±0.67	61.3±0.99
MS9	62.5±0.99	65±0.50	66.0±1.19

Table 4: In vitro drug release study of microspheres

Formulation e	% In vitro drug release (9hrs)	% In vitro drug release (12 hr)	$t_{1/2}$ (hrs.)
MS1	61.2±1.22	77.84±1.31	3
MS2	65.2±1.24	80.77±1.29	4
MS3	57.4±1.20	75.23±1.28	5
MS4	60.2±1.21	75.12±1.30	5.5
MS5	57.7±1.29	72.33±1.20	5.5
MS6	54.2±1.08	68.44±1.19	6
MS7	56.29±1.31	69.78±1.22	6
MS8	52.22±1.17	65.64±1.26	6
MS9	50.29±1.25	64.12±1.30	6.5

In vitro drug release study

In vitro drug release showed that formulation MS2 had percent drug release of 65.2 % and 80.7% at the end of 9 hrs and 12 hrs respectively. Overall drug release ranges from 50% to 65% at the end of 9 hrs and 64% to 80.7% at the end of 12 hrs. (figure 5, figure 6 and figure 7). HPC microspheres (1:1) showed highest drug release due to less viscosity of gel formed and smaller diffusion path around the microspheres than HPMC and MC microspheres. Also the high drug release is attributed to porous surface of HPC microspheres. These microspheres showed high drug entrapment efficiency. Among the three formulation of HPC viz MS1, MS2, and MS3; higher percent yield, higher entrapment efficiency and high percentage of retention of microspheres on mucosa was observed for MS2.

With increase in concentration of polymer, drug release was found to be decreased. This is due to increase in viscosity of polymer. Thus viscosity plays important role in drug release from HPC microspheres. This is in full agreement with the literature. $t_{1/2}$ was determined for all formulations. It represents time taken for 50% drug release. Formulation MS2 shown $t_{½}$ approx. 4 hrs. This is shown in table 4.

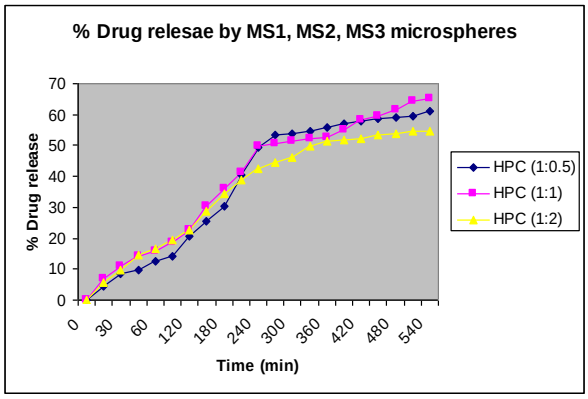

Figure 5: In vitro drug release of formulations MS1 to MS3

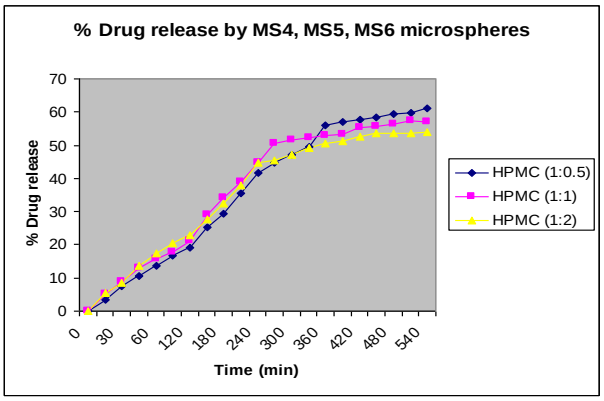

Figure 6: In vitro drug release of formulations MS4 to MS6

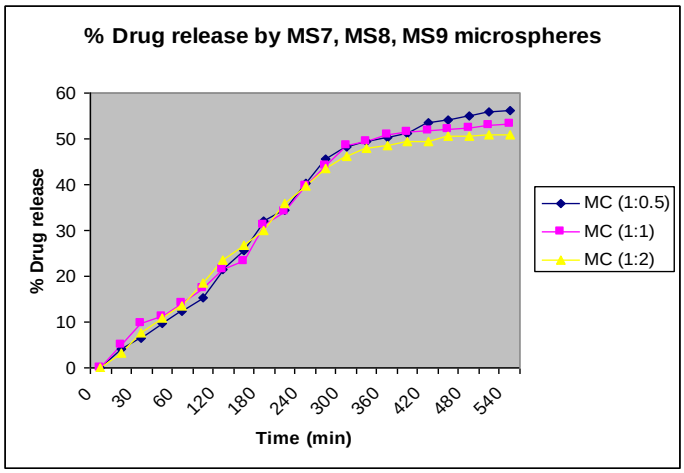

Figure 7: In vitro drug release of formulations MS7 to MS9

Study of effect of various factors

Effect of orifice diameter of needle

Effect of orifice diameter (needle no 18, 20 and 23) on formation of microspheres is summarized below. Small particle size with rigid nature of microspheres was possible with needle no 20 and 23. However, as viscosity plays important role in passage of solution from needle, a difficulty was observed for needle no 23.Therefore, needle no. 20 was suggested for this process (table 5).

Table 5: Effect of orifice diameter on formation of microspheres

Needle No. 18	Needle No.20	Needle No. 23
Loosely bound, containing high volume of calcium chloride solution in it.	Shape of microspheres was nearly spherical	Shape was spherical
Not spherical in shape.	The passage of solution from needle was easy.	Rigid microspheres
The passage of solution from needle was easy.	Size of microspheres less than that of earlier	Particle size still less than earlier The passage of solution from needle was difficult. More force was needed to pass solution than earlier.

Dropping height

Effect of dropping height on formation of microspheres is summarized in table 6. While doing practically, apart from distance of 15 cm and 6 cm, the observation was also noted for distance more than 15 cm. At this distance, no proper shape of microspheres was observed immediately after formation in beaker and even after drying. Elongated microspheres and sometimes elongation with flat surface of microspheres was observed. Wide particle size distribution was experienced. At distance of 15 cm, shape was slightly spherical but no integrity in surface was

observed immediately after formation and subsequent drying. But as the distance was reduced, significant change in shape, size and surface integrity was observed.

Table 6: Effect of dropping height on formation of microspheres

Distance 15 cm	Distance 6 cm
Shape was not spherical	Shape was spherical
Contain high amount of solution of calcium chloride	Contain less amount of solution of calcium chloride
No integrity in surface of microspheres	More integrity in surface of microspheres
Difficult to retain the shape of microspheres	No difficulty observed in retention of shape
After drying the shape was elongated	After drying shape was spherical

Stirring speed

Stirring speed affect on drug entrapment efficiency. It was found that drug entrapment efficiency decreases with increase in stirring speed.

CONCLUSION

To conclude, metformin hydrochloride microspheres can be prepared successfully by ionic gelation method. Formulation of microspheres MS 2 (Sodium alginate: HPC; 1:1) was found the best among all. Parameters like orifice diameter of needle, dropping height and stirring speed though look simple, influence significantly on size and shape of microspheres. While preparing microspheres by ion gelation method, one should pay considerable attention to these parameters.

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