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Formulation and Evaluation of Floating Microspheres of 1,1-Dimethylbiguanide

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ABSTRACT

1,1-Dimethylbiguanide is a hypoglycemic agent used in the treatment of non-insulin dependent Diabetes mellitus. It is a BCS Class –III drug having poor permeability. Plasma half life ranges from 1.5-3 hrs & oral bioavailability is 50-60%. Hence require frequent oral administration for adequate treatment of Diabetes in order to extend the gastric retention time oral sustained dosage form was developed in the form of microspheres using polymers (sodium CMC, HPMC K 100 M). The results presented that drug dissolution rate and drug entrapment increases while decreasing the polymer amount. All the formulations are evaluated for dissolution, entrapment efficiency, percentage buoyancy and 1,1-Dimethylbiguanide Microspheres of formulations, F-4 was found to be optimized formulation based on in-vitro release pattern and percentage buoyancy entrapment efficiency.

Keywords: 1,1-Dimethylbiguanide, half-life formulations, efficiency.

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INTRODUCTION

Oral delivery of drugs [1] is the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation etc. various attempts have been made to prolong the retention time of the dosage form in the stomach. The present study involved, preparation of 1,1-Dimethylbiguanide floating microspheres to improve the bioavailability by increasing residence time in stomach. Metformin is an anti- hyperglycemic agent which improves glucose tolerance in patients with type-2 diabetes. Its pharmacologic mechanisms of action are different from other classes of oral anti- hyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. 1,1-Dimethylbiguanide quite frequently causes gastrointestinal problems such as nausea, stomach pain, diarrhea. It has short half life (4-6 hrs) and is absorbed from upper intestine with in 6 hrs. So repeated administration required is to maintain effective plasma concentration. So our objective is to prepare a sustained release floating microspheres. Thus, the development of floating drug delivery systems would clearly be advantageous. Dosage forms that are retained in the stomach would increase the absorption, improve drug efficiency, and decrease dose requirements. Thus an attempt was made in this investigation to use HPMC K100M, sodium CMC polymers to prepare 1,1-Dimethylbiguanide floating Microspheres.

Floating microsphere drug delivery system

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content, increases gastric residence and fluctuation in plasma concentration. It also reduces chances of striking and dose dumping and produce prolonged therapeutic effect.

MATERIALS AND METHODS

1,1-Dimethylbiguanide was purchased from Yarrow chem. Products Mumbai, India, Hydroxyl proply methyl cellulose was purchased from K100M Ozone International Mumbai. Sodium Carboxy methyl cellulose was purchased from Ozone International Mumbai, Sodium bicarbonate and Calcium chloride was purchased from S.D. Fine chemicals, Ltd, Mumbai. Sodium alginate was purchased from Loba Chemie Pvt. Ltd. Mumbai.

The FT-IR spectra of pure 1,1-Dimethylbiguanide and microspheres loaded with 1,1-Dimethylbiguanide were recorded to check drug polymer interaction and stability of drug.

Process of Formulation

Floating alginate microspheres of 1,1-Dimethylbiguanide were prepared by ionotropic gelation technique using different proportion of polymers as shown in table No. 3. A 3% w/v solution of sodium alginate solution was added to weighed amount of Na CMC dissolved in required quantity of ethanol. Weighed quantity of drug and HPMC K100 M was triturated to form fine powder, and then added to above solution. Sodium carbonate, gas forming agent was added to this mixture.

Agitation

The above mixture was taken into beaker for which an agitator and the agitator is allowed to rotate at fixed speed. Now the above solution of drug and polymer was dropped into 100 ml of gently agitated calcium chloride (3 % w/v) solution using a 26 G syringe needle to obtain microspheres. The solution containing Microspheres was stirred slowly using magnetic bead for about 10 min. the Microspheres were further allowed to remain in the same solution for 20 min to improve mechanical strength.

Filteration

The formed Microspheres were filtered, by using whatmann filter paper and washed with distilled water, air-dried at room temperature and stored in desiccators.

Drying

After filtration microspheres were dried in the hot air oven at the temperature 35-45^{0}C for the period of 1- 2 hrs. Then the microspheres kept in desiccators.

Buoyancy Nature

Alginate microspheres were formed as alginate undergoes ionotropic gelation by calcium ions and carbon dioxide develops from the reaction of bicarbonate salt with acid which permeates through alginate matrix leaving gas bubbles or pores within microspheres, providing the buoyancy.

RESULTS AND DISCUSSIONS

Calibration curve of 1,1-Dimethylbiguanide by UV spectral analysis

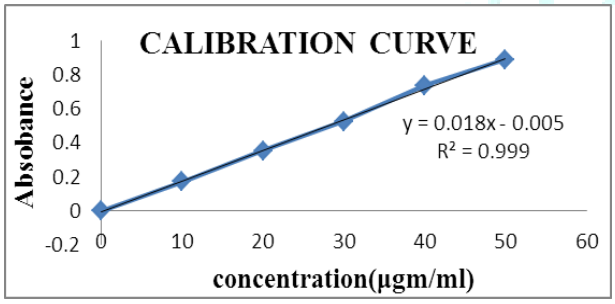

Fig No.5: Calibration curve for 1,1-Dimethylbiguanide in pH 1.2HCl buffer

Accurately weighed amount of 1,1-Dimethylbiguanide (100mg) was dissolved in p^H 1.2 buffer to form a clear solution and it was made up to the volume in 100 ml volumetric flask with p^H 1.2 HCL buffer. From this solution 1ml was transferred into 10 ml of volumetric flask and it was made upto volume with HCL buffer pH 1.2. The resulting solution (100 µg/ml). From this 1ml, 2ml, 3ml, 4ml, 5ml was pippeted out and diluted to 10 ml with pH 1.2 HCL to obtain 10ug/ml, 20ug/ml, 30ug/ml, 40ug/ml, 50ug/ml and scanned over the range 233 nm against pH 1.2 HCl buffer as blank UV spectrophotometer.

Preformulation Studies

Drug Excipient compatibility studies

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

Fourier transforms infra-red spectroscopy (FT-IR) analysis

The compatibility study between the drug and the polymer was done by I.R studies. No major peak shift was observed in the I.R graphs in major functional groups. Based on the compatibility studies obtained by I.R studies, the polymer HPMC K100 M, sodium CMC were taken for the optimization of the formulation, which is compatible with the drug. The FT-IR spectra of pure 1,1-Dimethylbiguanide and microspheres loaded with 1,1-Dimethylbiguanide were recorded to check drug polymer interaction and stability of drug.

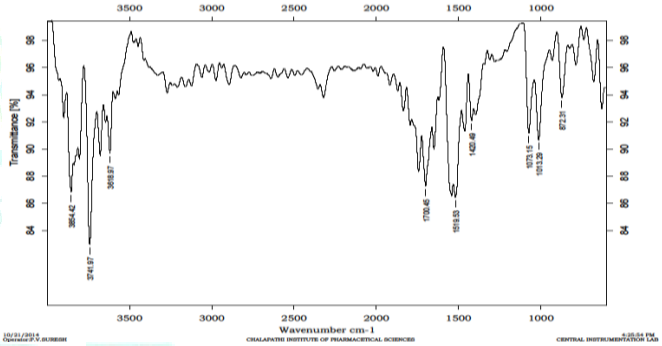

Fig No. 1: FTIR graph for the pure drug 1,1-Dimethylbiguanide

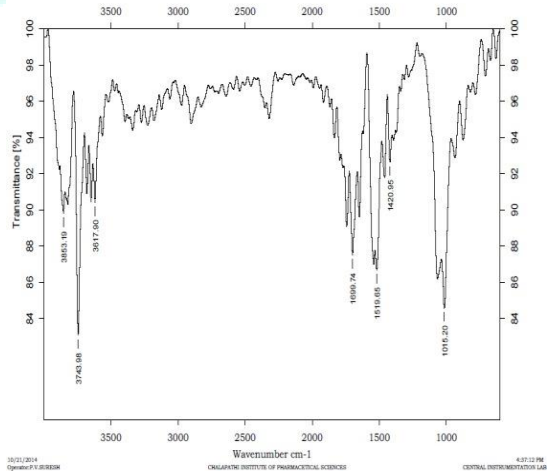

Fig No. 2: FTIR graph of polymer (Na CMC)

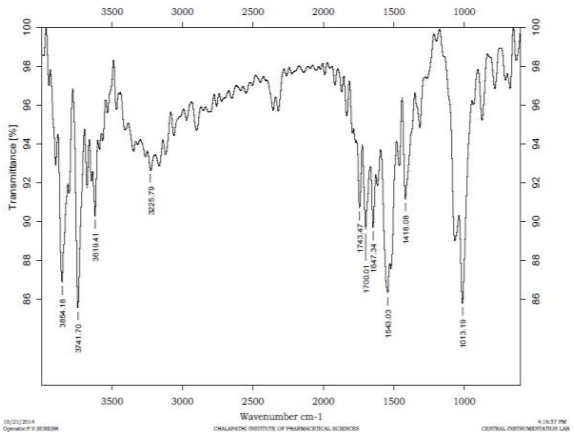

Fig No: 3 FTIR graph of Drug and Drug and Polymer (HPMC K 100 M)

Evaluation of prepared microspheres External morphological study Particle size

External morphology of microspheres was determined using scanning electron microscopy (SEM). Samples were diluted with ultra-purified water to obtain a suitable concentration. Then the samples were spread on a sample holder and dried using vacuum and examined by a scanning electron microscopy.

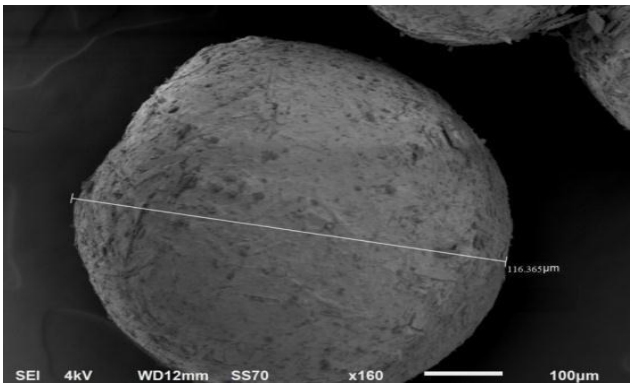

Fig No: 4 SEM of formulated Microspheres

Percentage yield

The prepared microspheres of all batches were accurately weighed. The measured weight of prepared microspheres was divided by total amount of all the excipient and drug used in preparation of the microspheres, which give the total percentage yield of floating microspheres.

It was calculated by using following equation.

$$PY(\%) = \frac{\text{Actual weight of product}}{\text{Total weight of excipient and drug}}$$

Table No1: Percentage yield of different formulations

Formulations	Total weight taken (mg)	Total weight of microspheres (mg)	Percentage yield (%)
F-1	1100	750	68.1
F-2	1050	700	66.6
F-3	1050	750	71.4
F-4	1000	720	72

Inference

From the above table the percentage yield of prepared Microspheres was found to be more for the formulation F- 4 (72%).

Drug content/entrapment efficiency

100 mg of prepared floating microspheres are dispersed in 100ml of pH1.2 HCL buffer. This dispersion kept a side overnight. Then samples were taken from this solution and absorbance values measured by UV spectrophotometer at 233 nm. By using drug content values we can measure the entrapment efficiency.

$$\text{Microencapsulation efficiency} = \frac{\text{Estimated percent drug content}}{\text{Theoretical percent drug content}} \times 100$$

In calculation of entrapment efficiency first measure amount of drug loaded in the total microspheres. For this U.V visible spectrophotometer is used for the analysis of drug.

Table No. 2: Entrapment efficiency of the different formulations

Formulations	Observed drug (mg)	Total amount taken (mg)	Entrapment efficiency(%)
F-1	45	100	67.5
F-2	47	100	65.8
F-3	46	100	69
F-4	49	100	70.56

Inference

From the above table Entrapment efficiency was found to be more for the formulation F – 4 i.e. (70.56%).

Percentage buoyancy

Microspheres (0.3g) were spread over the surface of a USP XXIV dissolution apparatus (type

II) filed with 900 ml 0.1 N HCL. The medium was agitated with 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 microspheres that remained floating and the total mass of the Microspheres.

$$\% \text{ Floating microspheres} = \frac{\text{Weight of floating microspheres at time t}}{\text{Initial weight of microspheres}} \times 100$$

Table No. 3: Buoyancy percentage of different formulations

Formulation code	Percentage buoyancy
F-1	81.66
F-2	83.33
F-3	85.1
F-4	86

Inference

From the above table the percentage buoyancy was found to be more for the formulation F -4.

IN VITRO DISSOLUTION DATA

Dissolution test

The dissolution profiles of floating microspheres of 1,1-Dimethylbiguanide were investigated with a dissolution apparatus (LAB INDIA DS-8000), according to type II paddle method, with the rotation speed of paddle was set on 100 and the bath temperature was kept at 37.0 ± 0.5°c. Equivalent 100 percent of drug preparation was filled into the empty capsule. The capsule was put into the vessel containing 900 ml of pH 1.2 HCl. To avoid the float of capsule sinkers were used. At specific intervals, 1 ml of aliquot of dissolution medium was sampled, filtered the sample by the U.V and visible spectrophotometer. Absorbance of the sample solution compared with the standard solution having a known concentration of 1,1-Dimethylbiguanide was drawn at 233 nm.

Table No.16: Comparative dissolution profile for formulation F1 – F4

S.NO	F-1 % CDR	F-2 % CDR	F-3 % CDR	F-4 % CDR
1	0	0	0	0
2	11.08	12.1	19.9	9.5
3	18	21.6	21.6	26.1
4	27	26.1	31.5	29.7
5	31.5	37.8	39.6	41.4
6	37.8	45	46.8	47.7
7	46.8	50.4	54	57.6
8	52.2	59.4	71.1	67.5
9	56.7	69.3	75.6	81
10	67.5	71.1	79.2	82.8
11	73.8	74.7	82.8	84.6
12	75.6	80.1	85.5	87.3
13	81	81	88.2	90

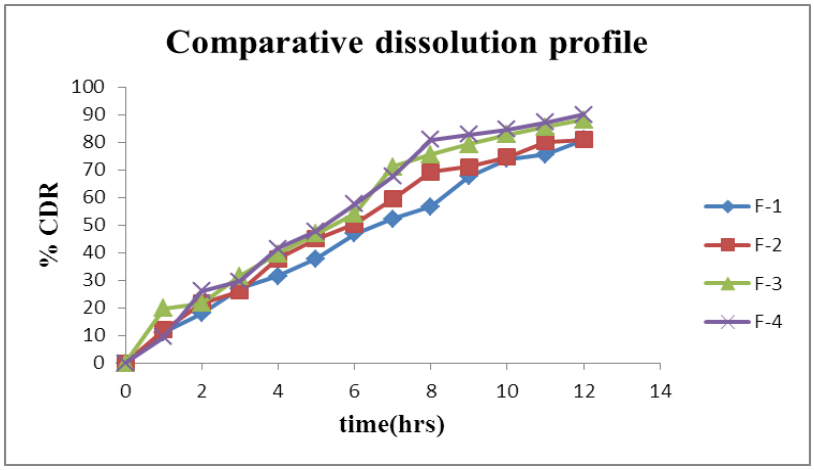

Fig No. 20: Comparative dissolution profile for formulation F1-F4.

Inference

From the above fig the dissolution profile for the formulation F-4 was found to be have the more cumulative % drug release.

DISSOLUTION – APPLICATION OF KINETICS OF F-4

Table NO. 17: Application of kinetics for dissolution profile of formulation F-4.

S.NO	TIME	% CDR	Log % CDR	Log % drug unreleased	Square root time	Log time
1	0.5	9.5	0.9777	1.9566	0.7071	-0.301
2	1	26.1	1.4166	1.8686	1	0
3	2	29.7	1.4727	1.8469	1.414	0.3010
4	3	41.4	1.6170	1.7678	1.732	0.4771
5	4	47.7	1.6785	1.7185	2	0.602
6	5	57.6	1.7604	1.6273	2.236	0.6989
7	6	67.5	1.8293	1.5118	2.449	0.778
8	7	81.0	1.9084	1.2787	2.645	0.845
9	8	82.8	1.9180	1.2355	2.828	0.903
10	9	84.6	1.9273	1.1875	3	0.954
11	10	87.3	1.9410	1.1038	3.167	1
12	11	90	1.9542	1	3.316	1.041

ZERO ORDER PLOT

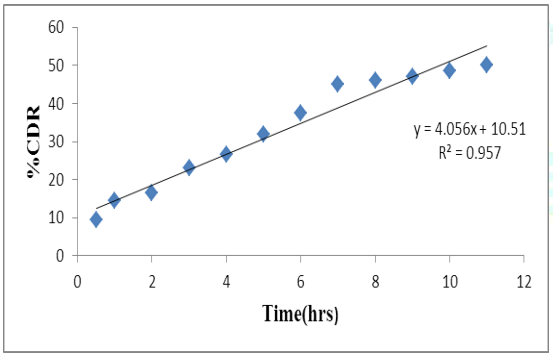

Fig No. 21: Zero order plot for optimized formulation F-4

FIRST ORDER PLOT

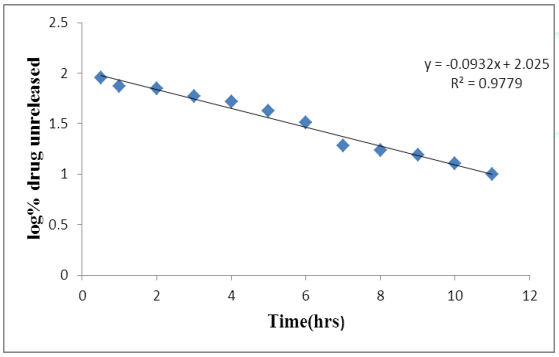

Fig No. 22: First Order Plot for optimized formulation F-4

Inference

From the above graphs the R^2 value is (0.977) and for zero order plot R^2 value is (0.957) which indicating that the order of release was first order.

HIGUCHI'S PLOT

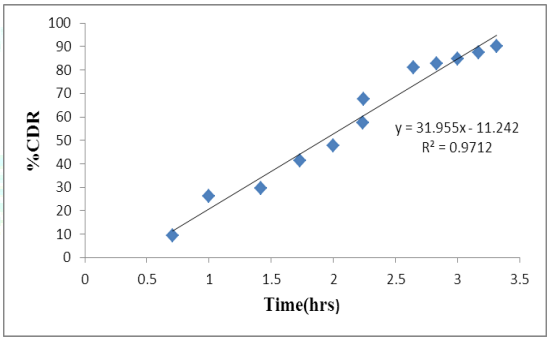

Fig No. 23: Higuchi's plot for optimized formulation F-4

KORSEMEYER- PEPPAS PLOT

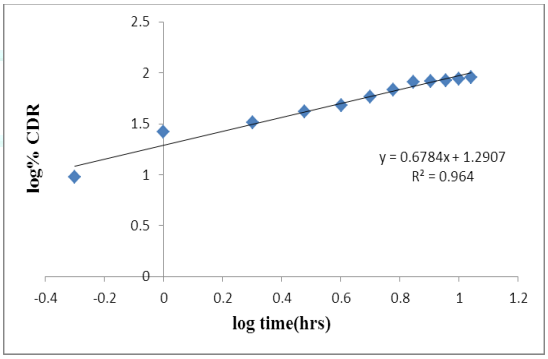

Fig No. 24: Korsemeyer -Peppas plot for optimized formulation F-4

Inference

As per the above plot Fig No. 17 and Fig No. 18. The R^2 value for Higuchi (0.974) and for Korsemeyer - Peppas plot (0.964), showing that the mechanism of drug release from the formulation was found to be Diffusion controlled release.

Stability studies

The accelerated stability study for the formulation at 40 ± 2^0C and 75 ± 5% RH was conducted for the 3 months, which includes the testing of parameters like identification of physical characters, identified by IR studies, dissolution profile and assay throughout period.

The stability studies on optimized formulation of 1,1-Dimethylbiguanide floating Microspheres were conducted according to the ICH guidelines.

CONCLUSION

The present study involved, preparation of 1,1-Dimethylbiguanide floating microspheres to improve the bioavailability by increasing residence time in stomach. Thus an attempt was made in this investigation to use HPMC K100M, sodium CMC polymers to prepare 1,1-Dimethylbiguanide floating Microspheres.

From the study, it was concluded that spherical and free flowing Microspheres of Metformin HCL could be successfully prepared by Ionotropic gelation technique with high entrapment efficiency and prolonged release characteristics.

It was concluded that

- Compatibility studies revealed no interactions between the drug and polymers used.
- Formulated Microspheres gave satisfactory result for various physic- chemical evaluations like physical appearance, surface morphology, entrapment efficiency, percentage drug loading, percentage buoyancy and In-vitro drug release.
- The prepared beads showed required drug release in about 12 hours as aimed for.
- From the research, it can be concluded that 1,1-Dimethylbiguanide can be formulated as Microspheres for the desired use in treatment of Diabetes Mellitus.

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