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DEVELOPMENT AND CHARACTERIZATION OF METFORMIN HOLLOW MICROSPHERES

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Abstract

Metformin used to treatment of Type 2 diabetes. The present work was to development the controlled release Metformin floating microspheres using Ethycellulose, Eudragit and HPMC used as polymers in various formulations poly vinyl chloride category was elasticity that free flow and water used as a ionotropic gelation technique. The formulated were examined by in vitro drug release studies and further perform the stability data for selected or optimized formulation. The work was aimed to develop the controlled release hollow Metformin microspheres.

Key words: API, HPMC, Ethylcellulose, Eudragit, ionotropic gelation technique, drug release.
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1. INTRODUCTION

Floating drug delivery systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate.[1] while the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach.[2] this results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating drug delivery systems (FDDS) or hydrodynamically balanced systems (HBS) are among the several approaches is developed in order to increase the gastric residence time (GRT) of dosage forms.[3] FDDS is divided into two systems viz. single and multiple unit systems. Oral controlled release drug delivery increases interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Microspheres defined as the flowing of the powders freely characteristics composed of proteins or synthetic polymers, which may be biodegradable. Microsphere states that as "a monolithic structure with the drug pass throughout the matrix either as a distribute of molecule or a particle dispersion, drop in the size range 1-1000 μm.[4] Metformin is an insulin-sensitizing, anti- diabetic drug from the Biguanide class of oral anti-hyperglycemic agent. Metformin HCl is 50-60% is a safe drug and it has a half-life of 1.5-3 hrs. It is not absorbed completely and poses low bioavailability problem. Almost 80-100% of the drug is excreted unchanged. The total daily requirement of metformin HCl is 1.5-3g, which leads to high incidence of GI side effects and toxicity. [5]The slow but complete drug release in the stomach increase bioavailability of the drug as well its complete utilization which result in lower dose and GI side effects. Keeping the above facts in

consideration the present study is performed with a view to formulate and evaluate floating microsphere of metformin hydrochloride in order to maintain a sustained drug concentration for longer period of time.[6]

Microparticles provides constant and prolonged therapeutic action. Microspheres prepared byusing emulsion solvent evaporation technique. [7]

2. MATERIALS AND METHOD

MATERIALS

Metformin were purchased from Micro lab, Hosur. Eudragit RS100, Ethylcellulose, HPMC k 4M PVA were purchased from Colorcon Asia pvt. Ltd, Goa. All other ingredients used throughout the study were of analytical grade and were used as received.

METHOD

Hollow microsphere containing Metformin were prepared using ionotropic gelation technique. The drug to polymer ratio used. The polymer content was a mixture of Eudragit RS 100, Ethylcellulose, and HPMC K4. The Metformin and synthetic polymer mixture dispersed in a mixture of suitable solvents. The solution was stirred with a propeller-type agitator at 40 C temperature for 1 hour at 300 rpm. Caland cleaned with distilled water and dried at room temperature in a desiccator. The various batches of hollow microsphere were prepared as follows.

Table-1: Formulation of Metformin hollow microspheres

Formulation	Metformin	HPMC	Eudragit RS100	EC	Cacl2
F1	100	-	500	-	Q.S
F2	100	-	-	500	Q.S
F3	100	500	-	-	Q.S
F4	100	-	250	250	Q.S
F5	100	250	-	250	Q.S
F6	100	-	250	250	Q.S
F7	100	250	250	-	Q.S

EVALUATION PARAMETERS[8, 9]

Yield of sustained microspheres

The yield of microspheres was measured by the amount of microspheres achieve and divided by the total amount of all non-volatile (excipients) components.

$$\%\text{Yeild} = \frac{\text{Actual weight of the microspheres}}{\text{Totla weight of all non-volatile components}} \times 100$$

B. Particle size and shape

The particle size of the microspheres was measured by optical microscopy.

D. Drug entrapment efficiency (DEE)

The accurate amount of drug entrapped was predicted by smash 50 mg of microparticles by mortar and pestle, the smashed microspheres make up with the 6.8 pH buffer by the using volumetric flask repeatedly. If it is not dissolved. The solution was poured in a beaker and kept under for sonication on sonication bath for 2 hours. Solution filtered and absorbance was measured after suitable dilutions spectrophotometrically at 276 nm.

$$\text{DEE} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

E. Swelling index

The floating Metformin microparticles were transferred in 0.1 N HCI (300 ml). The mixture was stirred with paddle at 100 rpm. The layer o floating microsphere were taken and separated by filtration .Particles of both types were dried in a desiccator until constant weight.

$$\%\text{Floating microsheres} = \frac{\text{Final Weight of floating microspheres}}{\text{Intial weight of floating microsheres}} \times 100$$

E. Floating time (Buoyancy study)

The prepared microspheres are undergo for buoyancy study by using franz diffusion cell. The developed floating microspheres are kept in donar cell .For buoyancy study 0.1N HCL was used as medium.The franz diffusion cell kept on magnetic stirring for 300rpm for 8hours.The floating and settled microspheres were recoverd seperatley. The microspheres are dried and weighed. %of buoyancy was measured by using formula,

$$\%\text{Buoyancy} = \frac{\text{Total Wt of floating microspheres}}{\text{Initial wt of microspheres}} X100$$

F. In vitro drug release study

In vitro drug discharge studies were carried out for all manufacturing microsheres in Franz diffusion cell. Microspheres equivalent to 10 mg of Metformin were poured into 1 ml aliquots were withdrawn at a predetermined intervals and equal volume of buffer medium was replaced to maintain sink conditions. The necessary concoction were constuct with 6.8 pH buffer and the solution was analysed for the spectrophotometrically using UV-Visible spectrophotometer (Model 2210, lab India) at 241 nm using buffer as a blank.

Mechanism of drug release [12, 13]

The obtained dissolution data was fitted into various kinetic models to understand the pattern of the drug release from sustained microspheres. The models used were zero order (equation 1) First order (equation 2) and Higuchi model (equation 3) and Koresmeyer Peppas model (equation 4).

i) zero order release kinetics:

$$R = K_o t \quad \text{-- (1)}$$

R=cumulative percent drug release

Ko=zero order rate constant

ii) First order release kinetics

$$\log C = \log C_o - K_1 t / 2.303 \quad \text{-- (2)}$$

where

C = cumulative percent drug release

K_1 = first order rate constant

iii) Higuchi model

$$R = K_H t^{0.5} \quad \text{-- (3)}$$

Where

R = cumulative percent drug release

K_H = higuchi model rate constant

iv) korsermeyer peppas model:

$$M t / M \alpha = K_k t^n$$

$$\log M t / M \alpha = \log K_k + n \log t \quad \text{-- (4)}$$

where

K_k = korsermeyer peppas rate constant

'M t / M α' is the fractional drug release,

n = diffusional exponent, which characterizes the mechanism of drug release

Stability studies [14]

For all the pharmaceutical dosage forms it is important to regulate the stability of the product. This will enclose storage at both normal and disabled temperature postures, with the necessary prognostication to establish the product will, over its shelf life, contribute medication for imbibing at the same rate as when originally formulated. The stability studies for the product does not undergo for any degradation or any microbial contamination.

Storage Conditions[15]

- Accelerated: 40±2^{0}C/75±5% RH
- Intermediate: 30±2^{0}C/65±5% RH
- Long term: 25±2^{0}C/60±5% RH

Testing Intervals for

- Accelerated: Initial, 1, 2, 3 & 6 months
- Long term: Initial, 3, 6, 9, 12, 18, 24 & 36 months.
- Intermediate: Initial, 3, 6, 9 & 12 months.

The formulation of f was optimized and selected for evaluation studies. Further stability study was done for f

3. RESULTS & DISCUSSION

Table-2: Calibration curve of Metformin

S.No	Concentration	Absorbance
1	0	0
2	1	0.158
3	2	0.257
4	3	0.388
5	4	0.499
6	5	0.587

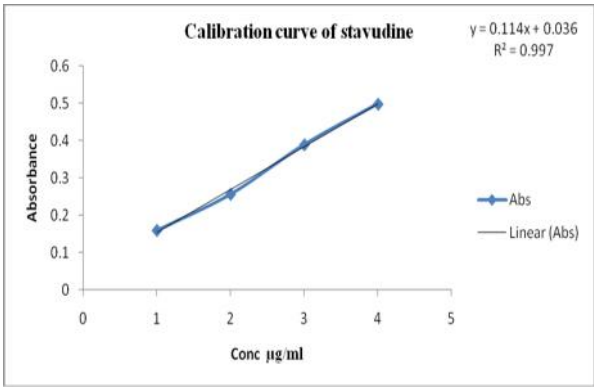

Figure-1: Calibration curve of Metformin

Table-3: Calibration curve of Metformin

S.No	Concentration µg/ml	Absorbance
1	0	0
2	10	0.188
3	20	0.363
4	30	0.557
5	40	0.734
6	50	0.954

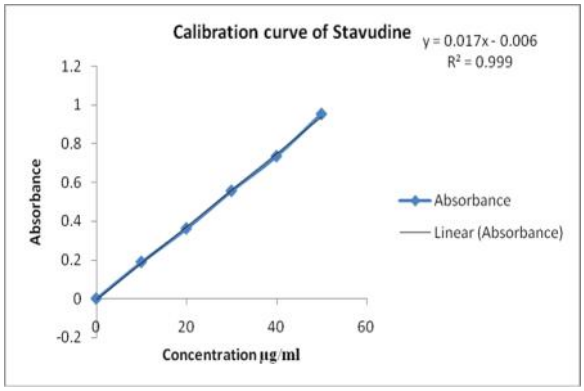

Figure-2: Calibration curve of Metformin

FTIR Studies

Compatibility studies were performed using IR spectrophotometer. It is determine the pure drug and excipient compatability studies. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum.

The physicochemical compatibility of the drug and excipients was obtained by FTIR studies

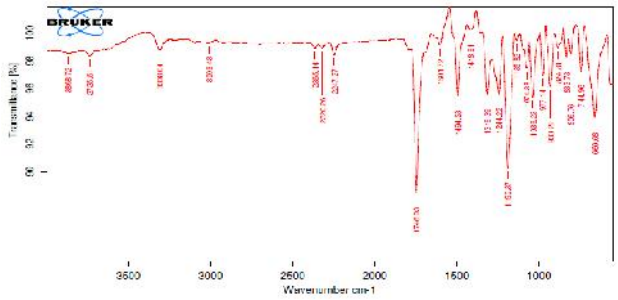

Figure-3: FTIR Spectra of Pure drug

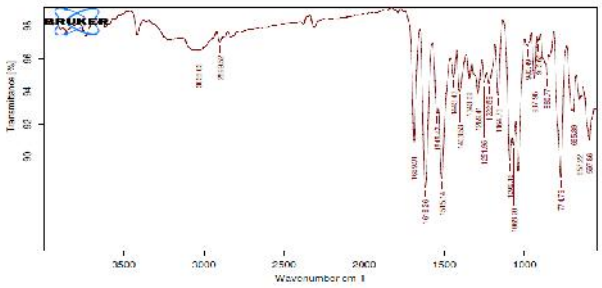

Figure-4: FTIR Spectra of Optimaization formulation

Surface topography by scanning electron microscopy (SEM)

A shows SEM photograph of optimized microspheres at 100× magnification, at 1000× magnification. SEM photographs showed discrete, spherical microspheres. SEM photographs also showed the presence of drug crystal on the surface of microspheres revealing that the microspheres were having some rough surface**.** The drug crystals on microspheres were may be due to the presence of un-entrapped drug in dispersion medium.

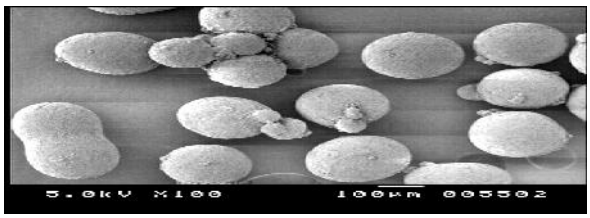

Figure-5: SEM analysis of Optimized formulation

Estimation of Metformin %Drug content, % of yield, swelling index

Table -4: Results of Prepared hollow microspheres

Formulation code	%Drug content	% Of Yeild	Swelling index	Floating time(Buoyancy study)
F1	87.12	73.56	1.33	69.5
F2	86.14	78.90	1.35	77.4
F3	89.62	79.52	1.36	83.56
F4	92.20	81.21	1.39	85.2
F5	94.66	86.73	1.46	82.5
F6	92.51	88.66	1.57	89.6
F7	97.51	92.23	1.62	83.90

The evaluation parameters such as % drug content,% of yield,% of swelling index, Buoyancy test results were found to be within range of of limits.

Estimation of *In-Vitro* Drug release study of Metformin hollow Microspheres

Table-5: All comparative drug release profile

Time	DR1	DR2	DR3	DR4	DR5	DR6	DR7
0	0	0	0	0	0	0	0
1	15.6	16.6	19.5	20.5	21.8	23.6	22.7
2	21.5	25.3	25.5	30.5	33.6	39.6	40.6
3	34.5	35.6	35.7	43.3	45.3	51.4	51.2
4	33.2	39.5	42.4	46.8	54.6	66.4	63.7
5	39.3	42.7	49.8	55.2	60.5	77.6	74.3
6	46.6	53.3	63.7	69.4	72.6	84.4	82.3
7	60.8	69.2	73.6	74.3	78.7	91.5	89.5
8	76.5	78.8	81.5	83.6	84.6	96.8	91.5

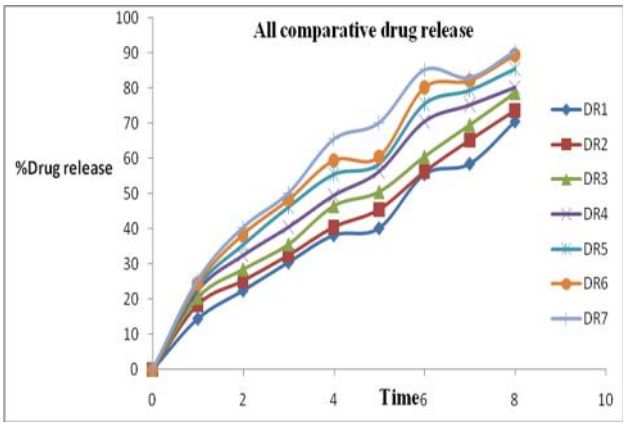

Figure- 6 : Drug release of all formulations

Mechanism of drug release

Table- 6: kinetic studies of metformin

Release kinetics	R^2
Zero order	0.921
First order	0.914
Higuchi	0.946
Korsmeyer peppas	0.729

Zero order kinetics

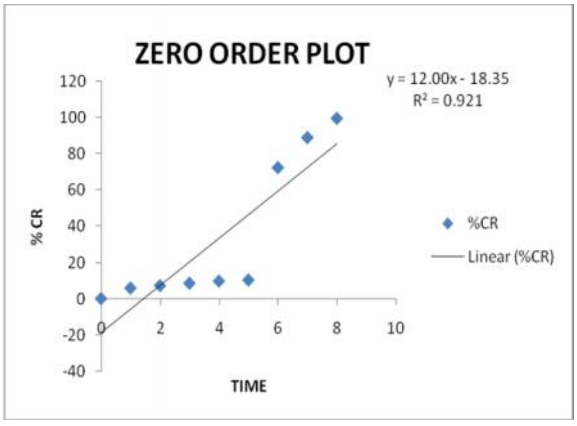

Figure -7: Zero Order Plot For Optimized Formulation

First order kinetics

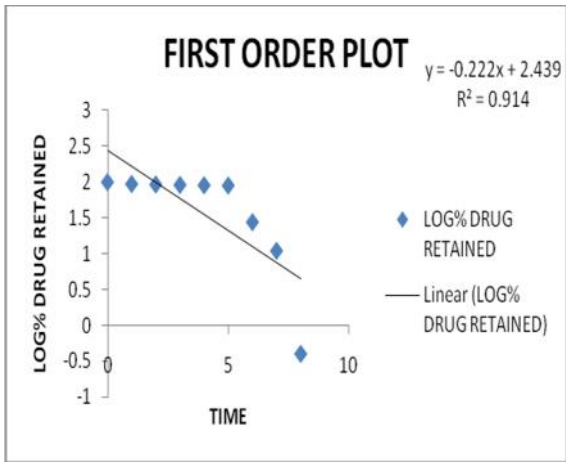

Figure-8 : First Order Plot for Optimized Formulation

Higuchi Model

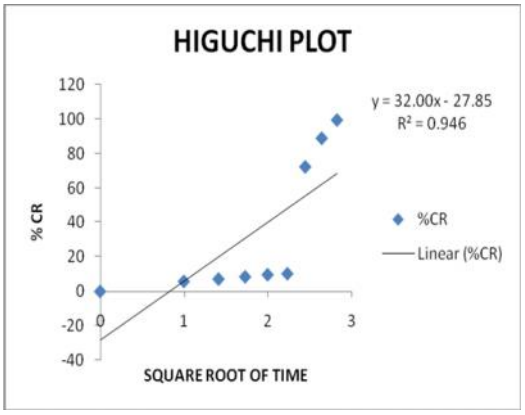

Figure -9 : Higuchi Plot for Optimized Formulation

Korsmayer Peppas equations

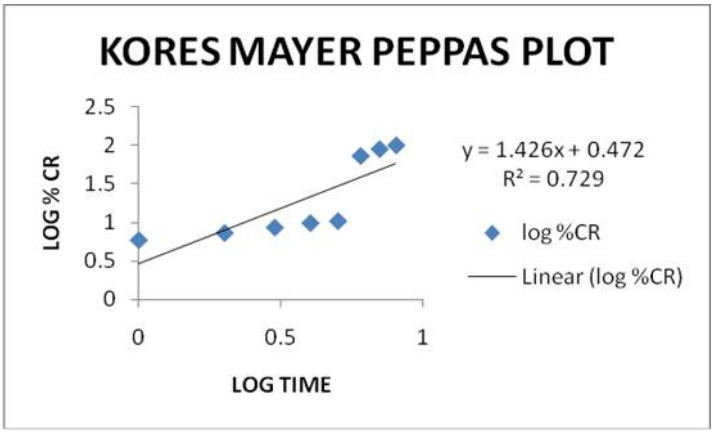

Figure-10 : Kores Mayer Peppas Plot For Optimised Formulation

It was achieve that the best preparation F6, followed zero order release where the regression value was found to be 0.989. It was also found that the drug was released by diffusion as the regression in Higuchi's plot was 0.870.

Stability Results

Stability samples are stored at

- Accelerated: 40±2^{0}C/75±5% RH
- Intermediate: 30±2^{0}C/65±5% RH
- Long term: 25±2^{0}C/60±5% RH

Table -7: Stability studies of best preparations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months for optimization formulation

Formulation Code	Initial	1st Month	2nd Month	3rd Month
F1	98.908	98.82	98.75	98.65
F1	98.908	98.80	98.74	98.56
F1	98.908	98.79	98.72	98.54

It was achieve that stability studies of the optimized was carried out using the samples at temperatures 40^{0}C ± 2^{0}C/ 75% ± 5%RH for a period one month, the Microspheres are observed and there is no significant change in the release characteristics and physicochemical properties and drug release of the capsules.

4. CONCLUSION

By using sustained release polymers such as HPMC and Eudragit and ethylcellulose All the manufactured formulations are carried out all evaluation tests like drug content ,swelling index, particle size, % yield test were done .

In-vitro dissolution studies Metformin hollow microspheres were was of F1-F7 formulations of sustained release Hallow microspheres are manufactured by incorporating eudragit and HPMC as a sustained release polymers in different formulations and PVA used in varying concentrations. The formulation F6 showing drug discharge of 96.8%. Finally, in this development and characterization of Floating Micro particles of Metformin were developed. All the physical parameters of the pure drug that is Metformin was calculated and *In-vitro* drug discharge properties were done. The F6 formulation showed good cumulative drug release profile. Stability study is carried out it is important parameter for optimized formulation to know about the any degradation is taking place for optimized formulation for 1st month at 40^{0}C±2^{0}C/ 75%±5% RH, according to ICH guidelines, the formulation was abounded to be stable. The kinetic drug discharge profile constructed by the Based on the regression values it was consummate that the finalized formulation, F6 follows zero order release where the regression value was found to be 0.988. It was also abound that the drug was discharge by diffusion as the regression in Higuchi's plot was 0.875.

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