Original

BUOYANT MICRO BALLOONS: A NOVEL APPROACH FOR IMPROVED BIOAVAILABILITY OF METFORMIN

Dr. M. SWETHA[1], S. SUPRIYA[2], B. JYOTHSNA[3], Dr. B. HAARIKA[4] , Dr. N. SRINIVAS[5], Dr. R. BALAJI[6]

Associate Professor, Dept. of Regulatory Affairs, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Secunderabad, Telangana, INDIA-500017[1]
M. Pharm. student, Department of Pharmaceutics, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Secunderabad, Telangana, INDIA-500017[2]
M. Pharm. student, Department of Regulatory Affairs, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Secunderabad, Telangana, INDIA-500017[3]
Professor, Department of Pharmaceutics, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Secunderabad, Telangana, INDIA-500017[4]
Professor, Department of Pharmaceutics, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Secunderabad, Telangana, INDIA-500017[5]
Associate Professor, Department of Pharmaceutics, Deccan School of Pharmacy, Hyderabad, Telangana, INDIA- 500001[6]

CORRESPONDING AUTHOR: Dr. M. SWETHA
Associate Professor& HOD, Department of Regulatory affairs
Email: swethasnvpm@gmail.com

Abstract

In this research we focus on enhancing the bioavailability of Metformin, chemically a biguanide anti hyperglycaemic drug with poor solubility and permeability in the gut by utilizing gastric retention techniques. The work involves formulating six Metformin hollow micro balloons using two acid resistant polymers i.e Ethyl cellulose & Eudragit RS 100, in varying ratios to prolong gastric retention. Micro balloons were prepared by Emulsion solvent evaporation method with dichloromethane (DCM) & ethanol as a solvent system which is dropped into 10% HCl solution with high shear stirring .Prepared micro balloons were evaluated for various parameters out of six f4 was optimized , comprising a 1:2 ratio (EC : ER RS 100) which exhibited significant characteristics including high buoyancy (80.19 ± 0.63%), excellent yield (88.84 ± 0.18%), substantial entrapment efficiency (85.63 ± 0.07%), and sustained drug release of 98.58 ± 0.45% over 12 hours. Scanning electron microscopy confirmed the desired hollow morphology and surface characteristics of the micro balloons. This optimized formulation holds promise for enhancing the therapeutic efficacy of Metformin through improved bioavailability and sustained release, potentially offering significant clinical benefits for patients with diabetes.
Keywords: Metformin, Ethylcellulose, Eudragit RS 100, DCM, Ethanol, entrapment efficiency. buoyancy, cumulative percentage drug release.

Article Highlights:

- ✓ Metformin HCl is the widely used anti diabetic drugfor treating type-II diabetes .The major challenge with Metformin conventional dosage form is low bioavailability ,it acts through complex mediated mechanism for drug absorption. Our study was aimed at addressing these challenges.

- ✓ Hence, we have designed micro balloons with pH sensitive polymers such as Ethyl Cellulose &Edrajit Rs100 to achieve sustain release of Metformin HCl through gastric retention by using simple laboratory equipment.
- ✓ By varying the ratio of polymers we prepared 6 batches, out of six f4 was optimized , comprising a 1:2 ratio (EC : ER RS 100) exhibited significant characteristics including high buoyancy, excellent yield, substantial entrapment efficiency and sustained drug release of 98.58 ± 0.45% over 12 hours.
- ✓ SEM confirmed the hollow structure of micro balloons which plays significant role in gastric retention**.**

1. Introduction:

Gastro retentive drug delivery system (GRDDS)

The group of oral controlled drug delivery systems known as gastro retentive drug delivery systems is able to keep drugs in the stomach after they have passed through the gastric transit. The term “floating drug delivery system” is also used to describe these dose forms. This can float in the stomach's contents and deliver the medication slowly over an extended period. The oral administration of drugs is the most favoured route of drug administration. Density, Size, Shape of dosage form, Fed or unfed state, Nature of the meal, Caloric content, Frequency of feed, Gender, Age, Posture, Biological factors, and Concomitant drug administration all are some of the factors affecting Gastro retentive system.[1-3]

Gastro retentive delivery cuts down on doses, improves compliance for fast-acting meds, and boosts availability for drugs broken down in the upper gut. All this leads to steadier drug release with fewer ups and downs. [4]

Limitation of GRDDS[5]

- ✓ Unsuitable for drugs with limited acid solubility. E.g. Phenytoin
- ✓ Unsuitable for drugs those are unstable in an acidic environment. E.g. Erythromycin
- ✓ Drugs that irritate or cause gastric lesions on slow release. E.g. Aspirin and NSAIDs
- ✓ Drugs that absorb selectively in the colon. E.g. Corticosteroid
- ✓ Drugs that absorb equally well through GIT. E.g. Isosorbide dinitrate, Nifedipine

Microballoons:[5-6]

Micro balloonsare also known as hollow sphere drug delivery systems. Micro balloons are in a strict sense, spherical empty particles without cores having an internal hollow structure with air

inside and 200 microns in size. They have a gastric retention drug delivery system (GRDDS), which can improve drug bioavailability and reduce stomach irritation. These floating micro balloons have the convenience that they stay buoyant and circulate uniformly over the gastric ingredients to withhold the variations of gastric emptying and release the drug for an extended period. Micro balloons release the drug in a controlled manner at the targeted site. Micro balloons incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs certain types of drugs can benefit from using gastroretentive devices. These include:

- ✓ Drugs acting locally in the stomach
- ✓ Drugs that are primarily absorbed in the stomach
- ✓ Drugs which are poorly soluble at an alkaline pH
- ✓ Drugs with a narrow window of absorption
- ✓ Drugs absorbed rapidly from the GI tract
- ✓ Drugs that degrade in the colon

2.METHODOLOGY

Materials: All materials used in study were procured from the store of Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Affiliated to Osmania University, Tarnaka, Hyderabad.

Pre-formulation studies: Pre formulation studies intend to engender data used for constructive contrive in mounting studies and bio available dosage forms. The various pre-formulation studies conducted are mentioned below [7]

- ✓ Solubility
- ✓ Drug Excipient compatibility studies
- ✓ Standard calibration curve

Solubility studies: Solubility was determined by using the shake flask method. The solvents- are pH 1.2, 4.5, 6.8 Phosphate buffer, and pH7.4 Phosphate buffer. Solubility was set on by append drug in little sum to a test tube having a fixed aggregate of different solvents. Shake and check the tube for un-dissolved particles and the results are shown in Table No.2. [8]

Drug & Excipient Compatibility Studies: Fourier-Transformed Infrared (FTIR) tested for Metformin & remaining excipients used in study. An FTIR spectrum was drawn for a Metformin and powder mixture of the formulation. Metformin and formulation powders placed on separate watch glasses and dried in an oven at 1oo^{o}C for 3o min, cooled to room temperature, and subjected

to IR spectroscopy. The sample was placed on the crystal, kept in the path of IR radiation, and scanned for 16 cycles. The samples scanned from 4000 - 600 cm-1and the results were shown in Fig. 1 & 2. [9]

Standard calibration curve:100 mg of Metformin was dissolved in 100 ml volumetric flask made volume to 100 ml using 0.1 N HCl, it formed stock-I solution. 1ml from stock-I solution dissolved into 10ml VF and volume made up to 10 ml with 0.1N HCl to form stock solution-II from this solution 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 ml was taken and made to 10ml with 0.1 N HCl and brought out 5, 10, 15, 20, 25, 30µg/ml solution respectively. Absorbance was measured at 232nm on a UV spectrophotometer. Results are shown in table no.3 &fig no-3.[10]

Preparation method of microballoons: Metformin micro balloons were prepared by using the Emulsion solvent evaporation method. Two different polymers in ratio as per formulation table no-1 considered to prepare the different formulations of microballoons. The drug polymer mixture (Eudragit RS -100 & Ethyl cellulose) is dissolved in a mixture of dichloromethane (DCM) and ethanol, this mixture is added in to 250 ml of 10% HCl and the resulting solution stirred with a propeller type agitator with 1500-1700 RPM for 6 hours formation of micro balloons were shown in Fig.1. The formed floating micro balloons were screened &washed with water dry at room temperature in desiccators.[11-12]

Table No. 1: Formulation of Metformin floating microballoons

Formulation Code (Quantity in mg)	Metformin HCl	Ethyl Cellulose	Eudragit Rs-100	DCM: Ethanol	HCl (%)
f1	100	100	250	1:1.	10
f2	100	250	250	1:1.	10
f3	100	500	250	1:1	10
f4	**100**	**250**	**500**	1:1	10
f5	100	250	750	1:1	10
f6	100	250	100	1:1	10

Fig. 1: Formed microballons under mechanical stirrer

Evaluation of micro balloons

Drug entrapment efficiency: The drug entrapment efficiency of micro balloons was estimated for dry powdered100 mg microballoons and the drug in pH 7.4 phosphate buffer with a magnetic stirrer for 2hrand decanted portion was estimated by UV spectrophotometer and drug content was calculated by using the formula method is triplicate**.** [12-15] Results were shown in Table No.5

$$\textbf{\% Drug entrapment} = \frac{\textbf{calculated drug concentration}}{\textbf{Theoretical estimateddrug concentration}} \times \mathbf{100}$$

Percentage yield: The actual weight of the prepared micro balloons divided by the total weight of powder materials used in preparation. [12-15] results are shown in table no-6.

$$\textbf{\% Yield} = \frac{\textbf{Actual weight of the product}}{\textbf{Total weight of the powder materials}} \times \mathbf{100}$$

In vitro buoyancy: 200 mg of Micro balloons are spread over the surface of a USP-II dissolution beaker & stirred with a paddle at 100 rpm for 1o hours after stirring floated portion of the micro balloons are strained & dried [12-15]. After calculating the dry weight the values are substituted in the given formula. Results are tabulated in table no-7.

$$\textbf{Buoyancy percentage (\%)} = \frac{\textbf{Micro balloons remained floating}}{\textbf{Total mass of balloons}} \times \mathbf{100}$$

Particle size: The optical diameter of all 6batches was measured by an ocular micrometer which was calibrated by a stage micrometer and 100particle's projected diameters size was calculated average particle size was determined and the method was triplicate**.** [12-15] **.** Images are shown in Fig. 5 & 6 and values are shown in Table No. 8.

Surface morphology by using scanning electron microscopy (SEM):

Uniformity of the surface and structure of micro balloons was measured by SEM (ZEISS scanning i**o**n microsc**o**pe -ORION Nan**o**Fab) equipped with a gas ion s**o**urce helium /neon i**o**n beam with high brightness. Sample fixed **o**n carb**o**n tape & fine g**o**ld sputtering applied in a high vacuum evap**o**rator.[12-15] Results were shown in **Fig. 7-12.**

RESULTS &DISCUSSION

Preformulation studies: Solubility studies

Table No. 2: Solubility studies

SOLVENT NAME	AMOUNT OF DRUG SOLUBILITY (mg/ml)
0.1 N HCl	0.102±.36
4.5pH phosphate Buffer	0.168±0.01
6.8pH phosphate Buffer	**0.275±0.04**

Metformin has a better solubility in 6.8pH phosphate buffer compared to other solvents.

Drug & Excipient Compatibility Studies

FTIR spectra of drug

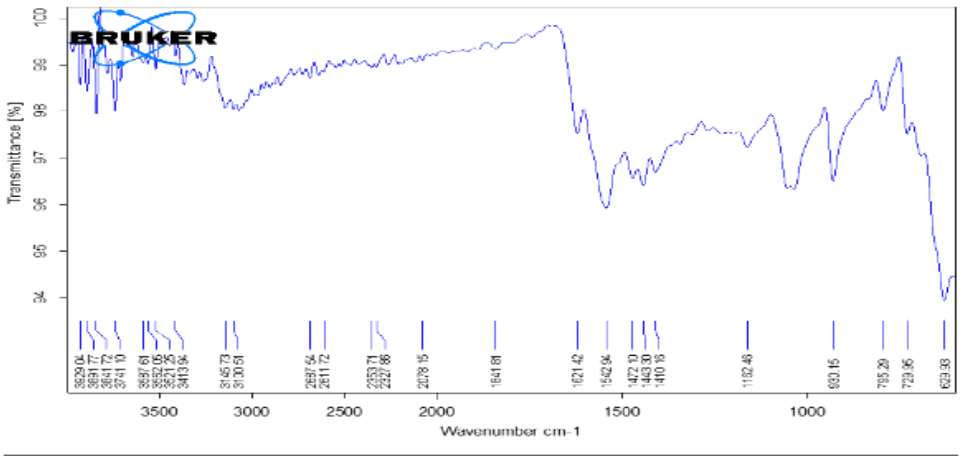

Fig. 2: Drug (Metformin) FTIR spectra

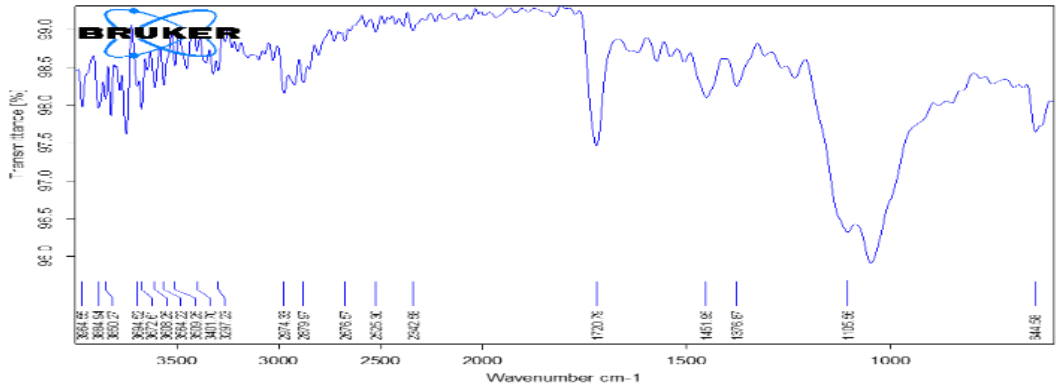

Fig. 3: FTIR spectra of physical mixture

Table No. 3: Functional groups

Functional group	Drug	Formulation
C=C	1443.30	1451.96
N-H	3413.94	3401.70
O-H	3521.25	3544.22

Peaks present in Metformin were also there in the physical mixture of formulation indicating no interaction between the drug & excipients.

Standard calibration curve

Table No.4 : Standard Calibration curve of Metformin HCl in 0.1 N HCl

S.No	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.032
3	10	0.059
4	15	0.089
5	20	0.111
6	25	0.142
7	30	0.172

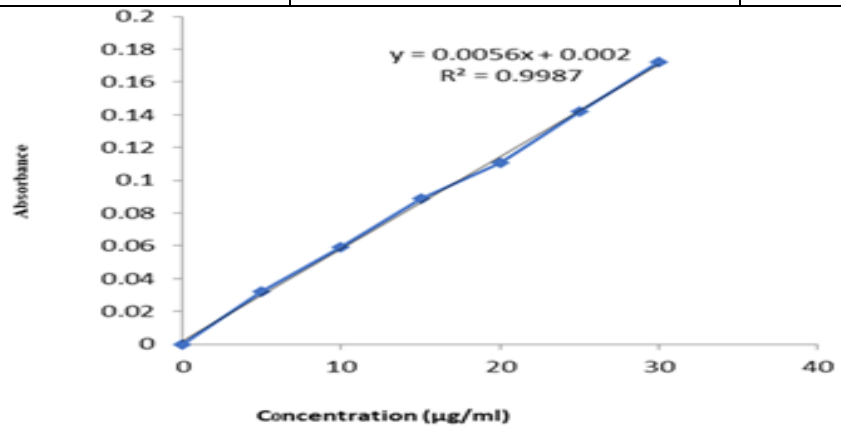

Fig. 4 : Standard Calibration curve of Metformin HCl in 0.1 N HCl

Evaluation of micro balloons

Drug entrapment efficiency

Table No. 5 : Drug entrapment efficiency

Formulation code	Entrapment efficiency (%)
f1	65.11±0.07
f2	70.59±0.08
f3	72.74±0.06
f4	85.61±0.07
f5	72.49±0.01
f6	80.23±0.07

From the results, we have observed all six formulations were shown drug entrapment efficiency above

65% and we have observed the change in value when the ratio of ethyl cellulose and eudragit RS-100 is changed. Out of six formulations EC:ERS-100 (1:2) has shown better entrapment.

Percentage yield

Table No. 6 : Percentage yield

Formulation code	Percentage yield
f1	42.36±0.11
f2	58.73±0.15
f3	79.44±0.1
f4	89.81±0.13
f5	78.60±0.12
f6	80.11±0.16

The percentage yield improved with the concentration of Eudrajit RS100. However, as the concentration of Eudrajit RS100 gone above 750 mg and ethyl cellulose has come down to 250 mg the percentage yield has changed.

In vitro buoyancy

Table No. 7: In-vitro buoyancy

Formulation code	Percentage of buoyancy
f1	42.41 ± 0.31
f2	63.48 ± 1.82
f3	68.89 ± 0.62
f4	**81.19± 0.6**
f5	77.51± 1.04
f6	73.64 ± 0.73

The buoyancy improved with increase in Eudrajit RS100 concentration.

Particle size

Table No. 8: Particle size

Formulation code	Particle size(µm)
f1	89.51±0.1
f2	88.5±0.23
f3	79.89±0.1
f4	128±0.1
f5	95±0.12
f6	110.10±0.8

Fig. 5 : Calibration of ocular micro meter

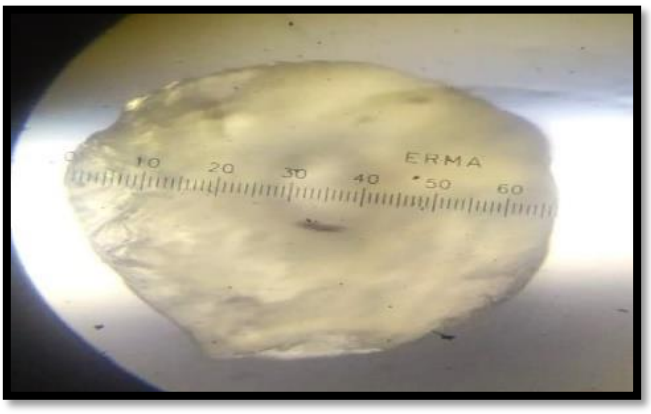

Fig. 6 : Optical views of micro balloon

Surface morphology: Scanning Electron Microscopy (SEM):

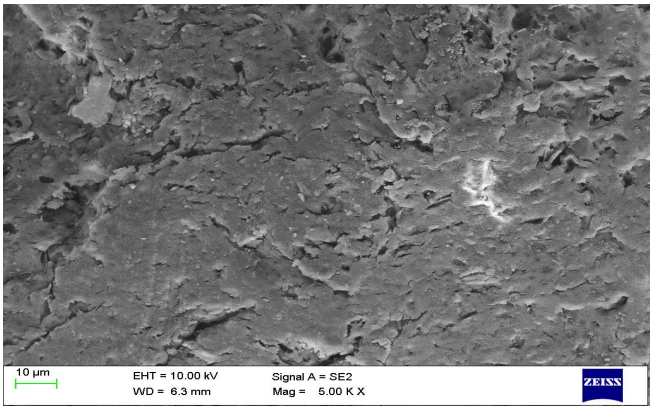

Fig. 7: Surface morphology under 5KX lense

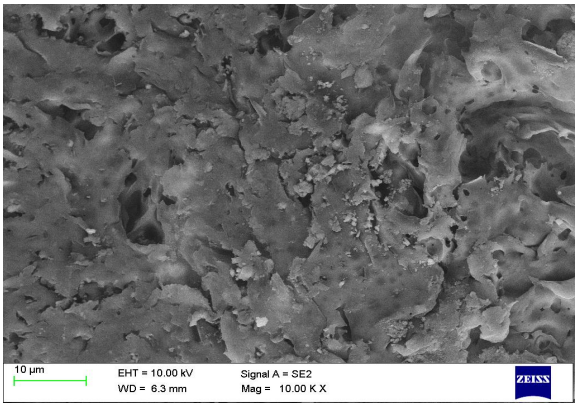

Fig. 8 :Surface morphology under 10KX lense

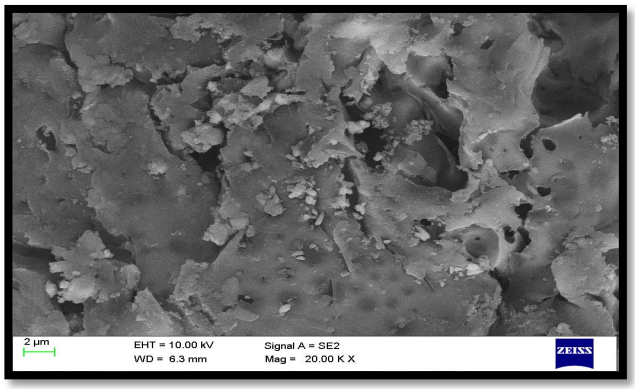

Fig. 9 :Surface morphology under 20 KX lense

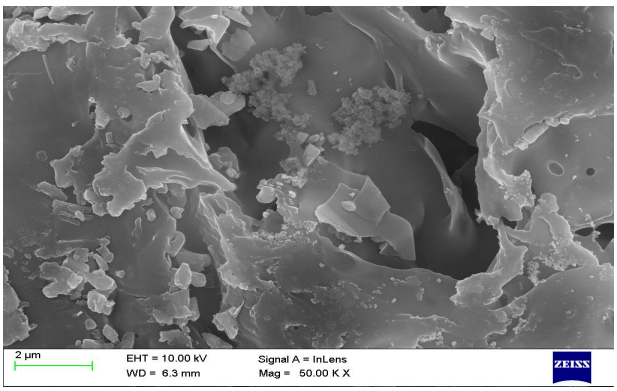

Fig. 10: Surface morphology under 50KX lense

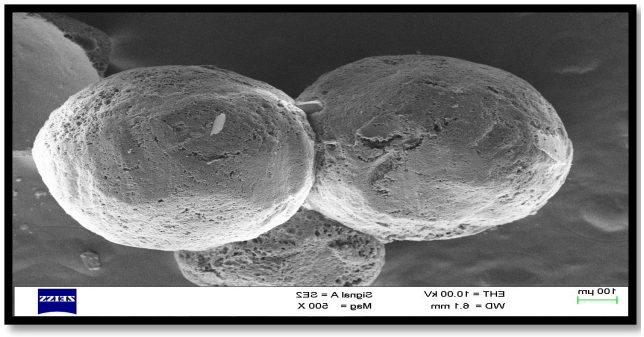

Fig. 11: Surface morphology under 500X lense

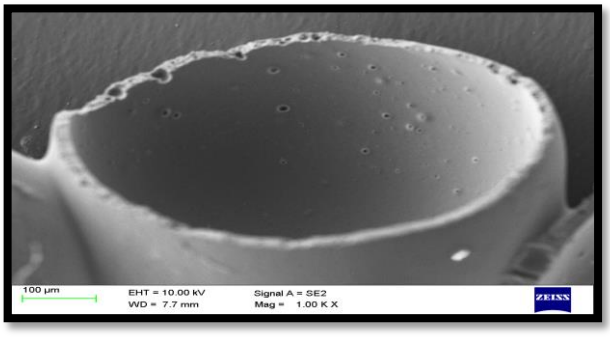

Fig. 12 : Surface morphology under 1KX lense

Scanning eletron microscopy studies were conducted for F4 formulation. Which shown uniform surface under different lenses. Under 1 KX lense, 1oo µm diameter and WD 7.7 mm, f4 has shown established hallow structure.

CONCLUSION

- ✓ As per the work we are concluding that Gastro Retentive Hollow micro balloons loaded with metformin prepared bytheemulsion solvent evaporation method by using different concentrations of acid-resistant polymers such as Ethyl cellulose, Eudragit RS 1oo dispersed in DCM and Ethanol as a solvent system are offering better gastric retention and sustained release.
- ✓ Hollow micro balloons had shown significantfloating ability, good surface morphology, entrapment efficiency, Buoyancy percentage-&sustained drug releasefor 12 hrs.*cumulative percentage drug release*of micro balloons influenced by polymer concentration.
- ✓ As per the results among all the formulations f4 formulation with 1:2 Ethyl cellulose &Eudragit Rs100showed 80.19 ± 0.63% buoyancy, 88.84±0.18 % yield,85.63±0.07% entrapment efficiency and 98.58±0.45% of invitro drug release at 12 hrs it shows the potent sustain release. Title is justified by improving the bioavailability of Metformin.

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