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FORMULATION AND EVALUATION OF METFORMIN SUSTAINED RELEASE TABLETS

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ABSTRACT

The objective of the present investigation was to design and develop sustained release of Metformin tablets. Metformin sustained release tablets were developed different polymers like HPMC K_4 M, Guar gum and Eudragit with different ratios. Totally three formulations were prepare. Sustained release tablets of Metformin were prepared by direct compression technique. The prepared tablets evaluated in terms of their Pre-compression studies like Tapped Density, Bulk Density, Angle of repose, Carr's Index and Hausner's ratio, Post-compression studies like hardness, thickness, friability and *in vitro* studies. The results of *in vitro* drug release studies showed that formulation-2 (API and Guar gum) has better drug release (97.74%) for 8hrs.

KEYWORDS

Metformin, HPMC K_4 M, Guar gum, Eudragit and *Invitro* study.

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INTRODUCTION[1]

Sustained release is defined as the delivery of drug as an initial (loading) dose immediately and the loading dose is followed by a slow constant release. It is the drug delivery system that is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients.

Drawbacks of Conventional Dosage Forms

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.

Metformin is effective only in the presence of insulin, and its Metformin improves hyperglycemia primarily through its suppression of hepatic glucose production (hepatic gluconeogenesis). Metformin activates AMP-activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats; activation of AMPK is required for metformin inhibitory effect on the production of glucose by liver cells. Activation of AMPK is required for an increase in the expression of SHP, which in turn inhibits the expression of the hepatic gluconeogenic genes PEPCK and Glc-6-Pase.

Chemical name: *N*, *N*-dimethyl imido dicarbon imidicdiamide.

Molecular formula : C4H11N5.

Molecular weight : 129.16364 (gm/ mole).

The chemical structure of metformin shown in the Figure No.1.

MATERIAL AND METHODS[1]

Metformin, HPMC K_4 M, Guar gum, Eudragit, PVP, Citric acid, Mg. Stearate and talc. All chemicals are provided by A.M. Reddy Memorial College of Pharmacy.

Method

All the ingredients according to formula was passed through sieve in order to enhance the flow and compaction properties and drug was triturated with polymer in a glass mortar and pestle to achieve a homogenous blend and geometrically mixing was done with effervescent agent, filler and other excipients according to the formulae were passed through the mesh and thoroughly the blend was mixed with lubricant ensure complete mixing. Then Tablets were compressed by using 10.0mm diameter, spherical tablet punches on a 16 station rotary compression machine.

EVALUATION PARAMETERS[1, 2]

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy

The Fourier transform infra-red analysis was conducted for the structure characterization. FTIR spectra of the pure drug, polymers and formulations were recorded by using BOMEN MB SERIES FTIR instrument. Approximately 5mg of samples were mixed with 50mg of spectroscopic grade KBr, samples were scanned in the IR range from 500 to 3500 cm^{-1}, with a resolution of 4 cm^{-1}.

Pre-compression studies of tablet granules

Bulk density

3gm of granules were weighed separately and transferred into 100ml measuring cylinder, initial volume was measured and calculated according to the formula

Formula

Bulk density = Mass / Volume

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the granules in the cylinder and this minimum volume, the tapped density may be computed.

Formula

Tapped density = Weight of granules/ Tapped volume of granules

Angle of Repose

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The most commonly used of this in angle of repose, which may be determined experimentally by number of methods. The method used to find the angle of repose is to pour the powder a conical on a level, flat surface and measure the included angle with the horizontal.

Formula

$$\theta = \text{Tan}^{-1} (h/r)$$

Where,

θ **= Angle of repose,**

h = Height of the powder cone,

r = Radius of the powder cone.

Compressibility Index or Carr's Index

Carr's Index is measured using the values of bulk density and tapped density.

The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where, TD = Tapped density**,** BD = Bulk density

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

Formula

Hausner's Ratio = Tapped density/Bulk density

Evaluation of tablets[3, 4, 5]

Hardness or Crushing strength Test

Hardness of the tablet was determined using the Monsanto hardness tester.

The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Sustained release tablets have a hardness of 10 -20 kg ; however, Oral disintegrating tablets normally have a hardness of 4 to 10 kg and hypodermic and chewable tablets have a hardness of 3 kg.

Thickness Test

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each tablet thickness was determined using a Vernier calipers and the reading was recorded in millimeters.

Friability Test

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The Conventional compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \times 100$$

Where,

I - Initial weight **F** - Final weight

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets was tested using a Strong- Cobb hardness test. Friability of the tablets was determined in a Roche friabilator. The thickness of the tablets was measured by Vernier caliper. Weight variation test was performed according to the official method.

Dissolution test[3, 4]

In vitro drug release from tablets was studied using a USP 24 dissolution apparatus type 2 (USP 2000) at 50 rpm. The study was carried out in 900 mL 0.1N HCl at 37±0.5 ºC for first 2 hours and then in 900 mL of phosphate buffer (pH 6.8) from 3 to 8 hours. Sink condition was maintained for the whole experiment. The paddle was rotated at 50 rpm at temperature ($37_0C \pm 0.5^0C$). Sampling was done at regular intervals and was replaced by media after each sampling interval. The samples are then analysed spectrophotometrically at λmax of the drug (FDA method).

RESULTS AND DISCUSSION

The tablets were evaluated for different parameters like weight variation, thickness, hardness, drug content and *invitro* evaluation studies and stability studies. Observations of all the formulations form physical characterization have shown that the formulations show optimum results.

The pre compression results are shown in the Table No.1.

The post compression results were tabulated and shown in the Table No.2 and *invitro* evaluation results are shown in the Table No.3 and Figure No.2-4.

Pre compression Studies

Table No.1: Flow Properties

Formulation code	Bulk Density	Tapped Density	Carr's index	Hausner's ratio	Angle of repose
F1	0.31	0.34	10.88	1.12	24.2
F2	0.37	0.44	15.9	1.18	24.2
F3	0.46	0.53	16.9	1.20	25.7

Table No.2: Post compression studies

S.No	Formulations	Hardness Test(kg/cm)	Thickness Test (mm)	Friability Test (%)
1	F1	12.25	5.09	0.576
2	F2	12.61	5.11	0.579
3	F3	12.12	5.1	0.605

Table No.3: *Invitro* Dissolution studies

Time (hrs)	F1	F2	F3
0	0	0	0
1	19.75	16.47	16.11
2	27.93	48.49	64.14
3	38.53	53.56	72.63
4	42.76	58.44	72.84
5	46.99	64.36	73.04
6	46.99	64.36	73.04
7	75.38	89.1	90
8	90.41	97.74	92.86

Table No.4: Standard Curve for Metformin

Concentration	Absorbance at 236 nm
0	0
2	0.148
4	0.377
6	0.536
8	0.721
10	0.932

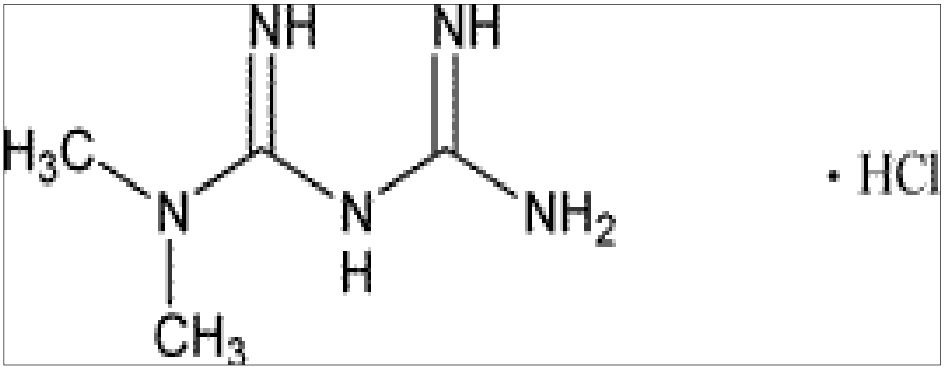

Figure No.1: Chemical structure of Metformin

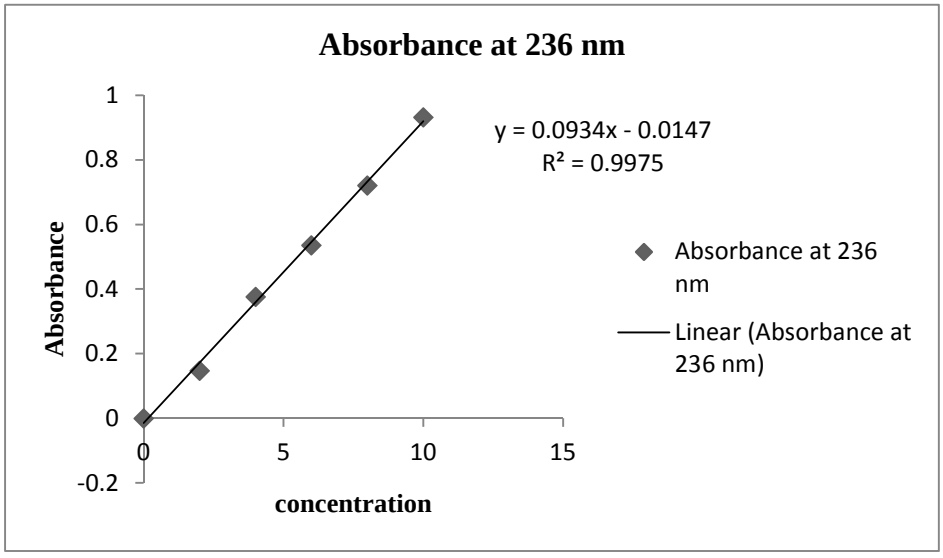

Figure No.2: Standard curve of Metformin

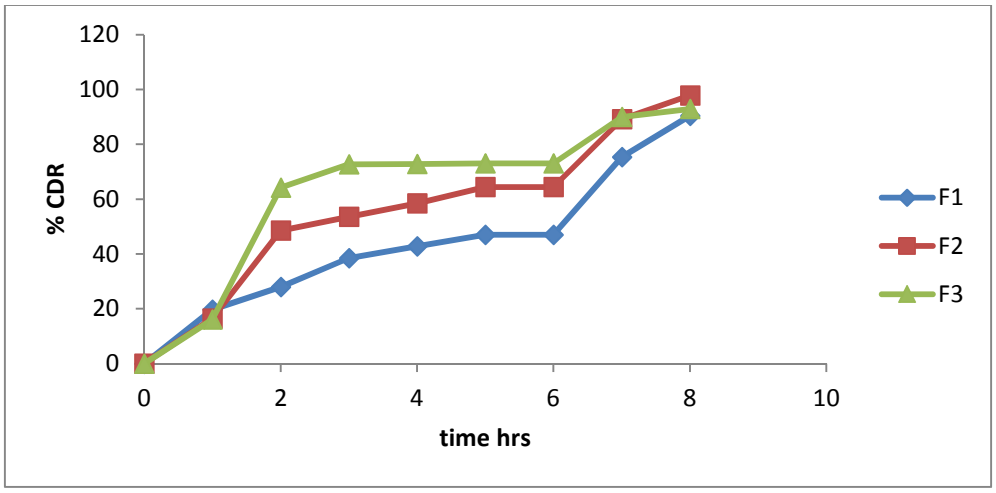

Figure No.3: *Invitro* Dissolution studies

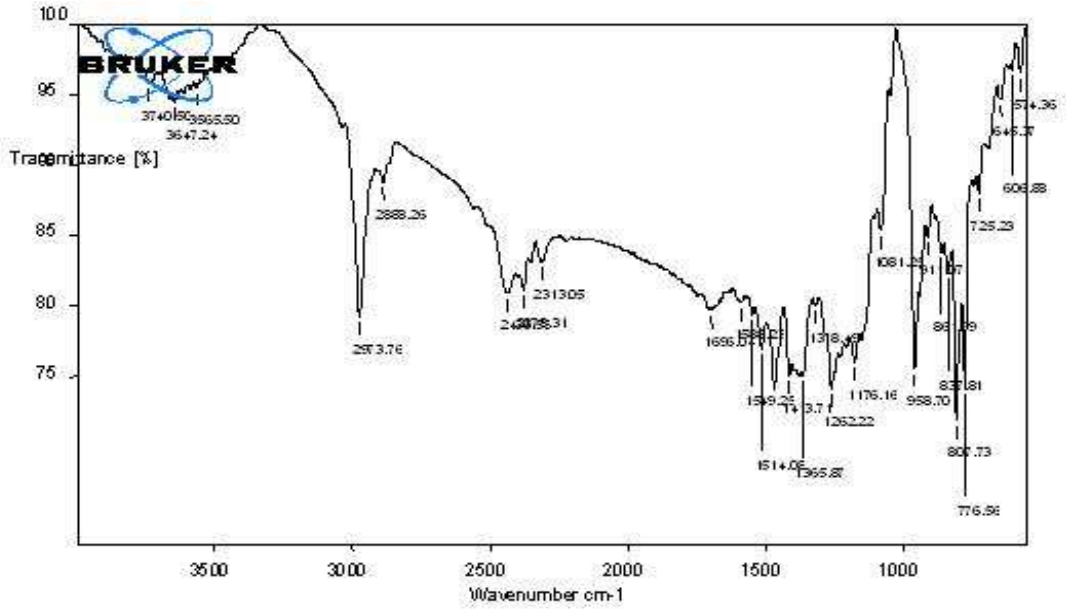

Figure No.4: FT-IR studies for Best formulation

CONCLUSION

Metformin in combination with HPMC K_4 M, Guar gum and Eudragit formulated sustained release formulations. FT-IR spectral studies indicated there was no interaction between Metformin and polymers used. Metformin tablets were prepared with combination of these polymers and evaluated. From the results, it was observed that all parameters were suitable for maximum stability of the prepared formulations.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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