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PREPARATION AND IN VITRO CHARACTERIZATION OF SUSTAINED RELEASE MATRIX TABLET OF METFORMIN HCL

Abhishek Dwivedi*, Dr. Arun Patel, Shailendra Patel and Neelesh Dwivedi

Shri Ram Group of Institute of Technology Jabalpur.

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***Corresponding Author**
Abhishek Dwivedi
Shri Ram Group of Institute of Technology Jabalpur.

ABSTRACT

The objective of this study was to prepare sustained release Metformin HCl matrix tablets using appropriate polymer in alone or combination and evaluate the *in vitro* release characteristics and to predict and correlate the release behavior of Metformin HCl from the matrix tablet and compare with marketed preparation. The low bioavailability and short half-life of Metformin Hcl (MH) make the development of sustained-release forms desirable. However, drug absorption is limited to the upper gastrointestinal (GI) tract, thus requiring suitable delivery systems providing complete release during stomach-to-jejunum transit. This study was undertaken to develop a MH sustained-release formulation in compliance with these requirements.

KEYWORDS: DIABETES, METFORMIN, CARBOPOL, SUSTAINED-RELEASE, DRUG RELEASE KINETICS, SODIUM ALGINATE.

INTRODUCTION

A matrix system consists of active and inactive ingredients that are homogeneously mixed in the dosage form. In matrix systems, the drug is uniformly dissolved or dispersed. A matrix (or monolith) device is easy to formulate and gives a higher initial release rate than a reservoir device and can be made to release at a nearly constant rate. A monolithic solution device contains drug solution within the polymer, whereas a monolithic dispersion contains dispersed solid drug in a rate-limiting polymer matrix. For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms. The presence of water decreases the glassy-rubbery temperature (for HPMC

from 184°C to below 37°C), giving rise to transformation of glassy polymer to rubbery phase (gel layer). The enhanced motility of the polymeric chain favours the transport of dissolved drug. Polymer relaxation phenomena determine the swelling or volume increase of the matrix. Depending on the polymer characteristics, the polymer amount in the rubbery phase, at the surface of the matrix, could reach the disentanglement concentration; the gel layer varies in thickness and the matrix dissolves or erodes. The concentration at which polymeric chains can be considered disentangled was demonstrated to correspond to an abrupt change in the rheological properties of the gel. Showed a relationship between rheological behavior of HPMC gels and their erosion rate, conforming that the polymer-polymer and polymer-water interaction are responsible for the gel network structure and its sensitivity to erosion. In turn, they affect drug release rate in the case of poorly soluble drugs.

MATERIAL AND METHOD

MATERIAL- The drug (Metformin HCl) was obtained as a gift sample from Novartis Pharmaceutical Mumbai, India. Sodium alginate, Magnesium stearate, Microcrystalline cellulose (MCC) and Talc were purchased from CDH laboratory Delhi. Carbopol was purchased from Hi-media, laboratory Mumbai. All the other reagents used during experiment were of analytical grade. Double distilled deionised water was used during the whole experiment.

EQUIPMENTS

Table no. 1: list of instruments used in analysis.

S. No.	Instrument	Manufacturer
1.	Double beam UV Visible Spectrometer	LABINDIA 3000+
2	FT-IR	BRUKERS ALPHA
3.	Dissolution Apparatus	LABINDIA DS-8000
4.	Electronic Balance	Wencer
5.	Hot air oven	Labotech India
6.	Melting point apparatus	Chemline

METHOD OF PREPARATION MATRIX TABLETS OF METFORMIN HCL

Matrix tablets containing 500 mg of Metformin HCl along with various amounts of polymers such as Sodium alginate, Carbopol-940, and other excipients (such as, magnesium stearate, talc and MCC) were used and tablets were prepared by direct compression technique. MCC was passed through mesh No.40. in the first step, the drug and the additives with the exception of magnesium stearate, talc were mixed in a mortal pastel for 5 minutes. Then magnesium stearate, talc was added and formulation was mixed for an additional 2 minutes.

Desired amount of blend was directly compressed into tablets using rotary tablet compression machine (RIMEC, MINI PRESS-1) 13 mm flat die punches. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate and talc. All the preparations were stored in airtight containers at room temperature for further studies.

MCC passed through mesh No. 40

Drug, Polymer and excepients were mixed in mortal pastel for 5 min

Magnesium stearate, talc were added and mixed for an additional 2 min.

Directly compressed into tablets using rotary tablet compression machine

CHARACTERIZATION PRE-COMPRESSIVE PARAMETERS

Table no. 2: Characterization pre-compressive parameters.

Formulation Code	Angle of repose	Loose Bulk density(g/ml)	Tapped Density(g/ml)	Hausner factor	Carr's Index (%)
MS-1	29.95±1.4	0.47±0.01	0.64±0.01	1.36	26.24±2.5
MS-II	28.67±1.3	0.46±0.01	0.64±0.03	1.39	27.56±6.1
MS-III	28.62±1.9	0.47±0.009	0.68±0.02	1.44	31.34±1.6
MS-IV	29.26±2.3	0.48±0.01	0.66±0.03	1.37	26.53±5.6
MS-V	26.71±2.6	0.49±0.01	0.64±0.01	1.30	23.54±3.2

The values ≤ 30 indicates the free flowing powder and values ≤ 40 suggest poorly flowing material.

CHARACTERIZATION FOR AFTER COMPRESSIVE PARAMETERS

20 tablets from each batch were randomly selected and were weighed accurately and then finely powdered. To a powder equivalent to 100 mg of Metformin HCl about.

Table no. 3: Characterization pre-compressive parameters.

Formulation code	Thickness (mm)	Hardnss (Kg/cm^2)	Weight variation (mg) (%devn.)	Friability (%)	Drug content (%)
MS-1	5.0±0.1	8.3±0.2	701.5±3.9	0.55±0.03	97.41±1.21
MS-II	5.1±0.1	8.4±0.2	701.05±4.3	0.69±0.01	97.68±1.16
MS-III	5.5±0.3	8.4±0.3	698.9±4.9	0.57±0.03	98.16±1.19
MS-IV	5.2±0.4	8.3±0.1	702.2±4.6	0.60±0.01	97.11±1.80
MS-V	5.5±0.3	8.8±0.2	701.9±4.02	0.57±0.03	96.31±2.22

Table no. 4: Cumulative Drug Release Profile Of Various Formulations.

Sr. no	Time (hr)	% Cumulative drug release (±s.d)				
		MS-I	MS-II	MS-III	MS-IV	MS-V
1.	1	20.04±1.21	22.54±1.23	28.88±1.88	13.22±0.72	10.17±1.25
2.	2	41.22±0.58	43.66±1.37	46.88±1.66	36.66±0.22	32.40±0.67
3.	3	48.44±1.22	56.17±1.44	56.22±1.44	45.22±1.12	43.21±1.24
4.	4	53.66±1.48	68.40±1.16	62.22±1.44	56.44±0.98	52.01±1.66
5.	5	61.74±0.58	74.22±1.33	63.66±1.08	61.78±1.12	61.41±1.24
6.	6	67.02±1.68	82.34±2.20	73.24±1.44	67.54±1.66	70.65±1.67
7.	7	75.22±2.60	84.56±1.37	75.24±1.46	71.44±0.88	75.65±1.28
8.	8	78.41±2.11	89.29±1.31	79.44±0.98	79.22±0.12	80.22±0.68
9.	9	81.27±1.80	93.66±1.10	85.22±0.22	80.46±1.88	83.12±0.66
10.	10	86.64±1.04	98.28±0.87	93.66±0.44	86.22±0.12	88.34±0.98

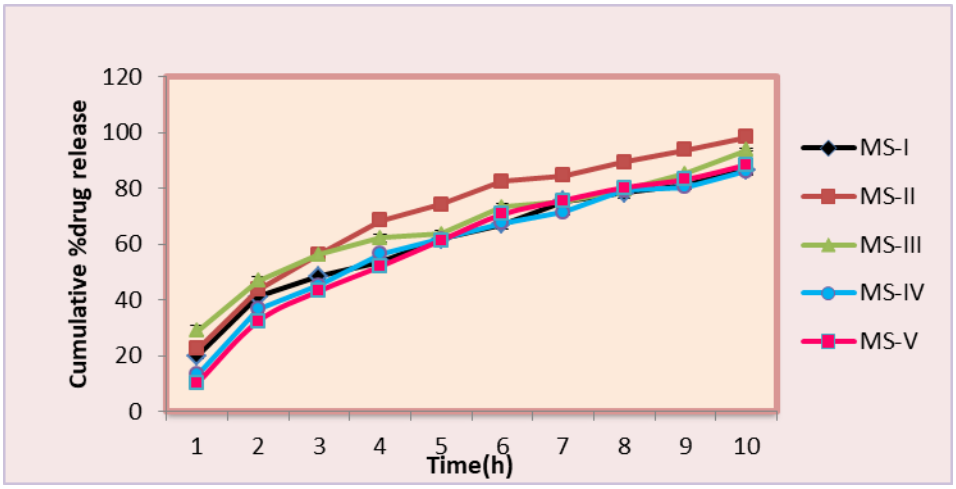


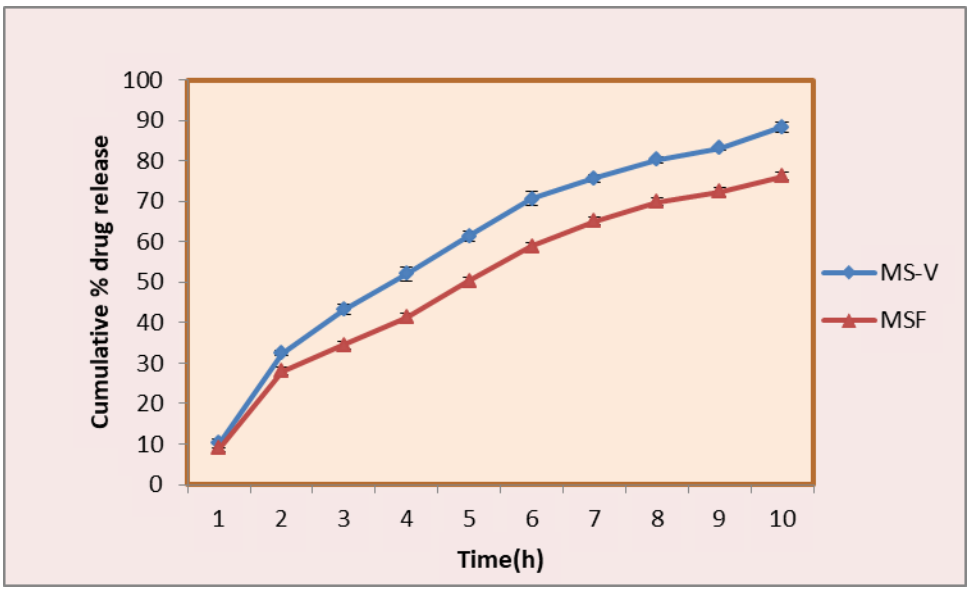
Fig 1: Cumulative % drug release from matrix tablets metformin HCl.

RESULT AND DISCUSSION

The marketed preparation has slower dissolution rate while formulated product also showed slower dissolution rate. The main region of slow dissolution rate of prepared product the change of concentration of polymer and the carbopol resins are hydrophilic substances that are not soluble in water. Rather, these polymers swell when dispersed in water forming a colloidal, mucilage-like dispersion. So release rate of metformin Hcl decrease; ratio of polymer concentration is increase.

Table no. 6: *In vitro* cumulative % release of drug from matrix tablets of metformin Hcl (formulated MS- V) *Vs* Marketed preparation (MSM).

S.No	Time (hr)	% Cumulative drug release (±s.d)	
		MS-V	MSM (marketed)
1.	1	*10.17±1.25*	*9.05±1.24*
2.	2	*32.40±0.67*	*28.07±2.06*
3.	3	*43.21±1.24*	*34.47±2.50*
4.	4	*52.01±1.66*	*41.31±0.85*
5.	5	*61.41±1.24*	*50.32±0.69*
6.	6	*70.65±1.67*	*58.87±1.57*
7.	7	*75.65±1.28*	*65.05±2.54*
8.	8	*80.22±0.68*	*69.87±0.64*
9.	9	*83.12±0.66*	*72.29±0.58*
10.	10	*88.34±0.98*	*76.21±0.90*



Sustained release matrix tablets of metformin Hcl were successfully prepared using some selected polymers as the release controlling matrices and by employing direct compression method. Direct compression methods can be used alternatively for wet granulation, because it is an easier, simplified and economical method of manufacturing of tablets. A number of research articles are available which are evident that the direct compression is a preferred method of tableting.

All the prepared formulations were evaluated for pre-compressive parameters such as; bulk density, angle of repose, Hausner's factor and compressibility index and after compressive parameters such as such as thickness in diameter, hardness, friability, weight variation, drug content, swelling characteristics and *in vitro* dissolution studies. The values obtained were

found to be satisfactory and they complies with pharmacopoeial standards and other research articles.

Sustained release matrix tablets of metformin Hcl were characterized to evaluate the pre compressive parameters and after compressive parameters. A quantity of 2.5 g of powder from each formula, the angle of repose found in range 26.71 to 29.95. The results of angle of repose (<30) indicate good flow properties. The values of Hausner's factor are under satisfactory ranges from 1.30 to 1.44. Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2.5 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10-mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2- second intervals. Both loose bulk density (LBD) and tapped bulk density (TBD) were found in range 0.46 to 0.49 g/ml (LBD) and.0.63 to 0.68 g/ml (TBD). The compressibility index of the powder was determined by Carr's compressibility index, it was found in range 23.54 to 31.34%.

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