Available online on 15.07.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

A Review: Formulation and Optimization of Sustained Release Eudragit Coated Metformin Hydrochloride

Ritu Verma*, Avinash Kumar Gupta, Vijay Sharma, Dr. Manish K. Gupta

Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

ABSTRACT

The basic rationale of sustained release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure of the disease is achieved. There are several advantages of sustained release (matrix) drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, reduction of fluctuation in steady-state drug levels, maximum utilisation of the drug, increased safety margin of potent drug, reduction in healthcare costs through improved therapy and shorter treatment period. Metformin hydrochloride is a biguanide antihyperglycemic agent which is a generally recommended first-line drug for the treatment of diabetes mellitus (Type II). When drug release is needed over a specific period of time or one would like to benefit from the advantages of multiparticulate or matrix formulations – Eudragit polymers can help to achieve desired release profile. Drug delivery can be controlled throughout the entire gastrointestinal tract to increase therapeutic effect and patient compliance.

Keywords: Eudragit, sustained release, Metformin hydrochloride(MTF), RL100 & RS100.

Article Info: Received 24 May 2019; Review Completed 25 June 2019; Accepted 29 June 2019; Available online 15 July 2019

Cite this article as:

Verma R, Gupta AK, Sharma V, Gupta MK, A Review: Formulation and Optimization of Sustained Release Eudragit Coated Metformin Hydrochloride, Journal of Drug Delivery and Therapeutics. 2019; 9(4):663-666

http://dx.doi.org/10.22270/jddt.v9i4.3074

***Address for Correspondence:**

Ritu Verma, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

1. INTRODUCTION:

Metformin hydrochloride is a biguanide antihyperglycemic agent which is a generally recommended first-line drug for the treatment of diabetes mellitus (Type II). The purpose of this investigation is to prepare sustained release matrix granules of metformin hydrochloride which are coated to extend the drug release over a longer time period.

Metformin hydrochloride (MTF) that could efficiently deliver the drug in active form and also increase its systemic bioavailability. In vitro and in vivo evaluations were performed to determine the efficacy of the formulation. MTF loaded microspheres were prepared by W/O/O double emulsion-solvent evaporation method and optimized by 32 full factorial design. The ratio of eudragit RL100 & RS100 (EL:ES) and the chitosan concentration were evaluated as independent variables for dependent variables viz. percent drug release (%DR), percent yield (%Y) and encapsulation efficiency (EE).[2]

The metformin hydrochloride pellets were coated in turn with talc powder and Eudragit as the isolating layer and sustained-release layer. The effects of the two layers on the in vitro release of the pellets were investigated. The results showed that the pellets covered with Eudragit NE30D-L30D 55(20:1) had a sustained-release property and was bioequivalent to reference preparation[3]

2. POLYMER PROFILE:

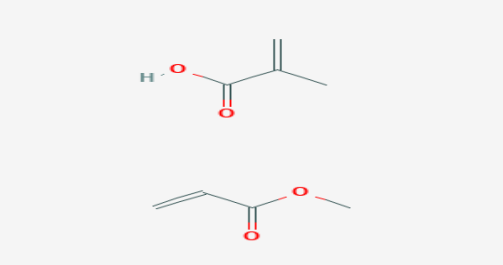

Fig 1: structure of Eudragit[5]

The release of water-soluble drug from a water-soluble polymeric platform is often rapid, and therefore hydrophobic polymer may be included within the matrix formulation to offer a greater control drug release. Among the various polymers, Eudragit RSPO and Eudragit RLPO are the hydrophobic polymers which have been used successfully to formulate appropriate sustained release matrix

formulations.Matrix tablets have been developed by direct compression based on combination of hydrophobic polymers (RSPO and RLPO) and a gelling hydrophilic polymer, HPMC 60SH, to achieve a 20-h sustained release formulation of diltiazem hydrochloride. Film coated matrix tablets using Eudragit NE30D produce a delivery system in which the release of diltiazem hydrochloride is pH independent (from 1.2 to 7.4). Eudragit RSPO was employed to delay the penetration of dissolution medium into the matrix, thereby decreasing drug release rate.[4]

Poly(meth)acrylates are known worldwide in the industry under the trade name Eudragit. These polymers allow the active in solid dosage form to perform during the passage of the human body. The flexibility to combine the different polymers enables to achieve the desired drug release profile by releasing the drug at the right place and at the right time and, if necessary, over a desired period of time. Other important functions are protection from external influences.

3. ADVANTAGES OF EUDRAGIT POLYMERS:

Benefit from Eudragit coatings with sustained release

- Time-controlled release of active ingredients
- Therapeutically customized release profiles
- Higher patient compliance due to reduced number of doses to be taken
- Cost-effective processing[6]

Table 1: Different grades of Eudragit polymers[6]

EUDRAGIT® Polymer	Availability	Dissolution Properties
L 30 D-55	30 % Aqueous Dispersion	Dissolution above pH 5.5
L 100-55	Powder	
L 100	Powder	Dissolution above pH 6.0
L 12,5	12.5 % Organic Solution	
S 100	Powder	Dissolution above pH 7.0
S 12,5	12.5 % Organic Solution	
FS 30 D	30% aqueous dispersion	
E 100	Granules	Soluble in gastric fluid up to pH 5.0.Swellable and permeable above pH 5.0
E 12,5	12.5 % Organic Solution	
EPO	Powder	
RL 100	Granules	Insoluble High permeability pH-independent swelling
RL PO	Powder	
RL 30 D	30 % Aqueous Dispersion	
RL 12,5	12.5 % Organic Solution	
RS 100	Granules	Insoluble Low permeability pH-independent swelling
RS PO	Powder	
RS 30 D	30 % Aqueous Dispersion	
RS 12,5	12.5 % Organic Solution	
NE 30 D 30 %	Aqueous Dispersion	Insoluble, low permeability, pH-independent swelling No plasticizer required Highly flexible
NE 40 D	40 % Aqueous Dispersion	
NM 30 D	30 % Aqueous Dispersion	

4. SUSTAINED-RELEASE FORMULATIONS:

When drug release is needed over a specific period of time or one would like to benefit from the advantages of multiparticulate or matrix formulations – Eudragit polymers can help to achieve desired release profile. Drug delivery can be controlled throughout the entire gastrointestinal tract to increase therapeutic effect and patient compliance. Different polymer combinations of Eudragit RL and RS grades allow custom tailored release profiles to achieve the desired drug delivery performance. Eudragit NE and NM grades are neutral ester dispersions which do not require addition of plasticizer.[6]

5. CRITERIA TO BE MET TO INCORPORATE THE DRUG INTO SUSTAINED RELEASE DOSAGE FORM:

Some physicochemical parameters for the Selecting of the drug to be formulated in sustained release dosage form which mainly includes the knowledge on the absorption mechanism of the drug form the Gastro Intestinal (G.I.) tract.[7]

Table 2: Physicochemical parameters for drug selection[7]

Parameters	Criteria
Molecular size	< 1000 Daltons
Aqueous Solubility	More than 0.1 mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability From all GI segments	Release Should not be influenced by pH and enzymes

Table 3: Pharmacokinetic parameters for drug selection[7]

Parameters	Comment
Elimination half-life	Between 2 to 8 hrs
Absolute bioavaliability	Should be 75% or more
Absorption rate constant (Ka)	Must be higher than release rate
Apparent volume of distribution(Vd)	Larger Vd and MEC, Larger will be the required dose
Total clearance	Not depend on dose
Elimination rate constant	Required for design
Therapeutic concentration (Css)	The lower Css and smaller Vd, the loss among of drug required
Toxic concentration	Apart the value of MTC And MEC safer the dosage form

6. DRUG PROFILE:

6.1 Metformin hydrochloride (MTF):

Metformin hydrochloride extended-release tablets contain an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin hydrochloride (N, N dimethylimidodicarbonimidic diamide hydrochloride) is a member of the biguanide class of oralantihyperglycemics and is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents.

The empirical formula of metformin hydrochloride is C4H11N5•HCl

Molecular weight is 165.63.

Its structural formula is:

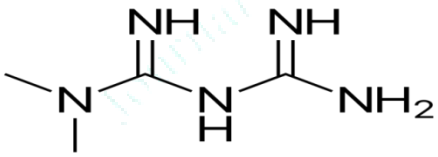

Fig 2: structure of Metformine(Drug)

Metformin hydrochloride is a white to off-white crystalline powder that is freely soluble in water

and is practically insoluble in acetone, ether, and chloroform.

The pKa of metformin is 12.4.

The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

Metformin hydrochloride extended-release tablets are designed for once-a-day oral administration and deliver 500 mg or 1000 mg of metformin hydrochloride.

In addition to the active ingredient metformin hydrochloride, each tablet contains the following inactive ingredients: ammonio methacrylate copolymer type A, ammonio methacrylate copolymer type B, colloidal silicone dioxide, crospovidone, dibutyl sebacate, hypromellose, magnesium stearate, microcrystalline cellulose and povidone.

USP dissolution test for metformin hydrochloride extended-release tablet is pending.[8]

7. PARAMETERS FOR FORMULATION OF SUSTAINED RELEASE DOSAGE FORM:

7.1 Study of physical interaction between drug and polymer:

Infrared spectrum will take by scanning the samples of pure drug and the polymers individually over a wave number range of 4000 to 400 cm^{-1} using Fourier transform infrared spectrophotometer) [9]

7.2 Preparation of Metformin hydrochloride matrix tablets:

Matrix tablets, each containing 500 mg metformin HCl will be prepare by a conventional non-aqueous wet granulation technique. The composition with respect to polymer combination will selected on the basis of trial preparation of tablets.[10]

7.3 Evaluation of granules:

The granules will evaluate for angle of repose, loose bulk density (LBD), tapped bulk density (TBD), compressibility index and drug content. Angle of repose will determine by funnel method. Bulk density and tapped density will determine by cylinder method, and Carr's index (CI) will be calculated using the following equation. Carr's index=(TBD-LBD)×100/TBD. Hausner's ratio will relate to interparticle friction and could be used to predict powder flow properties.[11-13]

7.4 Evaluation of tablets:

The prepared matrix tablets will evaluate for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets will tested using a Strong-Cobb hardness tester. Friability of the tablets will determined in a Roche friabilator. The thickness of the tablets will measured by vernier caliper. Weight variation test will performed according to the official method. Drug content was analyzed by measuring the absorbance of standard and samples at observed nm using UV/Vis spectrophotometer.[14-17]

7.5 *In vitro* drug release studies:

Drug release studies will be conducted using USP-22 dissolution apparatus-2, paddle type at a rotational speed of 50 rpm at 37±0.5°. The dissolution media use 900 ml of 0.1 mol/l HCl for first 2 h followed by pH 6.8 phosphate buffer solution for 12 h. Sink condition will maintain for the whole experiment.[18]

7.6 Statistical Analysis:

The data will subject to two ways ANOVA followed by Bonferroni posttest for analyzing the statistical difference using the software GraphPad Prism.[19-20]

8. CONCLUSION:

The patient compliance and efficiency of dosage form in eliciting desired therapeutic response related problems associated with the conventional dosage forms. Cost effectiveness and once-daily dose are the plus points along with other benefits. Hence, sustained-release matrix tablets trends towards the optimization of the dosage form design. Presently pharmaceutical industries are focusing on development of sustained release formulations due to its inherent boons. Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with

minimum side effects. Eudragit polymers can help to achieve desired release profile. Drug delivery can be controlled throughout the entire gastrointestinal tract to increase therapeutic effect and patient compliance. Different polymer combinations of Eudragit RL and RS grades allow custom tailored release profiles to achieve the desired drug delivery performance.

9. REFERENCES:

1. Brahmankar, HA and Jaiswal, SB (2000), "Biopharmaceutics and Pharmacokinetics A Treatise", Vallabh Prakashan, 337,348- 35.
2. Sahu AK, Verma A. Development and statistical optimization of chitosan and eudragit based gastroretentive controlled release multiparticulate system for bioavailability enhancement of metformin HCl. Journal of Pharmaceutical Investigation. 2016 Jun 1;46(3):239-52.
3. Hu LD, Tang X, Ding Y, Zhang Q. Preparation of Sustained-release Pellets of Metformin Hydrochloride Using Centrifugal Granulation Method. Chinese Journal of Pharmaceuticals. 2005;36(9):541.
4. Mehta R, Chawla A, Sharma P, Pawar P. Formulation and in vitro evaluation of Eudragit S-100 coated naproxen matrix tablets for colon-targeted drug delivery system. Journal of advanced pharmaceutical technology & research. 2013 Jan;4(1):31.
5. https://pubchem.ncbi.nlm.nih.gov/compound/Eudragits#section=Structures
6. Meenakshi Joshi Role of Eudragit In Targeted Drug Delivery Int J Curr Pharm Res, Vol 5, 2013 2, 58-62.
7. H.D.Zalte, R.B.Saudagar Review on Sustained Release Matrix Tablet IJPBS 3:4;|oct-2013;17-29
8. https://www.drugbank.ca/drugs/DB00331.
9. Krishnaiah et al. (2001), "Pharma Times", Vol. 33, 16-18. 3.
10. Shargel, L and Yu, ABC (1999), "Modified release drug products", Applied Biopharmaceutics and Pharmacokinetics, 4 th Ed., McGraw Hill, 169-171.
11. Schall, R and Luus, HG (1997), "Bioequivalence of controlled-release calcium antagonists", Clinical Pharmacokinetics, 32, 75-89.
12. Jantzen, GM and Robinson, JR (1995), "Sustained and controlled-release drug delivery systems", Modern Pharmaceutics, 3 rd Ed., Marcell Dekker, Inc. New York, 72, 575-609.
13. Qiu, Y; Zhang, G and Wise, DL (2000), "Handbook of Pharmaceutical Controlled Release Technology", New York, Marcell Dekker, 465-503.
14. Kamboj, S and Gupta, GD (2009), "Matrix Tablets: An Important Tool for Oral Controlled-Release Dosage Forms", Pharmainfo.net, 7(6).
15. Jantzen GM, Robinson JR(1995), "Sustained and controlled-release drug delivery systems", Modern Pharmaceutics, 3 rd Edi., Revised and Expanded, Drugs and The Pharmaceutical Sciences, Vol 72., Marcell Dekker, Inc., New York, 575-609.
16. Altaf, AS and Friend, DR (2003), "MASRx and COSRx Sustained-Release Technology", Modified Release Drug Delivery Technology, Marcell Dekker Inc., New York.
17. Wani, MS (2008), "Controlled Release System-A Review", 2 6 (1).
18. Vidyadhara, S and Rao, PR et al. (2004), "Indian J. Pharm Sci", 66, 188-192.
19. Reddy, KR; Mutalik, S and Reddy, S (2003), "AAPS Pharm. Sci. Tech.", 4, 1-9.
20. Mohammed, AD et al. (1999), "Phar. Dev. Tech.", 4, 313-324