Available online at www.icjpir.com

ISSN 2349-5448

INTERCONTINENTAL JOURNAL OF PHARMACEUTICAL INVESTIGATIONS AND RESEARCH

ICJPIR |Volume 2 | Issue 1 |Jan-Mar-2015

Research Article

Formulation of an alpha Glucosidase Inhibitors Drug as Mucoadhesive Microspheres – A Review

Piyali Dey, *K Jesindha Beyatricks, D Agilandeswari, M K Mohan Maruga Raja, S Preethi , V Tincy

Department of Pharmacy, Hillside College of Pharmacy & Research Centre, Bangalore

*Corresponding author's Email: **jolyjes@yahoo.co.in**

Abstract

α- glucosidase inhibitors are oral anti-diabetic drugs. These drugs are competitive inhibitors of the intestinal α-glucosidases and reduce post meal excursions by delaying digestion and absorption of starch and disaccharides. Their mechanism of action being limited to the intestinal brush border membrane, and owing to their structural features, they have limited systemic bioavailability, due to which they have much reduced side-effect profile compared to contemporary anti hyperglycemic drugs. Therefore, in the present investigation, an attempt will be made to develop mucoadhesive microspheres of α-glucosidase inhibitor (Miglitol) to enhance the bio- availability and to further reduce the dose and frequency of administration. Microspheres form an important part of novel drug delivery systems. They have carried applications and are prepared using assorted polymers. However, the success of these microspheres is limited owing to their short residence time at the site of absorption. It would therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres. Bioadhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site.

Key words: Microspheres, Miglitol, mucoadhesive, NIDDM.

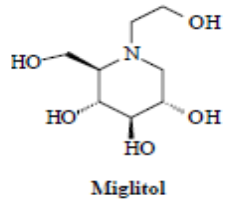
Introduction

Mucoadhesive microspheres include microparticles and microcapsules (having a core of the drug) of 1-1000μm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it, respectively (Mathiowitz E

et.al., 2001). Microspheres, in general, have the potential to be used for targeted and controlled release drug delivery; but coupling of mucoadhesive properties to microspheres has additional advantages. Mucoadhesive and biodegradable polymers undergo selective uptake by the M cells of payer patches in gastrointestinal (GI) mucosa (Heel K.A et.al., 1997) this uptake mechanism has been used for the delivery of protein and peptide drugs, antigens.

Miglitol

Miglitol (MIG) is chemically (2R, 3R, 4R, 5S)-1-(2-hydroxyethyl)-2-(hydroxy methyl) piperidine-3, 4, 5-triol an oral anti-diabetic drug. It reversibly inhibits membrane-bound intestinal alpha-glucosidehydrolyze enzyme which hydrolyzes oligosaccharides and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. In diabetic patients, this enzyme inhibition results in delayed glucose absorption and lowering of postprandial hyperglycemia. Metformin (MET) is chemically N, N-dimethyl imidodi carbonimidic di amide. It is a biguanide class of oral anti-diabetic drugs. It improves hyperglycemia primarily through its suppression of hepatic glucose production and activates AMP-activated protein kinase. It also increases insulin sensitivity, fatty acid oxidation, peripheral glucose uptake and decreases absorption of glucose from the gastrointestinal tract.



Miglitol

Fig.1. Structure of Miglitol

Development

• Slowly absorbable or lente carbohydrates and high fiber diets have been proposed as methods to delay glucose absorption and thus to blunt the postprandial increase in plasma glucose and insulin levels. While these dietary manipulations have been shown to be effective, most patients find the regimen difficult to follow.

• An alternative approach to prevent postprandial hyperglycemia involves the use drugs that function as competitive inhibitors of small intestinal brush-border alpha-glucosidases. By inhibiting these enzymes the digestion of nonabsorbable, poly- and oligosaccharides (starch, sucrose) is prevented and thus the formation of absorbable monosaccharides (glucose, fructose) is delayed.

Miglitol is the second alpha-glucosidase inhibitor approved for the treatment of Type II (NIDDM). In July of 1996 miglitol was authorized for marketing in the Netherlands under the trade name Diastabol. In December of 1996 the FDA granted clearance for the marketing of miglitol in the US. Miglitol is a simple aminosugar derivative

Pharmacology and Therapeutics

• Miglitol differs significantly from the sulfonylureas and biguanides in their mechanism of action. They function as a high affinity, reversible inhibitors intestinal alphaglucosidase enzymes, particularly pancreatic alpha-amylase and membrane-bound intestinal alpha-glucosidase. Pancreatic alpha-amylase hydrolyzes complex carbohydrates to oligosaccharides in the lumen of the small intestine while intestinal glucosidase hydrolyses oligosaccharides, trisaccharides and disaccharides to glucose and other absorbable monosaccharides in the brush border of the small intestine.

The inhibition of these enzymes thus reduces the rate of formation of "absorbable sugars" and thus delays the rise in blood glucose concentration following meals (postprandial). This action therefore results in attenuation of postprandial plasma glucose 30-35% reduction), as well as insulin, gastric inhibitory polypeptide and triglyceride peaks.

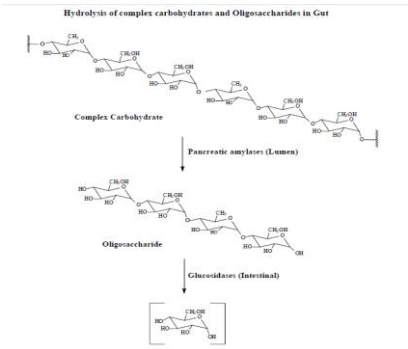
The beneficial effects of Miglitol on postprandial glucose levels have been confirmed in patients with NIDDM and IDDM. Data from clinical trials indicate that Miglitol lowers postprandial and fasting blood glucose levels in by about 20 and 10%, respectively and reduces glycosylated hemoglobin levels (0.6%) in NIDDM patients. The latter effect presumably occurs by an indirect mechanism. Postprandial insulin and triglyceride levels may occasionally lower. These actions also result in a rise in late postprandial plasma glucagon-like peptide 1 levels. Thus in individuals with normal or impaired glucose tolerance with hyperinsulinemia, glucosidase inhibitors decrease hyper insulinemia and improve insulin sensitivity.

The biological half-life of miglitol is 2 hrs. The elimination half - life of miglitol from plasma is approximately 2 hours. Miglitol is used along with a proper diet and exercise program to control high blood sugar in people with type 2 diabetes (Fernado et.al., 1995).

Adverse Reactions

The most common adverse reactions associated with 50 to 300 mg tid miglitol therapy are gastrointestinal in nature and include flatulence (77%), abdominal pain and distension or bloating (21%), diarrhea (33%) and borborygmus. Abdominal pain and diarrhea typically improves upon continued therapy, and the intensity of flatulence also decreases. All of the GI reactions may be minimized by initiating therapy at low doses (25 mg t.i.d). The GI tract symptoms are a manifestation of the mechanism of action of these drugs and are related to the presence of undigested carbohydrate in the lower GI tract where they are fermented by bacteria. Thus these drugs should be avoided in patients with IBD and other GI tract disorders!

• Systemic adverse events associated with miglitol have been reported only rarely. Anemia and elevated transaminase levels are reported to be significantly more common in miglitol than in placebo-treated patients, occurring in 3.8 and 1.1% of patients,



Simple sugar (Glucose etc)

Fig.2. Hydrolysis of complex carbohydrate and Oligosaccharides in Gut

Dose-response (karter aj et.al, 1996)

Results from controlled, fixed-dose studies of miglitolas monotherapy or as combination treatment with a sulfonylurea were combined to derive a pooled estimate of the difference from placebo in the mean change from baseline in glycosylated hemoglobin (HbA1c) and postprandial plasma glucose as shown in Figures 1 and 2:

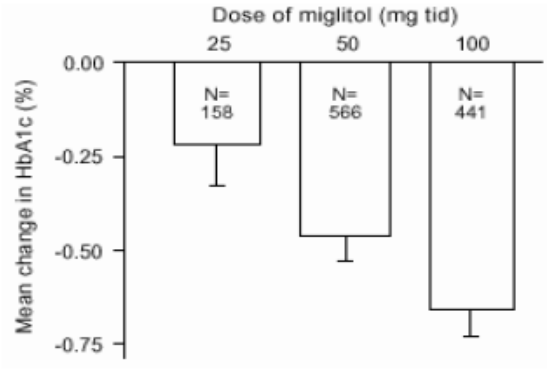


Fig.3. HbA1c (%) Mean Change from Baseline: Treatment Effect
Pooled Results from Controlled Fixed-Dose Studies

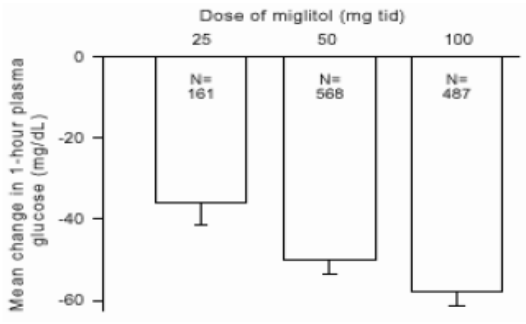


Fig.4. 1- Hour Postprandial plasma Glucose Mean change from baseline: Treatment effect pooled results from controlled fixed-dose studies

Because of its mechanism of action, the primary pharmacologic effect of miglitol is manifested as a reduction in postprandial plasma glucose, as shown previously in all of the major clinical trials. GLYSET was statistically significantly different from placebo at all doses in each of the individual studies with respect to effect on mean one-hour postprandial plasma glucose, and there is a dose response from 25 to 100 mg 3 times daily for this efficacy parameter.

Mucoadhesive Drug Delivery System

Adhesion can be defined as the bond produced by contact between a pressure - sensitive adhesive and a surface (D.E. Chickering and E.Mathiowitz, 1999; Jimenez-Castellanous, 1993). The American Society of testing and materials has defined it as the state in which two surfaces are held together by interfacial forces, which may consist of valence forces, interlocking action or both. (A.Ahuja, et.al., 1997) When the adhesion involves mucus or mucus membrane it is termed as mucoadhesion (J.H.Bhatt, 2009).

Mechanism of Mucoadhesion

The concept of mucoadhesion is one that has the potential to improve the highly variable residence times experienced by drugs and dosage forms at various sites in the gastrointestinal tract, and consequently, to reduce variability and improve efficacy. Intimate contact with the mucosa should enhance absorption. (J.O.Varum Felipeet.al., 2008) The mechanisms responsible in the formation of bioadhesive bonds are not fully known, however most research has described bioadhesive bond formation as a three step process:-

Step 1: The wetting and swelling:

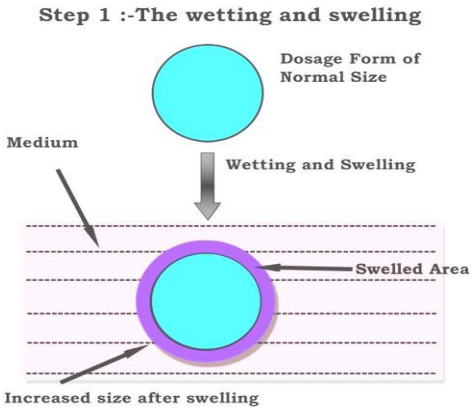


Fig.5. Wetting and swelling

Step 2: Interpenetration between the polymer chains and the mucosal membrane.

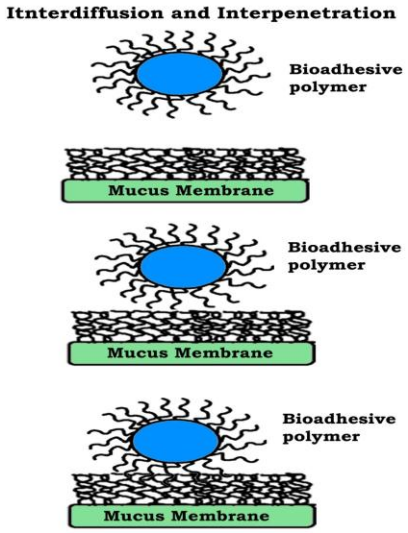


Fig.6. Interpenetration between the polymer chains and the mucus membrane

Step 3: Entanglement of Polymer and Mucus by Chemical bonds

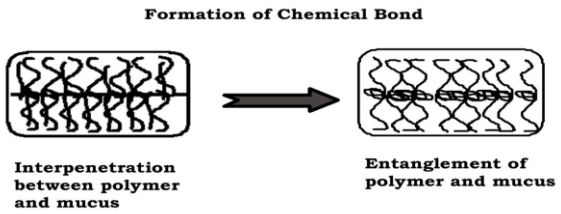


Fig.7. Entanglement of polymer and Mucus by chemical bonds

Conclusion

Alpha-glucosidase enzyme is present ubiquitously throughout the lumen of the small intestine. It is responsible for the breakdown of complex into simple carbohydrates. alpha-Glucosidase inhibitors such as miglitol, are drugs that have greater affinity towards this enzyme in comparison to carbohydrates. Miglitol regulates the postprandial glucose levels directly by inhibiting the enzyme reversibly and also indirectly by including the secretion of

glucagon like peptide-1 (GLP-1). The aims of this study are (i) to design a controlled release (CR) mucoadhesive micropsheres (in the intestine) formulation of miglitol which would inhibit the alpha-glucosidase enzyme for a longer duration of time (in comparison to the non-controlled release (IR) formulation) thus reducing the dosing frequency, and also controlling the postprandial glucose levels more effectively over a longer period of time; (ii) to assess the effect of different formulation parameters on the release of miglitol in vitro (iii) to evaluate the mucoadhesion characters of microspheres in the intestine ex vivo; (iv) to study the effect of formulation parameters on plasma GLP-1 levels; and (v) to find out the effect of formulations on postprandial glucose levels.

Reference

1. Ahuja A.; Khar R.K.; Ali J., (1997), Mucoadhesive drug delivery systems, *Drug. Dev. Ind. Pharm*., Vol.- 23, 489- 515.
2. Bhatt, J.H., (2009), Designing and Evaluation of Mucoadhesive Microspheres of Metronidazole for Oral Controlled Drug Delivery, Pharmainfo.net.
3. Chickering III D.E.; Mathiowitz E., (1999), Bioadhesive drug delivery systems. Fundamentals, Novel approaches, and developments., In Mathiowitz E., Chickering III D.E.; Lehr C.M.; eds., Definitions mechanisms and theories of bioadhesion., New York, Marcel Dekker., 1-10.
4. Fernado E, Conchita B. Efficacy and tolerability of miglitol in treatment of patients with non-insulin dependent diabetes mellitus. *Current therapeutic research*, 1995, 258-268.
5. Heel K.A, McCauley R.D, Papadimitriou J.M et. *al.*, Review-Payer's patches, *Journal of Gastro enterology and Hepatology*, 1997; 12: 122-136.
6. Jimenez-Castellanos N.R.; Zia H.; Rhodes C.T., (1993), Mucoadhesive drug delivery systems. *Drug. Dev. Ind. Pharm*., Vol.-19, 143-194.
7. Karter AJ, Mayer-Davis EJ, Selby JV, D'Agostino RB, Haffner SM, Sholinsky P, et al. Insulin sensitivity and abdominal obesity in African-American, Hispanic, and non-Hispanic white men and women. The Insulin Resistance and Atherosclerosis Study. Diabetes 1996; 45:1547-55.
8. Mathiowitz E, Chickering DE, Jacob JS, Mucoadhesive drug delivery system, *U.S. Patent,* 2001; 6: ,346.