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Design and Optimization of Metformin Hcl of Colon Targeted Drug Delivery System

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Abstract

The aim of the present study was to develop colon targeted matrix tablets of Metformin HCl using various conc. of selected polymers such as HPMC, Ethyl Cellulose Guar gum and combination of the same. Tablets were prepared by direct compression method and both pre-compression and post- compression parameters for all batches shows in the acceptable ranges. Short term accelerated stability studies was performed according to ICH guidelines temperature of 400±20 and relative humidity of 75%±5% RH to study any physical changes and chemical decomposition of drug, no formulation shown any physical or chemical changes.The compatibility of drugs, polymers and excipients were determined by FT-IR Spectroscopy results showed that the drug was compatible with polymers and all excipients. Dissolution studies were performed for 12 hours study in 1.2 pH for first 2 hrs then in 7.4 pHfor next 3hrs followed by 6.8pH phosphate buffer at the temperature of 37±0.50C at 100rpm.

Keywords: Polymers; post- compression parameters; chemical decomposition

Introduction

1.1 Conception-

The challenge of targeting medicines specifically to the colonic region of the gastrointestinal tract is one that has been embraced by scientists over the once two decades. The colon has lately been accepted as an decreasingly important point for medicine delivery. Among all the routes of medicine administration that have been explored for the development of controlled release systems the oral route has in far achieved the utmost attention and success. It's to the ease of administration as well as to the fact that gastrointestinal physiology offers further inflexibility in lozenge form design than utmost other routes1.

The scientific framework needed for development of a successful oral controlled medicine delivery consists of an understanding the furrowing aspects-

The physicochemical characteristics of the medicine.

Applicable GI deconstruction and physiology.

Lozenge form characteristics.

The factors to be considered in the design of colon-specific medicine delivery system deconstruction and physiology of colon pH in the colon

Gastrointestinal conveyance

Colonic micro foliage deconstruction and physiology of colon

The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from ileocaecal junction to the anus is divided into three main corridors. These are the colon, the rectum and the anal conduit. The colon is divided into caecum, thrusting colon, depatic flexure, transverse colon, the splenic flexure, descending colon and the sigmoid colon. It's about1.5 m long, the transverse colon being the longest and most mobile part and has an average periphery of about6.5 cm, although it varies in periphery from roughly 9 cm in the caecum to 2 cm in the sigmoid colon.

2. Review of Literature

Morishita M etal.,56 has estimated the utility of colon targeted DHA(docosahexanenoic acid) and EPA(eicosapentanoic acid) as a new diabetic specifics that promote natural glucagon- suchlike peptide- 1(GLP- 1) stashing. The end of this study was to estimate the goods of the long chain adipose- acids DHA and EPA on blood glucose situations, tube insulin and GLP- 1 attention. In addition, point-specific differences in these goods were determined using several intestinal parts, stomach, jejunum and colon.

Sanket D Gandhi etal.,57 has formulated and estimated the colon targeted tablets of secnidazole for the treatment of amoebiasis. The colon as a point for medicine delivery offers distinct advantages on account of a near neutral pH a much longer conveyance time, fairly low proteolytic enzyme exertion and a much lesser responsiveness to immersion enhancers. The formulated tablets were estimated for hardness, frangibility, weight variation, medicine content, in- vitro and stability study.

Kishor sahebrao salunkhe etal.,58 has formulated and estimated the dextrin matrix tablets of ibuprofen for colon specific medicine delivery. The formulated matrix tablets were estimated by different IPQC tests, content uniformity and in- vitro medicine release study. The results of in- vitro study indicate the matrix tablets containing dextrin as carrier and ethyl cellulose as binder are most suitable to deliver the medicine specifically in colonic region as compared to matrix tablets of dextrin with other binder systems.

Kishore G etal.,59 has developed and estimated the colon targeted tablets of praziquantel and its β- cyclodextrin complex to treat schistosomiasis. They planned to ameliorate the solubility of praziquantel by forming addition complex with β- CD. Different phrasings were prepared by changing the attention of matrix carriers and β- CD. phrasings containing xanthum goo and guar goo showed maximum medicine release in colonic terrain. These phrasings were perplexed with β- CD. After complexation of

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praziquantel with β- CD, praziquantel dissolution is significantly increased in colonic terrain.

3. Ideal

Need for the study

The end of the present exploration work was to develop matrix tablets of Metformin HCL targeted to colon.

The delivery of medicines to colon for systemic action or a original effect is precious in a variety of circumstances. These include the topical treatment of conditions similar as ulcerative colitis, Chron's complaint, perverse colon pattern, contagious complaint, colon cancer and the eventuality for the oral delivery of peptides and other labile medicines. Targeting of medicines to the colon via oral route can be achieved by different approaches including different expression system. For which the medicine release is controlled by different pH conditions, conveyance time and microbial foliage.

Metformin HCL is a BCS class- III(largely answerable- unwell passable) biguanide outgrowth that has been used worldwide for the treatment of type- II diabetes. In malignancy of its favorable clinical response chronic remedy with Metformin HCL suffers from certain specific problems of which, the most prominent being the high cure (1.5-2.0 g/ day), partial life is about1.5-3.5 hours, low bioavailability (60) and high prevalence of GI side goods (30 cases). The situation is complicated further with drop in immersion of medicine with food that detainments tmax by over to 35 mins.

Colon targeted medicine delivery systems are developed to increase the bioavailability of medicines since colon is composed of large quantum of lymphoid towel the medicine by passes the first- pass metabolism and enters into the systemic rotation. still Metformin HCL cannot cross the colonic epithelial subcaste since it belongs to BCS class- III. In order to increase the bioavailability of Metformin HCL saturation enhancers like succinic acid is used. therefore, it improves bioavailability there by frequence of dosing is reduced, minimize the GI side goods and improves the patient compliance through CDDS.

4. Medicine Profile

METFORMIN HCL86

Preface

Metformin HCl is an oral hypoglycaemic agent used to lower blood glucose attention in cases withnon-insulin dependent diabetes mellitus. It isn't chemically or pharmacologically related to any other classes of oral anti hyperglycaemic agents.

Structure:

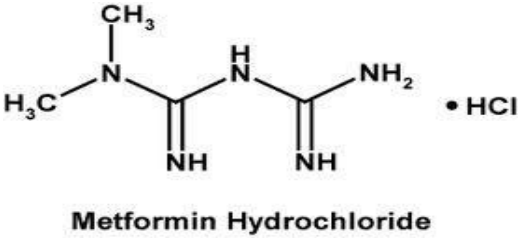

Figure: Structure of Metformin HCl

Chemical Name,1- dimethylbiguanide hydrochloride

Empirical Formula C4H11N5. HCl

Molecular Weight165.62

Melting point 2220C to 2260C

order Hypoglycemic agent

Cure0.5 to 3g daily in divided doses87

pKa12.4

Description White, crystalline greasepaint, hygroscopic.

5. POLYMERS Outline

HYDROXY PROPYL METHYL CELLULOSE91,92

Antonyms Cellulose, Hydroxy propyl methyl ether; HPMC; Propylene glycol Ether; Methocel; Pharmacoat, Methyl cellulose, Methyl hydroxy propyl cellulose.

Chemical Name Cellulose, 2- hyfroxypropyl methyl ether.

Molecular Weight roughly,000

Structure

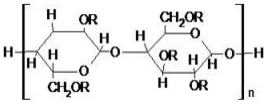

Figure: Structure of HPMC

Category Coating agent, film-former, stabilizing agent, suspending agent, tablet binder and density- adding agent.

Apparent viscosity0.25-0.75 g/ cm3

Description Hydroxy propyl methyl cellulose is an odourless, tasteless, white or delicate-white coloured stringy or grainy greasepaint.

Solubility Soluble in cold water, undoable in chloroform, ethanol and ether, but answerable in fusions of ethanol or methanol and Dichloromethane.

density The density of the polymer is in the range from 75- 140 of the declared value.

Stability and storehouse It's a stable material although it's hygroscopic after drying. Increase in temperature reduces the density of results. It undergoes a reversible response to gel metamorphosis upon heating and cooling independently. The greasepaint should be stored in a well-unrestricted vessel in a cool and dry place.

Incompatibility Extreme pH conditions, oxidizing accoutrements

6. Experimental Studies

Preformulation Studies

Description Visual examination of medicine was done and description as per specification was checked.

Melting point

Melting point of medicine was determined by capillary system in triplet. The melting point was set up to be in the range of 222oC-226oC.

Solubility in different dissolution media redundant quantum of the medicine is added to 100 ml distilled water, 100 ml phosphate buffer pH7.4(intestine), 100 ml phosphate buffer pH6.8(colon). After adding maximum quantum of the medicine shake each volumetric beaker in a shaker for further than 12 hrs for maximum achromatism of the result. also 5 ml of result was removed from each beaker and dilution was made as needed. Absorbance was taken at 233 nm in UV-Visible spectrophotometer.

Preparation of1.2 pH phosphate buffer result

Place 250 ml of0.2 M potassium chloride result (14.911 g/ litre of distil water) in a 1 Litre volumetric beaker add425.0 ml of0.2 M hydrochloric acid and sufficient volume of distilled water to produce 1000 ml blend it well.

Preparation of6.8 pH phosphate buffer result

gm of monobasic potassium phosphate was counted and adulterated up to 1000 ml to get stock result of monobasic potassium phosphate. 8gm Sodium hydroxide was counted and adulterated up to 1000 ml to get0.2 M sodium hydroxide result. 50 ml of the monobasic potassium phosphate result was taken from the stock result in a 200- ml volumetric beaker and22.4 ml of sodium hydroxide result from stock result of0.2 M sodium hydroxide result was added and also water was added to make up the volume.

7. Results and Conversations

Standard estimation wind of Metformin HCl in1.2 pH buffer

The absorbance was measured in a UV spectrophotometer at 233 nm against1.2 pH buffer

Sl no	Conc (µg/ml)	Absorbance			Avg	S.D
		Trial 1	Trial 2	Trial 3		
1	0	0	0	0	0	0
2	1	0.081	0.089	0.081	0.0836	0.0046
3	2	0.163	0.169	0.163	0.1650	0.0034
4	3	0.243	0.254	0.243	0.2466	0.0063
5	4	0.325	0.343	0.325	0.3310	0.0103
6	5	0.406	0.403	0.406	0.4050	0.0017
7	6	0.482	0.489	0.482	0.4843	0.0040
8	7	0.565	0.599	0.599	0.5763	0.0196
9	8	0.648	0.667	0.667	0.6543	0.0109

Table: Spectrophotometric Data for the Estimation of Metformin HCl in 1.2pH

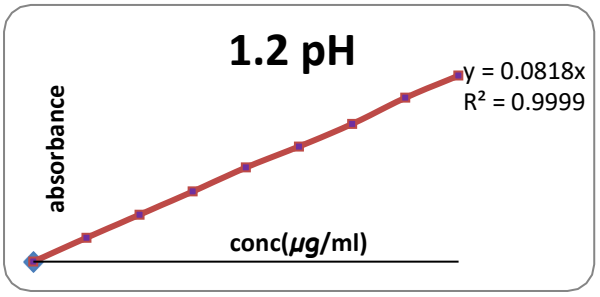

Figure: Calibration Curve of Metformin HCl in 1.2 pH buffer

8. Summary

Targeting of drug to the colon is recognised to have several therapeutic advantages because colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produce rapid production of antibodies and thus helps in effective vaccine delivery. The colon has longer retention time and appears highly responsive to an agent that enhances the absorption of poorly absorbed drugs. Absorption of drug molecules from the colon like other regions of GIT is a result of a complex series of events. Successful colonic uptake of a drug species requires both enzymatic stability and has to transport from the mucosal surface to the venous and or lymphatic capillaries located in the sub mucosa. The colonic epithelial permeability is insufficient to allow for the transport rate required for a therapeutic delivery. Then the co-administration of an absorption enhancing agent offers a potential means of overcoming this barrier mostly through the use of chemical enhancers like chelating agents, surfactant and dicarboxylic acids (succinic acid, lauric acid,etc.,)

The delivery of drugs to colon for systemic action or a local effect is valuable in a variety of circumstances. These include the topical treatment of diseases such as ulcerative colitis, Chron's disease, irritable colon syndrome, infectious disease, colon cancer and the potential for the oral delivery of peptides and other labile drugs. Targeting of drugs to the colon via oral route can be achieved by different approaches including different formulation system. For which the drug release is controlled by different pH conditions, transit time and microbial flora.

Metformin HCL was chosen as a model drug. It is a BCS class-III (highly soluble-poorly permeable) biguanide derivative that has been used worldwide for the treatment of type-II diabetes. In spite of its favourable clinical response chronic therapy with Metformin HCL suffers from certain specific problems of which, the most prominent being the high dose (1.5-2.0 g/day), half-life is about 1.5-3.5 hours, low bioavailability(60%) and high incidence of GI side effects(30% cases). The situation is complicated further with decrease in absorption of drug with food that delays tmax by up to 35mins

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