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TO PREPARE AN ORAL FORM OF GLICLAZIDE SR (SUSTAINDEDE RELEASE)-30 MG TABLET AND MANUFACTURING PROCESS DESCRIBING THE FORMULATION AND PROCESS PARAMETERS.

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Keywords

Field of the invention

Ingredients

Preformulation study

Process parameter

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Abstract

Gliclazide contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of 1-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-3-[(4 methylphenyl)sulphonyl]urea, The primary mechanism of action of gliclazide in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. Gliclazide has been shown have extra pancreatic effects like reduction in platelet adhesiveness and aggregation and increase in fibrinolytic activity. Minimize dosing frequency, Minimizes fluctuations in serum drug levels, for a drug having narrow therapeutic index, to achieve zero order release rate of drug, Patients compliance. In preparation of Gliclazide having ingredients CHPD, Mg-Sterate, Colloidal Silica, HPMC and Maltodextrin compatible with each other .In this preparation Gliclazide SR - 30 mg having less cost effective and Intended for single dose administration per day & better patient compliance with sharping effect against diabetic condition.

INTRODUCTION

Ideally a drug to provide desired therapeutic action should arrive rapidly at the site of action in optimum concentration, remain there for the desire time, be excluded from other site and get rapidly removed from the site of planned after its action. The fact that absorption rate of drug into the body can be decreased by reduction of the rate of release of the drug from the dosage form is one of the most recent and interesting result of pharmaceutical research. This ideal dosing regimen, which enhances patient compliance and helps guard against overdosing and side effects, is made possible by controlled release delivery systems, which use a variety of mechanisms to deliver and maintain the drug at a certain level in the patient's blood stream[1] This ideal dosing regimen, which enhances patient compliance and helps guard against overdosing and side effects, is made possible by controlled release delivery systems, which use a variety of mechanisms to deliver and maintain the drug at a certain level in the patient's blood stream[2].

Gliclazide is a second-generation hypoglycemic sulfonylurea that is useful in the treatment of Type 2 diabetes mellitus. Gliclazide shows good tolerability and a low incidence of hypoglycemia; a low rate of secondary failure inhibits platelet aggregation and increases fibrinolysis. Thus gliclazide appears to be a drug of choice in long-term sulfonylurea therapy for the control of Type 2 diabetes mellitus. It shows low aqueous solubility and dissolution rate and often shows low and irregular bioavailability after oral administration. The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of formulation development. The solid dispersion of poorly water-soluble drugs in water-soluble polymers enhances drug dissolution and bioavailability. The preparation and characterization of complexes of gliclazide with β-cyclodextrin have been reported. Complexation of gliclazide with β-cyclodextrinhydroxypropyl methylcellulose, which enhanced its hypoglycemic activity, has been reported. In addition, accelerated

absorption of gliclazide using PEG 400 was studied earlier. Solid dispersions of gliclazide in PEG 6000 have been developed to increase drug dissolution rate. Enhancement of the solubility of gliclazide using polyvinylpyrrolidone K90 has been reported. The molecular weight of the polymer may play a role in the performance of a solid dispersion. The rationale of the present study was to investigate the use of lower molecular weight PEG 4000 for the preparation of solid dispersions with the objectives of improving dissolution. The solubility and dissolution rate of gliclazide can be enhanced in SDs with PEG 4000. The solubilization effect of PEG 4000 rate of gliclazide and obtaining different behavior as compared with PEG 6000[3-6].

Sustained Release Drug Delivery System

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily. In fact the development of a pharmaceutical product for oral delivery, irrespective of its physical form involves varying extents of optimization of dosage form characteristics within the inherent constraints of GI physiology. Therefore a fundamental understanding of various disciplines, including GI physiology, pharmacokinetics, pharmacodynamics and formulation design are essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. The more sophisticated a delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system. In any case, the scientific framework required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects;

- Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.
- The anatomic and physiologic characteristics of the GIT.

- Physicochemical characteristics and the drug delivery mode of the dosage form to be designed.[7]

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained-release systems, the oral route of administration has by far received the most attention with respect to research on physiological and drug constraints as well as design and testing of products. This is because there is more flexibility in dosage form design for the oral route than there is for the parenteral route.[8] The goal in designing sustained or controlled-delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery[9] The enormous problems of patient compliance as well as the therapeutic desirability of controlled tissue drug levels over the time course of therapy are sufficiently compelling reasons to warrant placement of drugs in a sustained form of drug delivery[10] In the past, many of the terms used to refer to therapeutic systems of controlled and sustained release have been used in an inconsistent and confusing manner. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot, and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose[11]

It is an anti-daiabetic containg drug involved sulphonylureas having class mentioned below:

- **CATEGORY:** It is a **sulphonylureas**
- **USE:** Antidiabetic (in NIDDM-Non insulin Dependent Diabetes mellitus)
- **HALF LIFE:** 10.4 h (Duration of action is 10-24 h
- **BCS CLASS:** class II
- **DOSE:** 40-320 mg (in two divided dose) 30 & 60 mg(for MR)

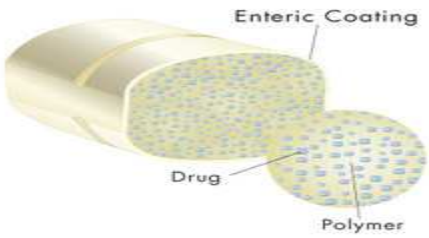
Field of the invention

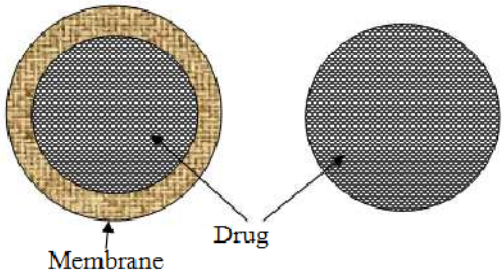
The present invention relates to matrix tablet that enables the prolonged release of gliclazide, the release being insensitive to variation in the pH of the dissolution medium, and that ensures regular and

continuous blood levels after absorption of the galenic form by ORAL ROUTE

By Matrix tablet invention

The controlled release is linear for a period of more than 8 Hrs and is such that 50% of the total amount of gliclazide has been release between 4 to 6 Hours after administration moreover





The Matrix tablet according to the invention enables prolonged release of gliclazide that results in Humans in blood levels of from 400 to 700 ng/ml 12 Hours at most after a single administration by the oral route of a tablet containing a dose of 30 mg gliclazide, and in blood levels of from 250 to 1000 ng/ml after a daily administration of a tablet containing a dose of 30 mg of gliclazide[12-15].

MATERIALS

Ingredient	Role	Justification
Glicalazide	API (active pharmaceutical ingredient)	Anti-diabetic action
Calcium hydrogen phosphate dehydrate (CHPD)	Enables improved granule fluidity and granule compressibility Also slow down the dissolution kinetics. To control the dissolution profile of the active ingredient	In the final blend •Compatible with API, Particle size needs control

Magnesium Sterate (0.25-4%)	Lubricant	• In the final blend. • Vegetable origin •Compatible with API • Particle size needs control
Colloidal silica	Flow agent	Enhance flow property Compatible with API
Hydroxyl propyl methyl cellulose (HPMC) Matrix forming polymer (5-20 %)	Granulation purpose To control dissolution profile	Particle size needs control . Compatible with API
Maltodextrine (0.25- 3 %)	Enabling release of active ingredient that is perfectly prolonged and controlled	Granulation Compatible with API.

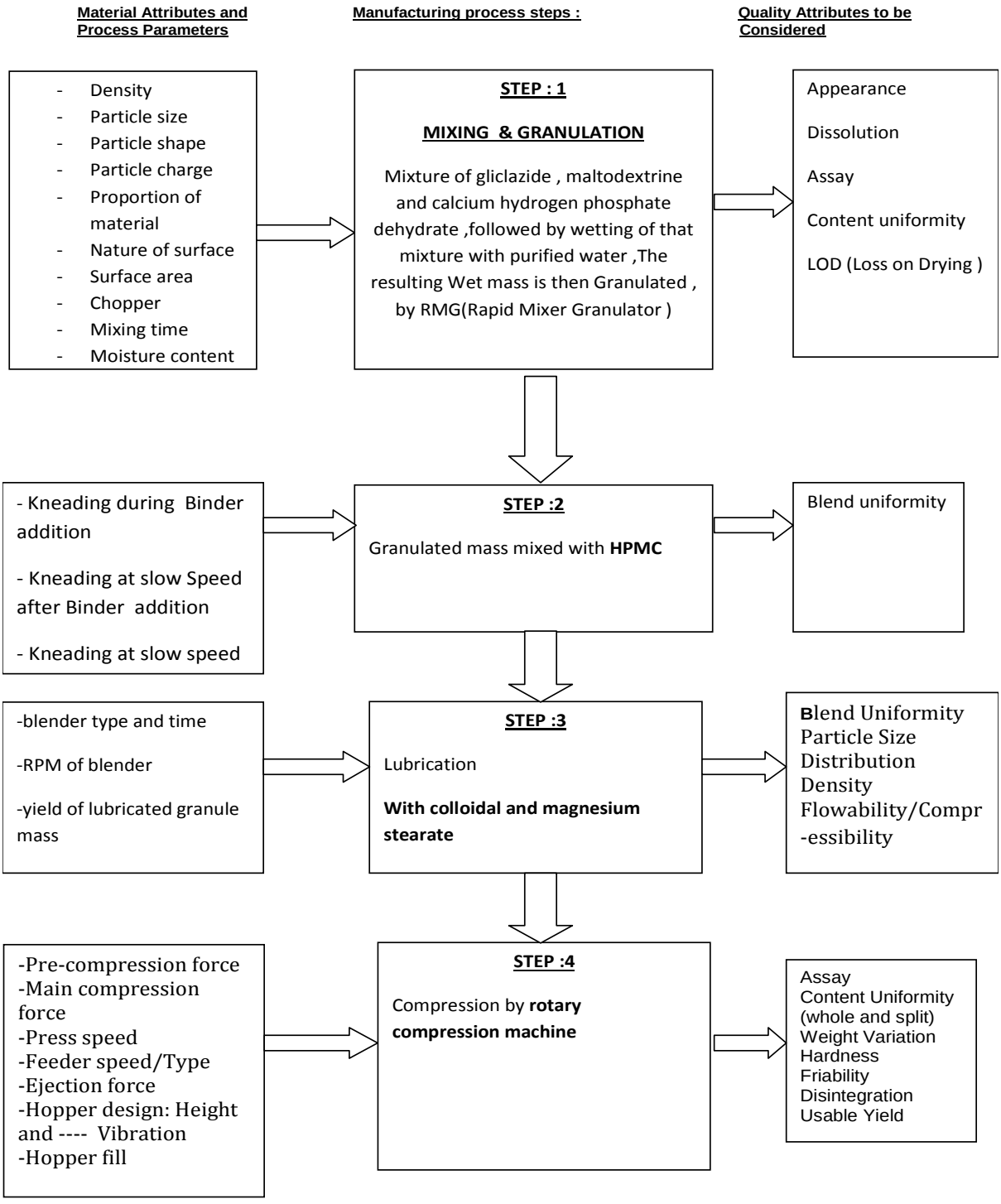
Preformulation Study

- Solubility Enhancement of GLICLAZIDE[16]
- **Method:** Solvent Melting Method
- **Carrier:** PEG 6000
- **Before:** 40 % drug release/1 min
- **After :**100% drug release/1 min

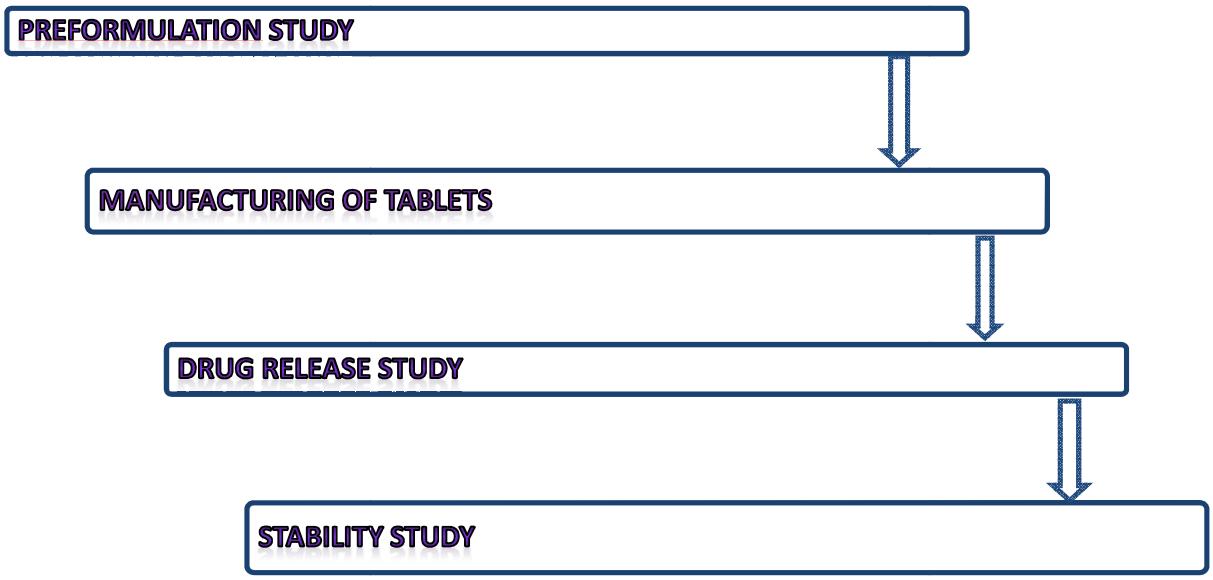
Profile Component	Method	Criteria
Flow Property	Angle of repose: Inversly prop. Carr's index: inversly prop, Hausner ratio,	<30 Φ
Solubility	In Water	1-10mg/ml
Melting point	1. Capillary melting 2. Hot stage microscopy 3. DSC	-
Stability (With all excipients to be used)	FTIR Spectroscopy ,DSC	Must be Compatible
Assay	UV (227 nm)	95-105%

PROCESS & PARAMETER

Manufacturing process and Process parameter



MANUFACURING PROCESS FLOW



***In vitro* Drug Release Study**

- Dissolution parameter:
- Medium: 0.1N Hydrochloric acid followed by 6.8 Phosphate buffer
- Volume: 900ml
- Apparatus: USP-I (Basket)
- RPM: 50 rpm
- Temperature: 37°C ± 0.5°C
- Time 24 hrs

Comparison with Market Preparation (Similarity study)

Stability Study

- Acelarated Stability study
- Tablets stored for 3 months 40.2 ^{o}C and 75.5% RH.
- Carry out DSC for excipient compatibility
- Carry out *in-vitro* dissolution study and compare it with before 3 months results

QTPP

Quality Target Product Profile

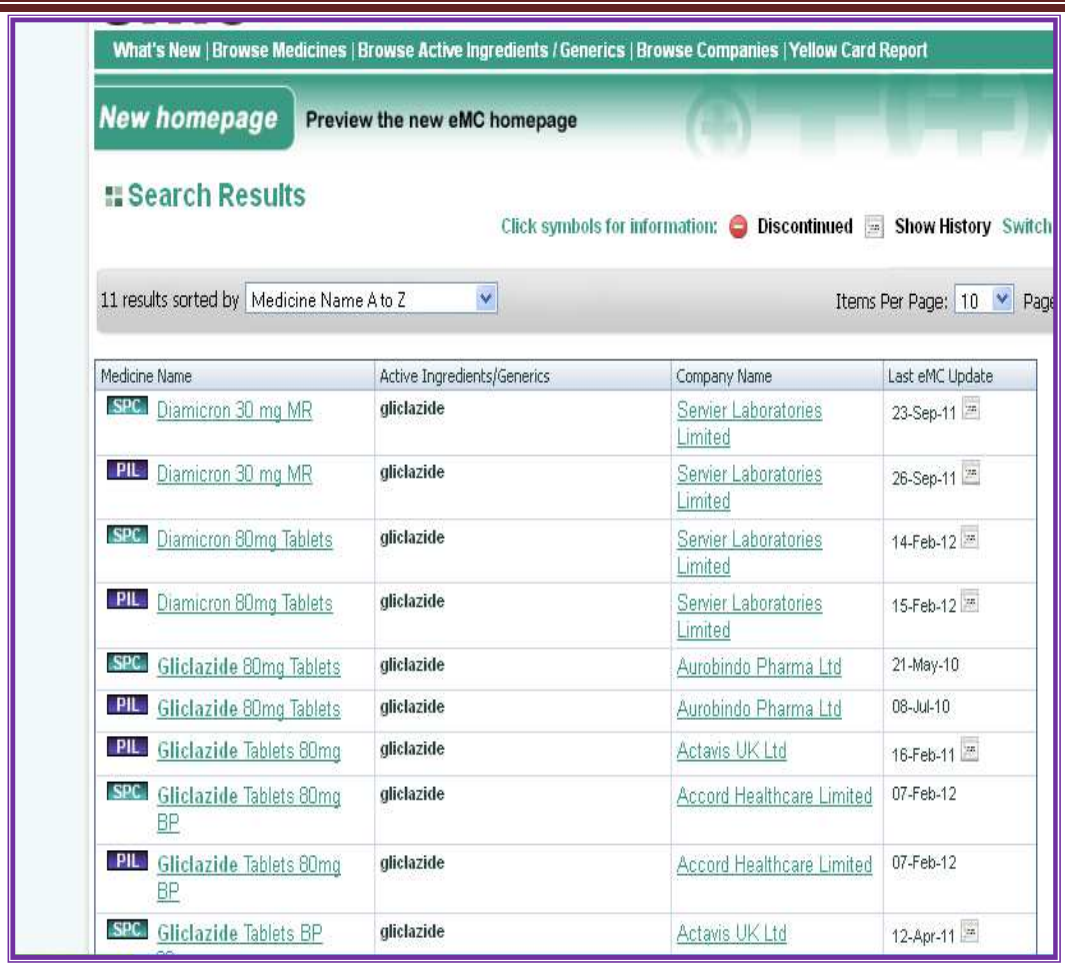
QTPP for Modified Release Product

Profile Component	QTPP Target	Rationale
Active Ingredient	Same	Pharmaceutical Equivalence Requirement
Dosage Form	Tablet	Pharmaceutical Equivalence Requirement Same Dosage Form
Strength	Dose: 30 mg	Pharmaceutical Equivalence Requirement Same Strength
Dosage Form Appearance and Characteristics	Conforming to Description, Shape and Size Same Scoring as RLD "Generally" similar in Size and Shape to RLD	Needed for Patient Acceptability Size and Shape Conducive to Patient Safety when Swallowing.
Assay	95-105%	Targeted for consistent clinical effectiveness
Impurity	Impurity A < 0.5 %	Ensure main degradation product remains below qualification threshold
CU	RSD < 3%	Targeted for consistent clinical effectiveness
Friability	NMT 1.0%	Needed for patient acceptability
Stability	24 month shelf life	Needed for commercial reasons

Summary

Diamicron 30 mg MR (Available Products in Regulated Marketed)

- Summary product characteristics emc (Electronic medicine compendium)
- It is marketed as Glizid, Glyloc and Reclide in India &
- Diamicron in Canada. In the Philippines, Servier markets it as Diamicron MR
- Many generic equivalents are also available e.g. Glubitor-OD, Clizid. It is not marketed in the United States (US)



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PIL Diamicron 30 mg MR	gliclazide	Servier Laboratories Limited	26-Sep-11
SPC Diamicron 80mg Tablets	gliclazide	Servier Laboratories Limited	14-Feb-12
PIL Diamicron 80mg Tablets	gliclazide	Servier Laboratories Limited	15-Feb-12
SPC Gliclazide 80mg Tablets	gliclazide	Aurobindo Pharma Ltd	21-May-10
PIL Gliclazide 80mg Tablets	gliclazide	Aurobindo Pharma Ltd	08-Jul-10
PIL Gliclazide Tablets 80mg	gliclazide	Actavis UK Ltd	16-Feb-11
SPC Gliclazide Tablets 80mg BP	gliclazide	Accord Healthcare Limited	07-Feb-12
PIL Gliclazide Tablets 80mg BP	gliclazide	Accord Healthcare Limited	07-Feb-12
SPC Gliclazide Tablets BP	gliclazide	Actavis UK Ltd	12-Apr-11

CONCLUSION

For above preparation of GLICLAZIDE SR-30 mg is best compliance of patient and their related to reducing cost , after better Intended for single dose administration per day Giving sharp effect against diabetic condition. Solubility enhanced by PEG -6000 and/or Beta –cyclodextrin. According to our preparation having more effective to turn against diabetes condition.

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