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Comparison of Solubility and Dissolution Rate of Poor Water Soluble Glipizide using Different Polymer by Matrix Formulation

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ABSTRACT

Sustained release (SR) or controlled release (CR) drug delivery systems have gained attention due to the challenges and costs associated with marketing new pharmacological entities. These methods can produce predictable and repeatable release rates, prolong the duration of action for medications with short half-lives, reduce toxicity, lower required doses, optimize therapy, and improve patient compliance. Hydrophilic polymer matrix systems are commonly used for oral sustained release delivery systems, such as HPMC K 100 and sodium salt of carboxy methyl cellulose. However, due to rapid drug diffusion, hydrophilic matrix alone is limited for prolonged drug release hydrophobic polymers, such as Eudragit, must be incorporated into the matrix system for enhancing solubility and dissolution rate.

Keyword: Glipizide IP, HPMC K 100, Sodium cmc, Eudragit L 100, Matrix tablet; Sustained release

Introduction

Oral drug delivery is the most widely utilized route of administration among all the routes. Which has been used for the systemic delivery of drugs via various pharmaceutical products of different dosage form. Nowadays most of the pharmaceutical product developed as an ideal DDS, this ideal system should have advantage of single dose for whole duration of the treatment and it should deliver the drug directly at specific target site.

Glipizide is one of the most commonly used anti-diabetic drug for treatment of type 2 diabetic mellitus. Glipizide stimulates insulin secretion from the β cells of pancreatic islets tissue, increases the concentration of insulin in the pancreatic vein and may increase the number of insulin receptors. Glipizide is a weak acid (pKa = 5.9) practically insoluble in water and acidic environment and highly permeable (class II) drugs according to the Biopharmaceutical Classification System (BCS). Due to poor solubility of drug, its bioavailability rate is limited by drug dissolution. In the present study, an attempt has been made to increase solubility of glipizide by matrix formulation using different polymers. Thus glipizide SR formulations maintain plasma levels for 8-12 hours may be sufficient for once-a-day dosing. SR products are needed to prolong Glipizide duration of action and improve patient compliance and also enhance the dissolution rate.

The major goal set in designing sustained or controlled delivery is to: Reduce the frequency of dosing

Increase effectiveness of the drug by localization at the site of action.

Reducing the dose required.

Providing the uniform drug delivery.

The hydrophilic polymers selected for the present study was hydroxylpropyl methyl cellulose K 100 (HPMC K 100) and sodium salt of carboxy methyl cellulose. Hydrophilic polymer matrix system are widely used for designing oral sustained release delivery systems because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Polymers forms transparent tough and flexible films from aqueous solution. The films dissolve completely in the gastrointestinal tract at any biological pH and provide good bioavailability of the active ingredient. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic matrix. For such drugs it becomes essential to include hydrophobic polymers in the matrix system as Eudragit L 100

Materials and methods

Materials

The sample of Glipiside and polymers selected were hydroxylpropyl methyl cellulose K 100 (HPMC K 100) and sodium salt of carboxy methyl cellulose was supplied by We-associates- 69A Manarcadu Kottayam. The distilled water was procured from college single distillation unit in Pharmaceutics department.

Methods

Preformulation studeies

The drug and excipients selected for investigation were subjects for various preformulation studies such as drug polymer interaction, Physical characterization of API and excipients

Preparation of matrix tablets

Different tablet formulations were prepared by wet granulation technique . All the powders were passed through sieve number 80. Required quantities of drug and polymer were mixed thoroughly and a sufficient volume of granulating agent was added povidone in isopropyl alcohol, slowly. After enough cohesiveness was obtained the mass was sieved through sieve number 22. The granules were dried at 55±5 °C for one hour. Once dried the granules retained on sieve number 44 were mixed with magnesium stearate and aerosil for 2 min. The practical weight of tablets, were calculated based on the drug content of the granulation's and the tablets were compressed using double punch tableting machine, equipped with beveled flat faced punch of size 8 mm of diameter. Each tablet contained 10 mg of Glipizide and other pharmaceutical ingredients as listed in Table 6. Prior to the compression the granules were evaluated for several tests.

Ingredient, mg	F1	F2	F3	F4
Glipiside	10	10	10	10
HPMC K100	25	25		
Sodium cmc				25
Eudragit		25	40	
Micro crystalline cellulose (mg)	61		27	61
Ethyl cellulose (mg)			20	
Lactose (mg)		5		
Povidone (mg)		5		
Isopropyl alcohol (ml)		qs		
Aerosil (mg)		0.5		
Magnesium stearate (mg)	2	1	1	2
Talc (mg)	2		2	2
Total (mg)	100	100	100	100

Evaluation of granules

The angle of repose was measured by using funnel method, which indicates the flow property of the granules. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD= weight of the powder / volume of the packing. TBD= weight of the powder / tapped volume of the packing. Compressibility index of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] ×100.

Evaluation of tablets

Hardness of the tablets was tested using a Monsanto Hardness Tester. Friability of the tablets was determined in a Roche Friabilator. The disintegration time of the tablet was measured in water (37± 2°c) according to disintegration test apparatus with disk.

Estimation of drug content

Glipizide content of the matrix tablets was estimated by UV spectrophotometric method based on the measurement of absorbance at 222 nm in phosphate buffer of pH 7.4. The method was validated for linearity, accuracy and precision. The method obeyed Beer's Lambert's law.

In vitro dissolution Test

The drug release rate from the tablet was determined by determined by USP apparatus II . The dissolution test was performed using 900ml of 7.4 phoshate buffer, The 5 ml of sample were withdrawn at intervals of 30 mins and done for 8 hours and replacement of withdrawn was done each time with equal amounts of fresh dissolution medium maintained at same temperature and tested for drug release.the samples are filtered through a whattsman filter paper. Absobance of the the solution was calculated at 222nm.

Accelerated stability studies

Accelerated stability studies were performed on best formulation by using ICH guidelines with necessary modification.sample was stored at condition of 40 2 c and 75% 5% RH for a period of 45 day.After the period of 45 days , sample was tested for appearance, hardness and drug content.

Result and discussion

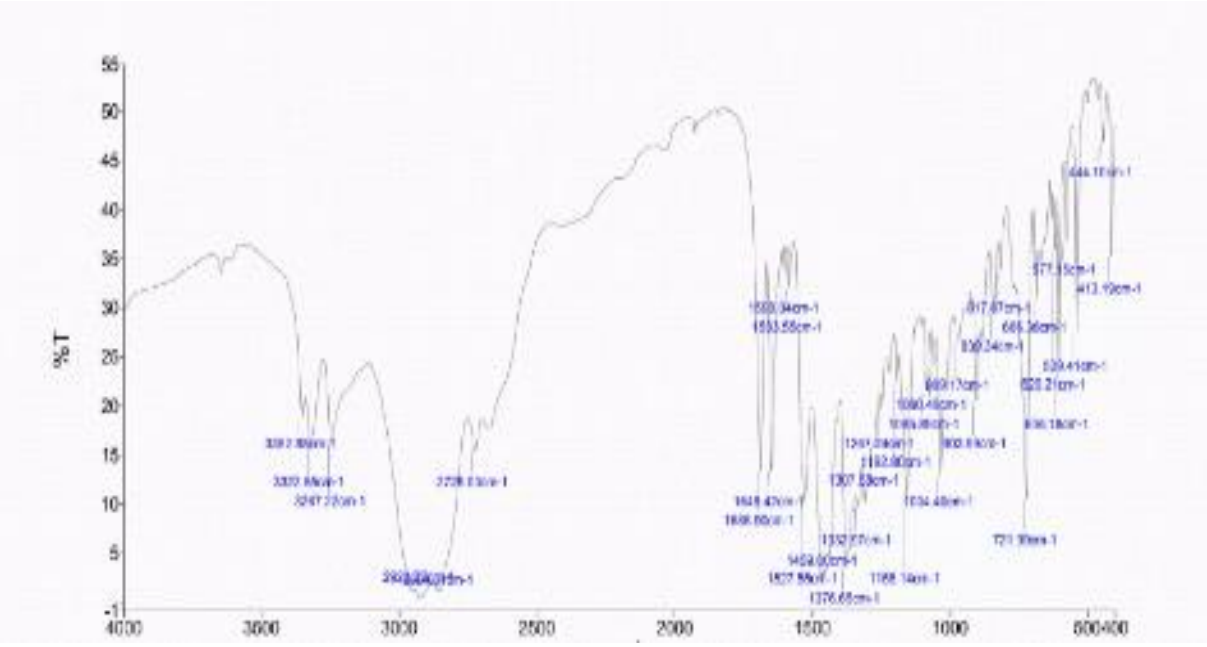
The matrix tablets were prepared by conventional wet granulation method as per formulae. Formulations F1 containe polymers HPMCK100M ande MCC, Formulations F2 containe polymers HPMCK100M and eudragit, Formulations F3 containe polymers eudragit, ethyl cellulose ande MCC. Formulations F4 containe polymers sodium- cmc and MCC. The combination of HPMCK100M and eudragit polymer formulation (F2) exhibited excellent release charecteristics. All the prepared tablets were evaluated for physical properties and drug release characteristics.

STANDARD GRAPH OF GLIPIZIDE:

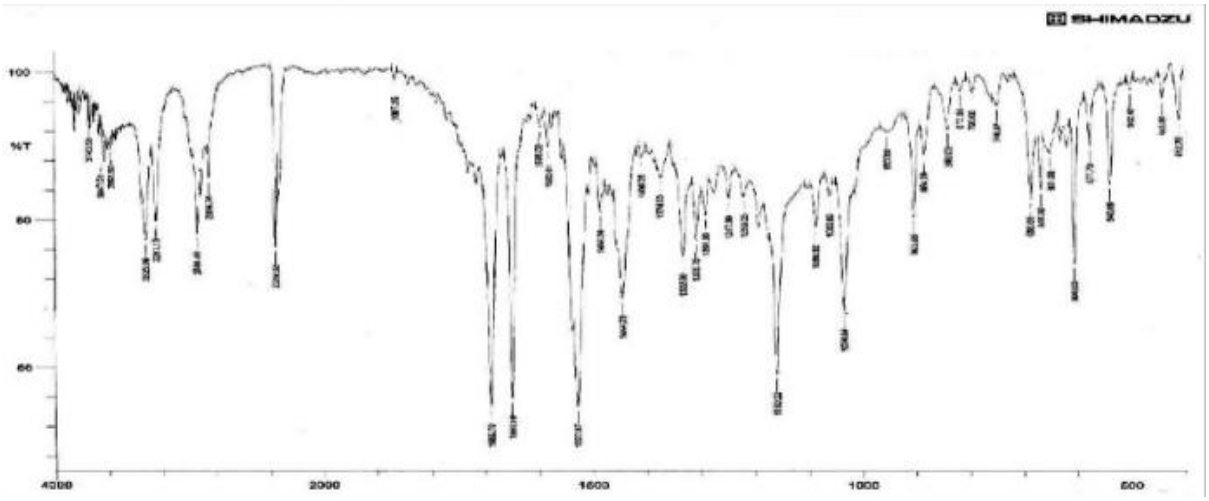
The scanning of 2.5 µg/ml of the volumetric solution of Glipizide in the UV range against deionised water and pH 7.4 phosphate buffer determined the lambda max of the absorbance at 222nm. The standard graph of Glipizide has shown good linearity with R2 value 0.9984 which suggest that obeys the Beer-Lamberts law

Concentration (µg/ml)	Absorbance (nm)
2.5	0.124
5	0.264
7.5	0.405
10	0.548
12.5	0.663
15	0.828

Calibration corve of glipiside in 7.4 buffer solution at 222nm



Infrared Spectrum of pure Glipizide



Infrared Spectrum of pure Glipizide HPMC K100 and Eudragit % Drug release from compressed tablets from developed formulations

Time Minute	**percentage Drug Release**			
	F1	**F2**	**F3**	**F4**
0	0.00	0.00	0.00	0.00
5	13.4	20	18	14
15	24	32.5	29	25.8
30	34	41.7	38.5	35.1
45	42	48.2	47.1	43.5
60	47	53.1	2.1	48
120	51.1	57.4	54.9	52.1
180	54.9	61.3	59.8	56.5
240	58.3	65.7	63.1	59.7
300	62	69.8	66.5	63.3
360	64.6	72.7	69.2	66.5
420	67.7	75.7	72.3	69.1
480	70.3	77.5	74.9	71.0

The formulation F2 with HPMC K 100 and eudragit released maximum percentage of drug. The highest percentage of drug released from formulation F2 was 77.5 at the end of 8 hours. The formulation F1 and F4 with micrc crystalline cellulose showed 70.3% and 71.0% of drug release in 8-hour duration . Formulation F3 was able to release 74.9% of drug after the completion of 8-hour dissolution study. As per the findings from in-vitro dissolution study, it was evident that optimization of the concentration of polymer is required to avail maximum percentage drug release

Accelerated stability studies

Accelerated stability studies were performed on best formulation by using ICH guidelines with necessary modification.sample was stored at condition of 40.0 c and 75% 5% RH for a period of 45 day.After the period of 45 days , sample was tested for appearance, hardness and drug content.

Time	**Appearance**	**Hardness**	**Drug content**
Initial	Pale white	6.1±2.1	99.52
45 days	Pale white	6.0±2.1	99.52

CONCLUSION

The mixture of (HPMC K100 and Eudragit L100) matrix demonstrates to particularly suitable obtaining directly compressed with appropriate technological properties and well reproducible release profiles.

Simplicity of the formulation, ease of manufacturing and complete dissolution of system is among the advantages of the developed matrix formulations. The results of release studies indicated the possibility of achieving a suitable modulation of matrix release rate by opportunely varying ratio of matrix tablets, taking advantage at the same time of moderate swelling properties of Eudragit. The kinetics of drug release was shown to be in accordance with kinetics of hydration/ swelling and Erosion of HPMC K 100 and Eudragit L100. Significantly greater swelling/hydration observed in HPMC K 100 is attributed due to higher concentration of the polymer and inherent water retention characteristic of HPMC. The stronger gel structure of HPMC K based formulation relative to that of Eudragit may provide superior quality in vivo performance in terms of matrix resistance to destructive forces within GIT. Therefore, further studies will be performed for the final setting up of the proposed dosage form, aimed on one hand at developing a gastro-resistant coating able to effectively protect the drug from acid degradation, and on the other, at adequately improving drug release rate, by adding suitable canalizing agents to the polymeric matrix.

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