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Formulation and Evaluation of Solid Dispersion of Glimepiride in to Sustained Release

Anusha Pagadala*, Madhuri Asiniparthi and Vaidehi Donti

Pharmaceutics Department, Gyana Jyothi College of Pharmacy, India

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***Corresponding author:** Anusha Pagadala, Pharmaceutics Department, Gyana Jyothi College of Pharmacy, Hyderabad-500039, India, Tel: 0939314418; Email: gyana.jyothi@gmail.com

Abstract

A sustained release tablet containing Glimepiride was formulated by using solid dispersion technique. Solid dispersions of glimepiride were prepared by using Urea and PEG 6000 as carrier in drug: carrier 1:1, 1:2, 1:3, 1:4 ratios by Fusion method. From these all solid dispersions formulation SDUF3 containing Urea shows better dissolution compared to other solid dispersions. This optimized solid dispersion is formulated into sustained release tablets by direct compression method using hydroxy propyl methyl cellulose and Ethyl cellulose polymers.

Keywords: Solid dispersion, Diabetes mellitus, Sustained drug release

Abbreviations: PVP: Poly Vinyl Pyrrolidone; HPMC: Hydroxy Propyl Methyl Cellulose; FTIR: Fourier Transform Infra Red; MCC: Micro Crystalline Cellulose

Introduction

The objective of sustained release [1] dosage form is to preserve therapeutic blood or tissue levels of the drug for an extended period. This is commonly accomplished by attempting to gain zero order release [2] from the dosage form. Zero order release establishes drug release from the dosage form that is autonomous of the extent of drug in the delivery system (a constant release rate). Sustained release system in general do not achieve this form of release and regularly try to simulate Zero order release given that drug release is in a slow first order manner (concentration dependent).Systems that are selected as prolonged release can also be measured as efforts at attaining sustained release delivery. Repeat-action tablets [3] are an another techniques of sustained release in which several doses of the drug are confined within a dosage system, and each dose is free at a episodic interval. Delayed release system in difference, is usually not sustaining. Generally, the release rate of drug is not changed and does not effect in sustained delivery once drug release has commenced. The word solid dispersion [4] denotes a group of solid products comprising of a minimum two diverse constituents, largely a hydrophilic matrix and a hydrophobic drug. The matrix can be any crystalline or amorphous. The drug could be disseminated molecularly, either in amorphous state or in crystalline state furthermore, it is the preparation method but not the molecular arrangement which determines the properties of solid dispersions.

Methods of Preparation of Solid Dispersions

Melting method

The melting or fusion method [5], comprises the preparation water-soluble carrier and physical mixture of a drug and then heating it directly until it reaches a melting point. Then in an ice –bath with vigorous stirring the melted mixture is solidified. Then in the final stage the solid mass is crushed, pulverized and sieved.

Solvent method

In the solvent method [6], in a common solvent the physical mixture of the drug and the carrier are mixed together, and then evaporated till a clear, solvent free film is left. Then the film is additionally dried to constant weight.

a. Diabetes mellitus: [7] or only diabetes, is defined as where a person has high blood sugar, either the cells do not respond to the insulin, or the pancreas do not produce enough insulin.. This high blood sugar is characterised by polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) [8].

b. Type 1 diabetes: mellitus [9] is described as loss of the insulin-producing beta cells in the pancreas, which leads to insulin deficiency. The common of type 1 diabetes is of immune-mediated nature, where beta cell loss is mediated by T-cell autoimmune attack. There is no certain precautionary measure against type 1

diabetes, which is responsible for 10% of diabetes mellitus cases in North America and Europe. When onset occurs affected people are healthy and with healthy weight. In the early stages sensitivity and responsiveness to insulin are generally normal.

c. Type 2 diabetes: Type 2 diabetes mellitus [10] is described as resistance to insulin where it is combined with fairly decreased insulin secretion. This is said to involve the insulin receptor. This is the most common of types.

d. Gestational diabetes: Gestational diabetes mellitus (GDM) [11] bear a resemblance to in most of the aspects, with decreased insulin secretion and its response. It is seen in 2-3% of pregnancies and it may improve or disappear after pregnancy which is completely treatable. This may require medical observation during the pregnancy period.

e. Other types: Prediabetes [12]. Is a state where the person's glucose levels are higher than the normal but cannot be diagnosed for type 2diabetes? Persons who develop diabetes type 2 spend most of their years in Prediabetes state which is termed as "America's largest healthcare epidemic" [13]. Latent autoimmune diabetes of adults (LADA) [14] is a condition which develops in adults and is of type 1. The aim of the present investigation was to develop and evaluate a direct compressed sustained release tablets developed by solid dispersion technique. The tablet investigated in the current study consists hydroxyl propyl methyl cellulose which helps in the sustained release of the tablet. Solid dispersion prepared by using urea showed better dissolution rate than with PEG6000 (Table 1&2).

Table 1: List of chemicals.

S. No	Name of chemicals	Source
1.	Drug Glimepiride	Gift sample obtained from the Madras Pharmaceuticals Ltd, Chennai
2.	Polymer PEG4000	Drugs India, Hyderabad
3. 4. 5. 6. 7. 8.	Excipients MCC PVP-K_{30} Isopropyl Alcohol Talc Magnesium Stearate Aerosil	Drugs India, Hyderabad Drugs India, Hyderabad Kawarlal & Co., Chennai Ridesh Chemicals Pvt Ltd., Mumbai Harish Chemicals Pvt Ltd., Ahmadabad Cabot Sunmar Pvt Ltd., Naddoor

Table 2: Formulation of Solid Dispersion.

Solid dispersion composition	Method	Drug-Polymer ratio	Formulation Code
Glimepiride: Urea	Fusion method	1:1	SDUF1
		1:2	SDUF2
		1:3	SDUF3
		1:4	SDUF4
Glimepiride: PEG 6000	Fusion method	1:1	SDPF1
		1:2	SDPF2
		1:3	SDPF3
		1:4	SDPF4

Physical mixture of Glimepiride with the combination of PEG 6000 was prepared thoroughly by mixing the accurately weighed amount of drug and polymer in glass motor and pestle for 5 minutes and sieved through 0.25mm sieve (#60) and stored in desiccators for 24hours for further studies.

Preparation of solid dispersion by fusion method

Physical mixtures were melting in water bath with gradual increasing temperature up to the value necessary for the complete melting. The molten mass was rapidly cooled with constant stirring with a glass rod. The resulting solid dispersion was stored in desiccators for 24hrs,after then the prepared solid dispersion was grounded in motor for 2min ,and passed through 0.25(#60) mesh and used for further studies. Solid dispersion into sustained release Glimepiride tablet is prepared through wet granulation method [7] accordingly. Steps like sieving, dry mixing, preparation of binder solution, granulation and drying are involved. This preparation was passed through no.20 sieve. Solid dispersion of glimepiride, HPMC, Ethyl cellulose and MCC were mixed thoroughly in a poly bag to ensure uniform mixing with the drug for 5 minutes. 9mg of PV K-30 is weighed accurately and then mixed with IPA to form a binder solution which was added slowly to the dry mix to form uniform granules. The wet granules are then dried by air drying as IPA is corrosive and gets evaporated quickly. The dried samples are removed at random at regular time intervals and then passed through sieve no.20 and lubrication was done (Table 3).

Table 3: Formulations of Sustained Release Tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Glimepiride SD	128	128	128	128	128	128
HPMC	80	100	120			
EC				80	100	120
MCC	176	156	136	176	156	136
Magnesium Stearate	8	8	8	8	8	8
Talc	8	8	8	8	8	8

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Results and Discussion

Analytical methods

From the standard stock solution (1000 µg/ml), appropriate aliquot were transferred to series of 10 ml volumetric flasks and made up to 10 ml with desired solvents so as to get concentration of 5,10,15,20... or 2,4,6,8... µg/ml. the absorbance of the solution were measured at 230 nm for Glimepiride. This procedure was performed in triplicate to validate calibration curve and a graph is plotted (Figure 1).

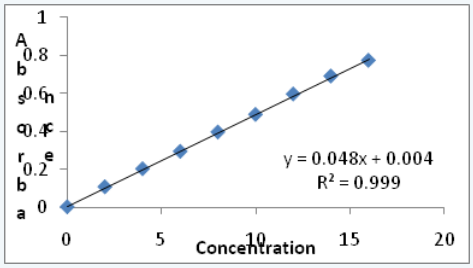

Figure 1: Glimepiride standard curve in 7.8pH phosphate buffer.

Compatibility studies

FT-IR spectroscopy is employed to establish the compatibility of drug with polymer and individual drug. Both the spectra were compared for confirmation of common peaks. Glimepiride with polymers showed no significant variation in height, intensity and position of peaks, suggesting that drug and recipients were compatible. Interaction between drug and polymer has not been established. Hence it can be determined that the drug is in Free State and can be released easily (Figure 2-11), (Tables 4-7).

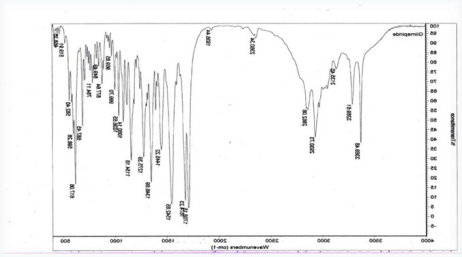

Figure 2: FTIR spectrum of Glimepiride drug.

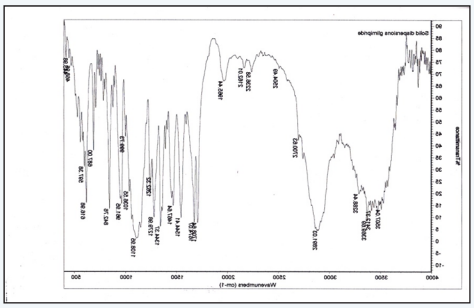

Figure 3: FTIR spectrum of Glimepiride Solid dispersion.

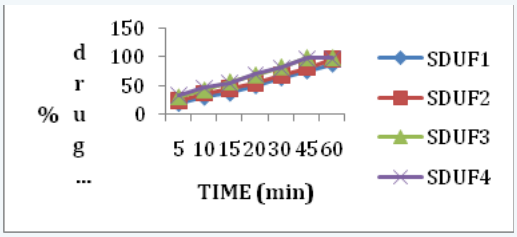

Figure 4: Drug release profile for solid dispersions SDUF1 to SDUF4.

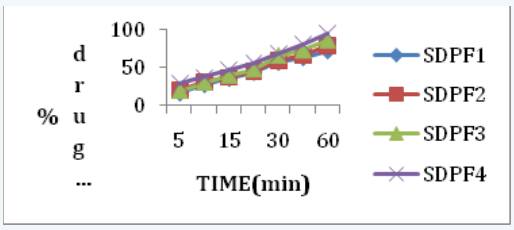

Figure 5: Drug release profile for solid dispersions SDPF1 to SDPF4.

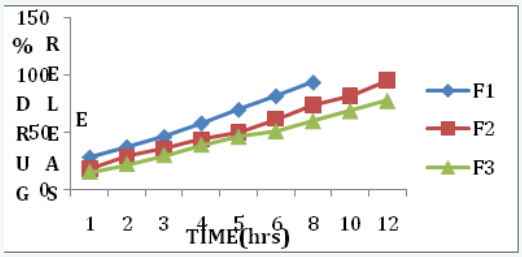

Figure 6: Dissolution profile of F1, F2, F3 formulations.

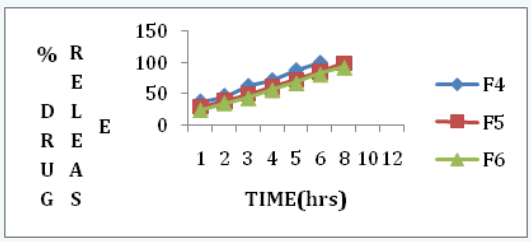

Figure 7: Dissolution profile of F4, F5, F6 formulations.

Based on the drug release within the required time period F2 was optimized and further formulated for sustained release.

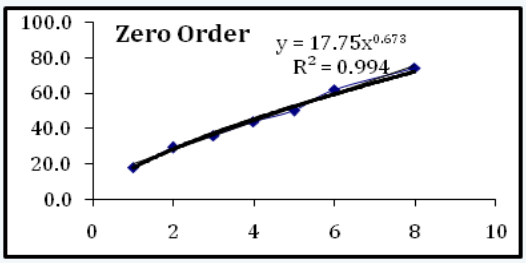

Figure 8: Zero order plot for Final formulation.

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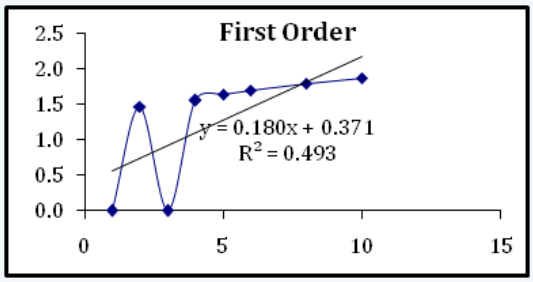

Figure 9: First order plot for Final formulation

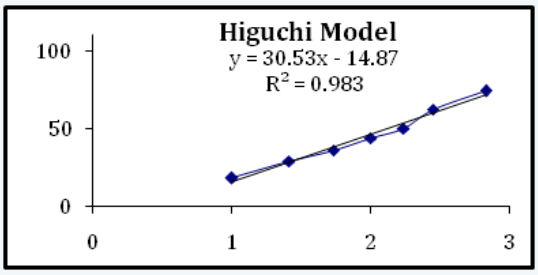

Figure 10: Higuchi model plot for Final formulation.

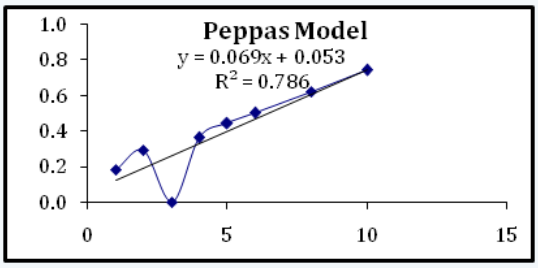

Figure 11: Peppas model plot for Final formulation.

Table 4: of FTIR spectrum of Glimepiride pure drug and Solid dispersion.

	Drug	C-N stretching vibration	N-H stretching	C-H stretching
Glimepiride	3369cm-1	1345cm-1	1153cm-1	2886 cm-1
Glimepiride Solid dispersion	3369.69 cm-1	1344.37 cm-1	3288.44 cm-1	2891.03 cm-1

Table 5: In vitro dissolution results for solid dispersion form.

	API+Urea	API+Urea	API+Urea	API+Urea	API+PEG 4000	API+PEG 4000	API+PEG 4000	API+PEG 4000
TIME	SDUF1	SDUF2	SDUF3	SDUF4	SDPF1	SDPF2	SDPF3	SDPF4
5min	18	22	30	32	17	20	19	29
10min	29	35	42	46	28	31	30	37
15min	36	44	56	54	36	37	39	46
20min	49	53	68	69	44	45	47	55
30min	63	67	82	80	57	59	65	68
45min	75	80	98	97	63	66	72	80
60min	87	96	98	97	72	79	85	99

Table 6: In vitro dissolution studies for final drug.

Time (hrs)	F1	F2	F3	F4	F5	F6
1	28	18	15	37	29	24
2	37	29	22	46	38	35
3	46	36	30	62	49	43
4	58	44	39	71	60	56
5	70	50	46	87	72	67
6	82	62	51	99	85	81
8	94	74	60		98	92
10		82	69			
12		96	78			

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Table 7: Release Kinetics.

Release Kineitcs				
	Zero	**Higuchi**	**Peppas**	**First**
	1	2	3	4
	Q Vs T	Q Vs √T	Log C Vs Log T	Log % Remain Vs T
Slope	7.5011	31.7597	0.6729	-0.0146
Intercept	10.8445	-17.0330	1.2494	2.3366
Correlation	0.9854	0.9952	0.9982	-0.9424
R 2	0.9710	0.9903	0.9965	0.8881

Conclusion

In the 6 trials, the optimized formulation was F2 which releases the drug Glimepiride in a sustained fashion up to 12 hours with96% of drug release.

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