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Formulation and Evaluation of Anti-Diabetes by Nanoparticles

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ABSTRACT

Glimepiride is used for the treatment of type 2 diabetes mellitus, one of the third generation sulfonylurea drugs having poor aqueous solubility, slow dissolution rate and low elimination half life. The Aim of the present study was to prepare Glimepiride Nanoparticles by using Eudragit RL 100 and Chitosan polymers by o/w solvent evaporation method using high speed homogenizer. Prepared Nanoparticles were characterized for the drug content, encapsulation efficiency. There is no changes was observed in stability studies in the extent of degradation of product during 3 weeks in which, nanoparticles were stored at various temperatures. Physical state of the drug, polymer and Nanoparticles were determined by, Fourier transform infrared spectroscopy (FTIR). Particle morphology was observed by FE-SEM. Non Fickian diffusion was confirmed as the drug release mechanism from these nanoparticles. Based on two polymers Eudragit RL100 gives as a good sustain release of the drug with 86%. From this study we can conclude that the Glimepiride loaded eudragit RL100 nanoparticles were successfully prepared and these nanoparticles seem to be promising for sustain release application leading to improve patient compliance.

Key words: Nanoparticles, Glimepiride, Eudragit RL 100, Chitosan, Solvent evaporation method.

INTRODUCTION

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as poly (ethylene glycol) (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes.

Anti-diabetic medications treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide, and pramlintide, all are administered orally and are thus also called oral hypoglycemic agents or oral antihyperglycemic agents. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors. Diabetes mellitus type I is a disease caused by the lack of insulin. It must be used in Type I, which is administered parenterally. Diabetes mellitus type II is a disease of insulin resistance by cells. Treatments include (1) Agents that increase the amount of insulin secreted by the pancreas, (2) Agents that increase the sensitivity of target organs to insulin, and (3) Agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract. Several groups of drugs, mostly given by mouth, are effective in Type II, often in combination. The therapeutic combination in Type II may include insulin, not necessarily because oral agents have failed completely, but in search of a desired combination of effects. The great advantage of injected insulin in Type II is that a well-educated patient can adjust the dose, or even take additional doses, when blood glucose levels measured by the patient, usually with a simple meter, as needed by the measured amount of sugar in the blood.

Insulin

Insulin is usually given subcutaneously, either by injections or by an insulin pump. Research of other routes of administration is underway. In acute-care settings,

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insulin may also be given intravenously. In general, there are about four types of insulin, characterized by the rate which they are metabolized by the body [1].

Sensitizers

Insulin sensitizers address the core problem in Type II diabetes—insulin resistance.

Biguanides

Biguanides reduce hepatic glucose output and increase uptake of glucose by the periphery, including skeletal muscle. Although it must be used with caution in patients with impaired liver or kidney function, metformin, a biguanide, has become the most commonly used agent for type 2 diabetes in children and teenagers. Among common diabetic drugs, metformin is the only widely used oral drug that does not cause weight gain

- Metformin may be the best choice for patients who also have heart failure, but it should be temporarily discontinued before any radiographic procedure involving intravenous iodinated contrast, as patients are at an increased risk of lactic acidosis.
- Phenformin was used from 1960s through 1980s, but was withdrawn due to lactic acidosis risk.
- Buformin also was withdrawn due to lactic acidosis risk.

Metformin is usually the first-line medication used for treatment of type II diabetes. In general, it is prescribed at initial diagnosis in conjunction with exercise and weight loss, as opposed to in the past, where it was prescribed after diet and exercise had failed. There is an immediate release as well as an extended-release formulation, typically reserved for patients experiencing GI side effects. It is also available in combination with other oral diabetic medications.

Thiazolidinediones

Thiazolidinediones (TZDs), also known as "glitazones," bind to PPARγ, a type of nuclear regulatory protein involved in transcription of genes regulating glucose and fat metabolism. These PPARs act on peroxysome proliferator responsive elements (PPRE [1]). The PPREs influence insulin-sensitive genes, which enhance production of mRNAs of insulin-dependent enzymes. The final result is better use of glucose by the cells.

Some examples are:

- Rosiglitazone (Avandia): the European Medicines Agency recommended in September 2010 that it be suspended from the EU market due to elevated cardiovascular risks.
- Pioglitazone (Actos)
- Troglitazone (Rezulin): used in 1990s, withdrawn due to hepatitis and liver damage risk.

Multiple retrospective studies have resulted in a concern about rosiglitazone's safety, although it is established that the group, as a whole, has beneficial effects on diabetes. The greatest concern is an increase in the number of severe cardiac events in patients taking it. The ADOPT study showed that initial therapy with drugs of this type may prevent the progression of disease, as did the dream trial. Concerns about the safety of rosiglitazone arose when a retrospective meta-analysis was published in the *New England Journal of Medicine*. There have been a significant number of publications since then, and a Food and Drug Administration panel8 voted, with some controversy, 20:3 that available studies "supported a signal of harm," but voted 22:1 to keep the drug on the market. The meta-analysis was not supported by an interim analysis of the trial designed to evaluate the issue, and several other reports have failed to conclude the controversy. This weak evidence for adverse effects has reduced the use of rosiglitazone, despite its important and sustained effects on glycemic control.9 Safety studies are continuing. In contrast, at least one large prospective study, proactive 05, has shown that pioglitazone may decrease the overall incidence of cardiac events in people with type 2 diabetes who have already had a heart attack.

Sulfonylurea

Sulfonylurea was the first widely used oral anti-hyperglycemic medications. They are *insulin secretagogue* triggering insulin release by inhibiting the KATP channel of the pancreatic beta cells. Eight types of these pills have been marketed in North America, but not all remain available. The "second-generation" drugs are now more commonly used. They are more effective than first-generation drugs and have fewer side-effects. All may cause weight gain. Sulfonylurea binds strongly to plasma proteins [2]. Sulfonylurea is useful only in Type II diabetes, as they work by stimulating endogenous release of insulin. They work best with patients over years old who have had diabetes mellitus for under ten years. They cannot be used with type I diabetes, or diabetes of pregnancy. They can be safely used with metformin or glitazones. The primary side-effect is hypoglycemia.

- First-generation agents
- Tolbutamide (Orinase brand name)
- Acetohexamide (Dymelor)
- Tolazamide (Tolinase)
- Chlorpropamide (Diabinese)
- Second-generation agents
- Glipizide (Glucotrol)
- Glyburide (Diabeta, Micronase, Glynase)
- Glimepiride (Amaryl)
- Gliclazide (Diamicron)

Nonsulfonylurea secretagogue

Meglitinide

Meglitinides help the pancreas produce insulin and are often called "short-acting secretagogues." They act on the same potassium channels as sulfonylureas, but at a different binding site. By closing the potassium channels of the pancreatic beta cells, they open the calcium channels, thereby enhancing insulin secretion. They are taken with or shortly before meals to boost the insulin response to each meal. If a meal is skipped, the medication is also skipped.

- Repaglinide (Prandin)
- Nateglinide (Starlix)

Adverse reactions include weight gain and hypoglycemia.

Alpha-glucosidase inhibitor

Alpha-glucosidase inhibitors are "diabetes pills" but not technically hypoglycemic agents because they do not have a direct effect on insulin secretion or sensitivity. These agents slow the digestion of starch in the small intestine, so that glucose from the starch of a meal enters the bloodstream more slowly, and can be matched more effectively by an impaired insulin response or sensitivity. These agents are effective by themselves only in the earliest stages of impaired glucose tolerance, but can be helpful in combination with other agents in type 2 diabetes.

- Miglitol (Glyset)
- Acarbose (Precose/Glucobay)

These medications are rarely used in the United States because of the severity of their side effects (flatulence and bloating). They are more commonly prescribed in Europe. They do have the potential to cause weight loss by lowering the amount of sugar metabolized. Research has shown that the culinary mushroom *maitake* (*Grifola frondosa*) has a hypoglycemic effect possibly due to the mushroom acting as a natural alpha glucosidase inhibitor [3].

Alternative medicine

A number of medicinal plants have been studied for the treatment of diabetes, however there is insufficient evidence to determine their effectiveness.36 Cinnamon has blood sugar-lowering properties, however whether or not it is useful for treating diabetes is unknown. While chromium supplements have no beneficial effect on healthy people, there might be an improvement in glucose metabolism in those with diabetics, although the evidence for this effect remains weak. Vanadyl sulfate, a salt of vanadium, is still in preliminary studies. There is tentative research that thiamine may prevent some diabetic complications however more research is needed [4,5].

MATERIALS

The following materials of pharmacy grade or the best possible laboratory reagent (LR) were used as supplied by the manufacturer. The double distilled water was used in all experiments (Table 1).

Formulation of Glimepiride Nanoparticles

Nanoparticles, containing anti-diabetic drug a core material were prepared by solvent evaporation method. Accurately quantity of drug 50mg was dissolved in acetone 5ml and polymer in acetone 10ml sperately and added in to aqueous phase 100ml distilled water containing surfactant 0.45% tween 80 using a high speed homogenizer at s rpm for 20 min and 35000 rpm for 3 min at 40c, by adding organic phase in to aqueous phase. Then emulsion was passed through the high speed homogenizer at a pressure of 500 bar for one cycle. The emulsion was kept on lab stirrer at 1000 rpm for 3 hrs at room temperature for the evaporation of organic solvent, after that the nanoparticles were collected by centrifugation for 5 min at 10000 rpm Eudragit RL 100 were dissolved in water soluble surfactant, during centrifugation it was removed along with decant. Trace amount tween80 present in nanoparticles were removed by washing with distilled water. After washing nanoparticles were lyophilizer for 48 hrs . To minimize the potential risk in patient treated with sustained released. Glimepiride the lowest effective dose should be used for shortest possible duration.

By follow the above mentioned procedure five other batches of nanoparticles in the ratio of 1:1, 1:2, 1:3, 1:4 and 1:5 were prepared and named F1, F2, F3, F4 and F5 respectively.

Similarly above mention procedure was applied to polymer of chitosan for the preparations of glimepiride nanoparticles [6,7].

Evaluation of Nanoparticles

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

1. Particle size

The surface morphology (roundness, smoothness, and formation of aggregates) and particle size were studied by scanning electron microscopy (SEM).

2. Drug recovery

$$\text{Drug recovery} = \frac{\text{mass of nanoparticles recovered}}{\text{mass of polymer drug\&excipient} \times 100}$$

3. Nanoparticleyield

$$\text{Percentage yield} = \frac{\text{Actual weight of product}}{\text{Total weight of excipient\&drug} \times 100}$$

4. Drug entrapment efficiency

$$\text{Drug entrapment \%} = \frac{\text{Mass of drug in Nanoparticles}}{\text{Mass of drug used in formulation} \times 100}$$

5. Drug content

Drug content was determined by centrifugation method. The redispersed nanoparticles suspension was centrifuged at 15,000 rpm for 40 min at 25° to separate the free drug in the supernatant. Concentration of glimepiride in the supernatant was determined by UV-Vis spectrophotometyrically at 228 nm after suitable dilution.

6. *In vitro* release studies

In vitro release studies were carried out by using dialysis tubes with an artificial membrane. The prepared glimepiride nanoparticles and 10 ml of phosphate buffer ph 7.4 was added to the dialysis tube and subjected to dialysis by immersing the dialysis tube to the receptor compartment containing 250 ml of phosphate buffer pH 6.8.The medium in the receptor was agitated continuously using a magnetic stirrer a temperature was maintained at 37±1°. 5ml of sample of receptor compartment were taken at various intervals of time over a period of 8 h and each time fresh buffer was replaced. The amount of drug released was determined spectrometrically at 228 nm [9].

Kinetic analysis of in-vitro release rates of glimepiride nanoparticles:

The results of in-vitro release profile obtained for all formulations were plotted in modes of data treatment as follows,

- Zero order kinetic model- cumulative % drug released versus T.
- First order kinetic model – Log cumulative % drug retained versus T.
- Higuchi's model - cumulative % drug released versus square root of T.
- Korsemeyer equation or peppa's model - Log cumulative % drug released versus log T.

a. Zero order kinetics

It describes the system in which the drug release rate in independent of its concentration.

$$C = Co - Ko\ t$$

C = Concentration of drug to undergo reaction at time t
Co= Initial amount of drug in the solution, which is often Zero
Ko= Zero order release constant.

If the zero order drug release kinetic is obeyed, then a plot of C versus t will be give a straight line with a slope of Ko and an intercept at zero.

b. First order kinetics

It describes the drug release from the systems in which the release rate is concentration dependent.

$$LogC = logCo - kt/2.303$$

Where,
C= Amount of drug released in time t.
Co= Initial amount of drug in the solution
K = First order release constant

If the first order drug release kinetic is obeyed, then a plot of log (Co-C)versus t will be give a straight line with a slope of k/2.303 and an intercept at t=0 of log Co.

c. Higuchi model

It describes the fraction of drug release from a matrix is proportional to square root of time.

$$Mt/M\infty = KH\ t^{1/2}$$

Where,
Mt/M∞ are cumulative amounts of drug release at time t,
KH= Higuchi dissolution constant reflection formulation characteristics.

If the Higuchi model of drug release (i.e.Fickian diffusion) is obeyed, then plot of **Mt/M**∞ versus $t^{1/2}$ will be straight line with slope of kH.

d. Korsemeyer- peppas model (power Law)

The power law describes the drug release from the polymeric system in which release deviates from Fickian diffusion, as expressed in following equation.

$$Mt/M\infty = K\ t^n$$

$$Log[Mt/M\infty] = log\ k + n\ log\ t$$

Where,
Mt and **M**∞ are cumulative amounts of drug release at time t and infinite time (i.e. fraction of drug release at time t),
K = Constant incorporating structural and geometrical characteristics of CR devices.
n = diffusional release exponent indicative of the mechanism of drug dissolution.

To characterize the release mechanism, the dissolution data {**Mt/M**∞ < 0.6} are evaluated. A plot of log {**Mt/M**∞ } versus log t will be linear with slope of n and intercept gives the value of log k. Antilog of log K gives the value of K. the value of release exponent changes with change in the geometry of nanoparticles.

- In general if the exponent value n is 0.5, the release rate is termed "fickian" or square root of time dependent. Release is rapid at first, and then tailing off over time until 100% of the drug is released. In this type of release, the dominant mechanism for release is diffusion.
- If n is between 0.45<n=0.89, the release rate is described as "non-fickian", or "anamolous". Release is rapid at first, although slower than the fickian release rate, again tails off over time.
- If n=0.89,"case II transport" has been achieved.

Stability studies

Introduction

Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not change deleteriously.

The International conference on Harmonization (ICH) guidelines titled "Stability testing onf New Drug substance and products" (QIA) describes the stability test requirements for drug registration applications in the Europian Union, Japan and the United States of America.
ICH specifies the length of study and storage conditions.
Long –Term Testing: 25^0 C±2^0 C/60% RH ±5% for 12 months.
Accelerated testing: 40^0 C±2^0 C/75% RH ±5% for 6 months

Stability studies were carried out at 25^0 C, 30^0 C and 45^0 C for the selected formulation for three months.

Method

The stability study was carried out all formulations glimepiride containing nanoparticles were stored at elevated temperature and relative humidity (25±2^0C /60%±5% RH, 40±2^0C/75%±5% RH) in a over a period of time. Samples were kept for 30 days for stability analysis and after 30 days, drug release of nanoparticles was compared. The stability of drug loaded nanoparticles was evaluated in terms of its drug content. The stability of nanoparticles was evaluated in PBS (pH 6.8.) After specified time intervals, the suspension was centrifuged at 15,000 rpm for 40 min, supernatant was removed and nanoparticles were dissolved in dichloromethane. After adding of water and separation, the amount of drug was detected by UV-Vis spectrophotometyrically method at 228 nm [10,11].

Table 1. List of Materials

S.No.	Materials	Sources
1	Glimepiride	Hetero drugs
2	Eudragit RL 100	Evonik industries
4	Chitosan	Geltec.Bangalore
5	Tween 80	Yarrow chemicals. Mumbai
6	Acetone	Yarrow chemicals. Mumbai

Table 2. Comparison of some common anti-diabetic agents

Agent	Mechanism	Site of action	Main advantages	Main side-effects
Sulfonylureas	Stimulating insulin production by inhibiting the KATPchanne1	Pancreatic be ta cells	□ Effective □ Inexpensive	□ Hypoglycemia □ Weight gain
Metformin	Decreases insul in resistance	Liver	□ May result in mild weight loss □ Does not cause hypoglycemia	□ GI symptoms, including diarrhea, nausea, abdominal pain □Lactic acidosis VitaminB12 □deficiency □ Metallic taste
Acarbose	Reduces intestinal glucose absorpti	GI tract	□ Low risk	□ GI symptoms, including diarrhea, abdominal cramping, flatulence, Hepatoxicity
Thiazolidinediones	Reduce insulin resistance by activating PPA R-γ.	Fat, muscle		

Table 3. Formulation of glimepiride nanoparticles with Eudragit RL 100 by using solvent evaporation method

Ingredients(mg)	F_1	F_2	F_3	F_4	F_5
Glimepiride	1	1	1	1	1
Eudragit RL 100	1	2	3	4	5
Acetone(ml)	5	5	5	5	5
Tween 80(ml)	10	10	10	10	10

Table 4. Formulation of glimepiride nanoparticles with Chitosan by using solvent evaporation method

Ingredients(mg)	F_1	F_2	F_3	F_4	F_5
Glimepiride	1	1	1	1	1
Chitosan	1	2	3	4	5
Acetone(ml)	5	5	5	5	5
Tween 80(ml)	10	10	10	10	10

RESULTS AND DISCUSSION

Table 5. Evaluation parameters of all formulations

Formulation code	Drug polymer ratio	Drug content (%)	Particle size (nm)	Entrapment efficiency (%)	Drug recovery (%)	Percentage yield (%)
GERL F1	1:1	84	543±6.4	62±0.82	85	76.12
GERL F2	1:2	81	510±3.2	65±0.51	80	79.23
GERL F3	1:3	76	584±1.09	68±0.24	77	81.49
GERL F4	1:4	73	624±8.12	73±0.19	74	84.64
GERL F5	1:5	70	651±1.32	82±0.42	70	86.28
GC F1	1:1	83	432±5.04	70±0.23	84	72.12
GC F2	1:2	80	473±4.2	69±0.56	82	73.07
GC F3	1:3	78	502±8.9	73±0.58	79	75.31
GC F4	1:4	74	540±10.5	76±0.42	75	80.42
GC F5	1:5	71	568±10.7	81±0.36	72	81.08

Table 6. *In vitro* drug release profile for GERL

Time(hr)	% Drug Release				
	F1(1P:1D)	F2(2P:1D)	F3(3P:1D)	F4(4P:1D)	F5(5P:1D)
0	0	0	0	0	0
5	4.3	3.8	3.2	2.7	2.2
10	8.6	7.6	6.4	5.4	4.4
15	20.2	18	14	10	8
30	23.2	21.2	18.2	16.1	13.2
45	36	33	28	26	22
1:00	47	43	39	33	28
1:30	48	44	41	35	32
2:00	50	46	42	38	34
2:30	59	55	48	45	39
3:00	64	61	56	52	48
3:30	68	65	59	56	52
4:00	70	67	62	59	56
5:00	79	76	71	69	65
6:00	84	81	78	76	72
7:00	89	87	85	83	81
8:00	95	91	87	85	86

Table 7. Pharmacokinetic studies

Time in hours	√T	Log T	Cumulative % drug release	Log Cumulative % drug release	Cumulative % drug remain	Log cumulative % drug remain
0	0	0	0	0	100	2
1	1.0	0	28	1.4471	72	1.8573
2	1.414	0.301	34	1.5314	66	1.8195
3	1.732	0.477	48	1.6812	52	1.7160
4	2.0	0.602	56	1.7481	44	1.6434
5	2.236	0.698	65	1.8129	35	1.5440
6	2.449	0.778	72	1.8573	28	1.4471
7	2.645	0.845	81	1.9084	19	1.2787
8	2.828	0.903	84	1.9242	16	1.2041

Table 8. Stability studies for glimepiride+ Eudragit RL100

Stability studies for GERL F1

Sl .o	$25^{O}C$	$30^{0}C$	$45^{O}C$
Initial	95	95	95
I^{st}week	94	93	93
2^{nd} week	93	92	91
3^{rd}week	93	92	91

Stability studies for GERL F2

Sl .o	$25^{O}C$	$30^{0}C$	$45^{O}C$
Initial	91	91	91
I^{st}week	91	90	89
2^{nd} week	90	88	88
3^{rd}week	90	89	87

Stability studies for GERL F3

Sl .o	$25^{O}C$	$30^{0}C$	$45^{O}C$
Initial	87	87	87
I^{st}week	87	86	85
2^{nd} week	86	85	85
3^{rd}week	86	84	84

Stability studies for GERL F4

Sl .o	$25^{O}C$	$30^{0}C$	$45^{O}C$
Initial	85	85	85
I^{st}week	85	84	83
2^{nd} week	83	82	82
3^{rd}week	83	81	81

Stability studies for GERL F5

Sl .o	$25^{O}C$	$30^{0}C$	$45^{O}C$
Initial	84	84	84
I^{st}week	84	83	82
2^{nd} week	83	82	81
3^{rd}week	83	82	80

Fig. 1. Drug polymer interactions studies by FTIR for GERLF1

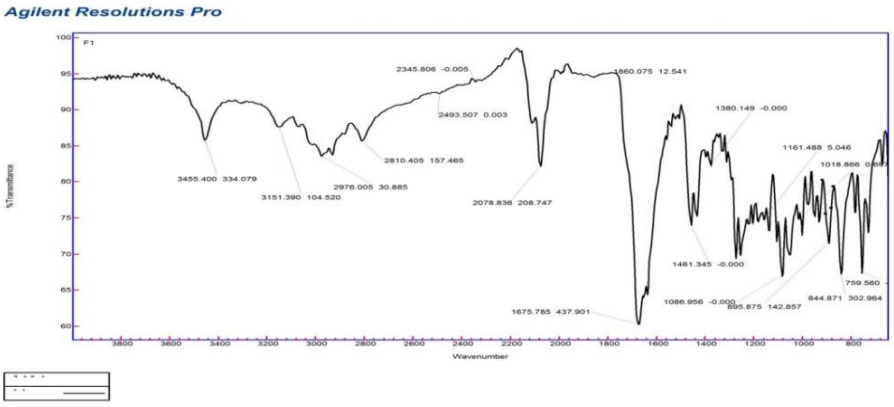


Fig. 2. Typical SEM image of Optimized Formulation GERL F5

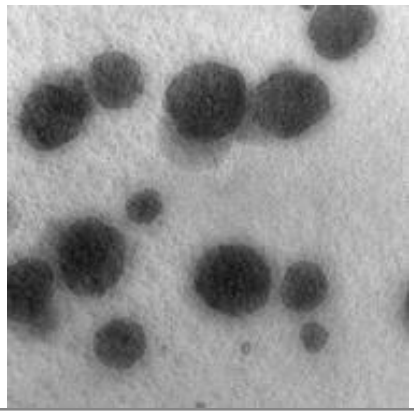
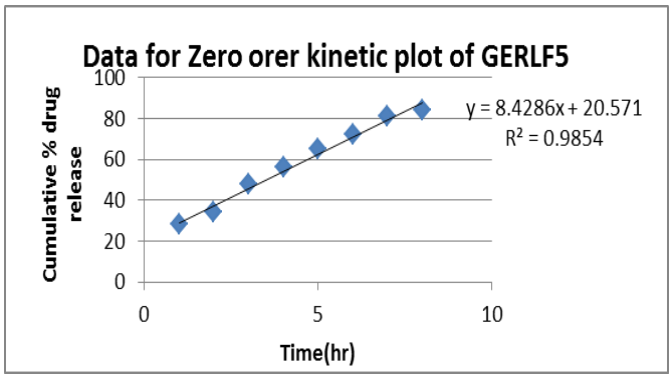
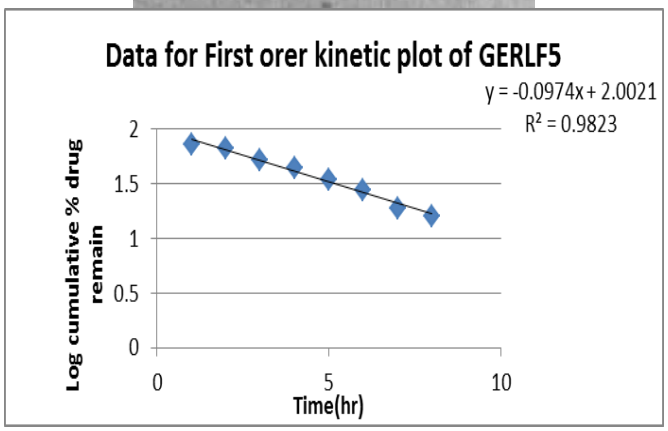


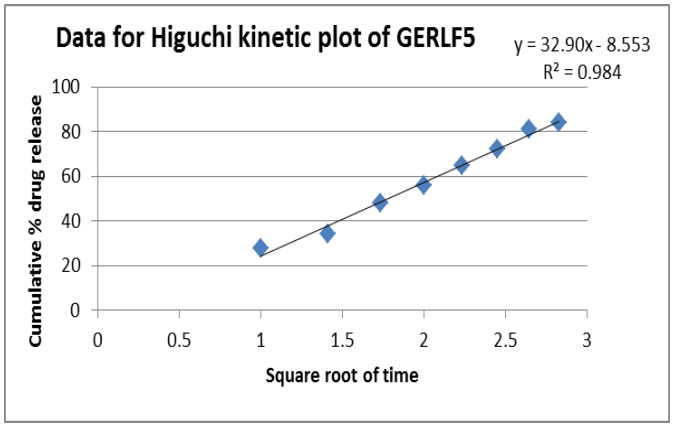
Fig. 3. Kinetic plots of formulation GERL5



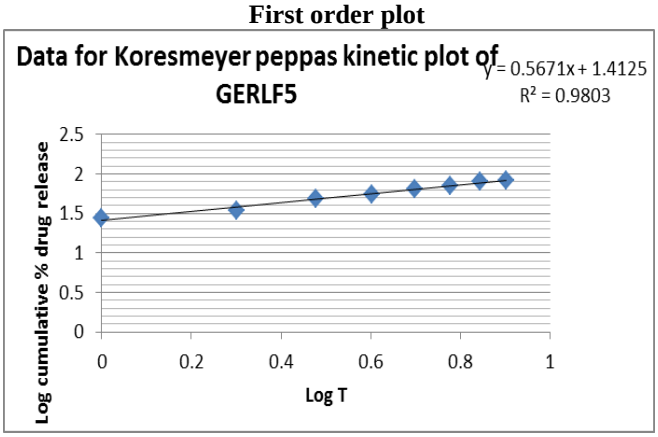
Zero order plot



First order plot



Higuchi plot



Korsmeyer peppas plot

Kinetic values obtained from GERLF5 plot formulation

Formulation	Zero order r^2	First order r^2	Higuchi r^2	Korsemeyer peppas slope'n'
GERLF5	0.985	0.982	0.984	0.814

FTIR studies

There is no physical and chemical interaction observed in the FTIR spectrum between drug and polymer.

Particle size

The particle size distribution of the nanoparticles was determined by SEM (scanning electron microscopy). The nanoparticle dispersions were added to the sample dispersion unit containing stirrer and stirred to reduce the aggregation between the nanoparticles. The average volume-mean particle size was measured after performing the experiment in triplicate [12-15].

Stability Study

The stability studies of the all formulation were carried out by storing in different storage conditions of (25 ± 2^0C/60%±5% RH, 40 ± 2^0C/75%±5% RH) for a period of 3 weeks (Table 8).

CONCLUSION

The major problem in oral drug formulations is low and erratic bioavailability which mainly results from poor aqueous solubility. The method of preparation of nanoparticles of glimepiride was found to be simple and reproducible. The slow and constant release of glimepiride from nanoparticles maintain constant drug plasma concentration thereby increasing therapeutic efficacy. The developed formulation overcome and alleviates the drawbacks and limitations of a glimepiride sustained release formulations.

As a result of this study it may be concluded that the glimepiride nanoparticles containing Eudragit RL 100 can be used to increase the sustain release of the in a sustained manner. The concept of formulating nanoparticles of glimepiride offers a suitable and practical approach in serving desired objectives of nanoparticles.

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