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To Formulation and Evaluation of Immediate Release Tablet of Sitagliptin for Diabetes

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ABSTRACT

The ideal of this study was to design and estimate Sitagliptin Phosphate immediate release(IR) 50 mg tablet using Response face Methodology for the managemant of Type- II diabetes mellitus. Response face methodology(RSM) calculations for this optimization study were performed employing Minitab 16. Different phrasings of immediate release were prepared by applying 2 factor 2 position Central Composite Design(CCD) using Minitab 16 which gave 13 expression for each subcaste. The quantum of Sodium Starch Glycollate(SSG) and Croscarmellose Sodium(CCS) in IR subcaste were used as independent variables and the percent medicine release at 15 twinkles were named as dependent(response) variables for optimization. All the expression were prepared and estimated using applicable logical technology. Grounded on the in- vitro dissolution data(dependent variable/ response), the composition of expression with optimum medicine release for immediate release were linked and employed to formulate optimized tablets followed by its evaluation. All the physico- chemical parameters of the tablets were set up satisfactory. The optimized Sitagliptin Phosphate IR tablet disintegrated in 14 sec and showed an original release of Sitagliptin 99.072 within 15 twinkles.

Keywords: Response Surface Methodology, immediate release, Sitagliptin Phosphate, Type-II diabetes mellitus, Superdisintegrant

INTRODUCTION

- **Tablet**

Tablets are unit solid lozenge forms containing one or further cures which are substantially prepared either contraction or by molding I It has multitudinous advantages, which offers rapid-fire medicine release or controlled release and therefore reduce the frequence of dosing. The stability of tablet is superior to other lozenge form.

- **Types of Tablets**

Multiple compressed tablets

- Compression coated tablets

1. Layered tablets

2. Inlay tablets

Standard compressed tablets

Modified release tablets

Delayed release tablets

Chewable tablets

- Dispersible tablets

INTRODUCTION TO IMMEDIATE RELEASE FORMULATION

Immediate release tablet is administered orally that minimizes immersion time and improves its bioavailability in lower time. These tablets are fabricated substantially to disintegrate and release their medicine with no particular rate controlling 4 point.

- **Merits**

1. Increased stability.
2. Improved patient compliance
3. Economical
4. Quick onset of action
5. Ability to provide the advantages of liquid medication and rapid action.

- **Demerits**

l) Dose dumping

2) Reduced dose adjustment

- **DIABETES MELLITUS**

Diabetes Mellitus is a chronic disorder; it is mainly classified into Type-I and Type-2 Diabetes Mellitus. For Type-I and type-2 diabetes, patients are treated with inuslin and oral antidiabetic drugs respectively.

- **Facts of diabetes**

The following statement explains statistics of diabetes. In the time 198530 million people had diabetes, in 2000- 150 million people were affected, by 2010- 285 million people set up diabetes and it may anticipate 435 million people by 2030.

Treatment of older diabetic is directed towards two goals: Prevention of acute complications like hyperosmolar coma and hypoglycemia; Prevention of chronic complications like retinopathy and nephropathy .

The followings are the important merits in Combination Therapy

- Improved glycemic control can be obtained by two drugs have dissimilar mechanisms of action,
- There are fewer side effects with lower dose of two drugs when compared with great dose of one drug,
- Two drugs are in single pharmaceutical dosage form, the cost will be lower10

Availability of numerous Sulfonyl Urea Oral Hypoglycemic agents globally, Sulfonyl urea oral anti-diabetic drugs play a vital role in diabetic therapy, because Sulfonyl urea drugs are available as minimum dose of I mg and a maximum dose of 80mg.

Based on the available literature Sulfonyl urea anti diabetic drugs are important dose in anti diabetic treatments.

Gliclazide is one of the most frequently used sulfonylureas in the treatment of Type-2 diabetes. It stimulates beta cells to release insulin. The conventional formulation required twice daily administration. In a randomized study on Type-2 diabetic patients, once daily Gliclazide modified release was found as effective in reducing glycosylated haemoglobin I.

- **Ideal attributes of a good Fixed Dose Combination (FDC) therapy**

1. l. Different mechanism of action of each ingredient.
2. If feasible, submaximal dose of each ingredient.
3. Drugs with similar therapy
4. Adverse drug reaction of each drug differs
5. FDC should be cheaper

Materials And Methods

Gliclazide, Sitagliptin Phosphate, HPMC (Different grades), PVP, Dicalcium Phosphate, Cyclodextrin, Magnesium Stearate, Koliidon SR, Aerosil, Cros Carmellose Sodium, Sodium Starch Glycolate, Microcrystalline Cellulose, Polyvinyl Alcohol, Streptazotocin.

Preparation of Immediate Release Tablet of Sitagliptin Phosphate by Wet Granulation Method

Sitagliptin Phosphate Immediate Release subcaste tablets were prepared by the wet granulation system using Sitagliptin Phosphate, Super disintegrants(CCM.Na, SSG), color(Iron Oxide Red) and other constituents. PVP- K- 30 was used as a binder and the wet mass was passed through Sieve No. 12. The grains were dried, and the dried grains were passed through Sieve No. 22 superimposed with Sieve No. 44. Magnesium stearate was used as a lubricant. The grains were compressed into tablets using 8 mm punch on Rotary Tablet Press I(Rimek) each importing 215 mg.

Table: Preparation of Immediate Release Tablets of Sitaglintin.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Sitagliptin phosphate	64.26	64.26	64.26	64.26	64.26	64.26	64.26	64.26	64.26	64.26
Sodium starch glycolate	4	4	4	4	4	4	4	4	4	4
Dibasic calcium phosphate	103.8	103.8	103.8	103.8	103.8	103.8	103.8	103.8	103.8	103.8
MCC	20	20	20	20	20	20	20	20	20	20
Magnesium stearate	8	8	8	8	8	8	8	8	8	8
Simvastatin	20	20	20	20	20	20	20	20	20	20
Lactose	141.5	141.5	141.5	141.5	141.5	141.5	141.5	141.5	141.5	141.5
Micro crystalline cellulose	10	10	10	10	10	10	10	10	10	10
Butylated hydroxyanisole	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
Ascorbic acid	5	5	5	5	5	5	5	5	5	5
Citric acid	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Acacia	_	_	20	_	_	10	_	_	10	10
Pregelatinised starch	_	_	_	20	10	_	10	_	10	_
Starch potato	_	20	_	_	_	_	10	10	_	10

EVALUATION OF PRE COMPRESSION PARAMETERS

- **Angle of Repose**

Angle of repose was measured according to fixed channel system and it was calculated by using the equation reported.

- **Bulk Density**

Suitable quantum of grains from each expression was transferred to 100 ml graduated cylinder. original volume was noted and it can be calculated by the following formula.

- **Tapped Density**

Tapped viscosity was measured by tapping the grains for a constant volume.

- **Compressibility Index**

The compressibility indicator indicates greasepaint inflow parcels. It's expressed in chance and calculated by following formula,

Evaluation of Post Compression Parameters

Trial batches of all tablets and Bilayer tablets were estimated for the following parameters. All the batches of trial phrasings were estimated for colorful post contraction parameters like General Appearance, Thickness and Diameter, Hardness, Frangibility, Weight variation, Content uniformity, Wetting time, Water immersion rate, In vitro decomposition time, In vitro dissolution studies, comparision with retailed phrasings as per pharmacopoeia norms

- **General Appearance**

The general appearance of the tablets is veritably important for consumer magnet.

- **Thickness and Diameter**

Thickness in millimeter of ten tablets is measured by Vernier Caliper.

- **Hardness**

Six tablets are aimlessly named and measured the hardness by Pfizer Hardness Tester.

- **Weight variation**

Twenty tablets were named from every batch and counted collectively to check for weight variation. later the average weight and standard divagation were calculated

- **Drug content Uniformity**

Twenty tablets were counted and its average weight was taken. The greasepaint fellow to one tablet weight of Sitagliptin Phosphate(100 mg) was counted and dissolved in 5 ml of water in 200 ml standard beaker make up the volume with 0. IN Hcl. After acceptable dilutions the absorbance was measured at 267 nm by using UV — Spectrophotometer

- **Wetting Time**

A towel paper was placed in a petri dish containing 6 ml of water. The tablet was kept at the top. The time taken for entire wetting of tablet was recorded.

- **In- vitro decomposition time**

One tablet was placed in each of six tubes of the handbasket of decomposition outfit. The complete decomposition time of the tablet was measured in water as per USP system at 37 ± 0.5' C temperature. Six individual tablets of decomposition time were reported.

- **In- vitro dissolution study**

The dissolution studies of the named tablets were done by USP dissolution outfit Il (paddle system). The study was carried out using 900 ml of acidic pH 1.2 medium at 37 ± 0.5 0 C and 50 rpm. 5 ml of the sample was withdrawn at regular 5 nanosecond intervals for 30 twinkles. The samples were replaced with same volume medium. Absorbance was measured at 267nm using (LabindiaDiss02000) UV Spectrophotometer. The study was carried out for all the phrasings and the stylish release profile was named for the bilayer expression.

Result and Discussion

- **Melting Point Analysis**

Table: Melting Point Analysis

Drug	Observed Melting Point *	Reported Melting Point ('C)
Sitagliptin phosphate	200 0.75	198 - 202
Gliclazide	169 ± 0.43	169 - 171

All values are expressed as Mean ± S.D, n — 3

The observed melting points ofpure drugs were found to be similar to that of their respective reference standards.

- **Solubility studies**

Table: Solubility Profile of Drugs

S. No.	Medium	Sitagliptin Phosphate	Gliclazide
	Water + Drug	Very Soluble	Insoluble
2	pH 1.2 (0.1N Hcl) + Drug	Very soluble	Insoluble
3	pH 4.5 Acetate buffer + Drug	Soluble	Slightly soluble
4	pH 6.8 Phosphate buffer + Drug	Soluble	Soluble
5	pH 7.4 Phosphate buffer + Drug	Soluble	Soluble
6	Acetone + Drug	Slightly soluble	Slightly Soluble

- **Determination of max**

The pure drug absorption spectrum was scanned between 200-400 nm in 0.1N Hcl.

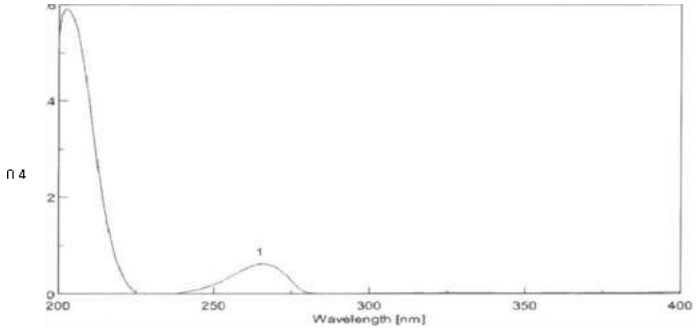

Figure : Absorption Spectrum of Sitagliptin Phosphate

- **Calibration Curve of Sitagliptin Phosphate measured using UVSpectrophotometry at 267nm**

S. No	Concentration (gg/ml)	Absorbance at 267 nm
1	20	0.122
2	40	0.230
3	60	0.338
4	80	0,467
5	100	0.579
6	120	o. 702

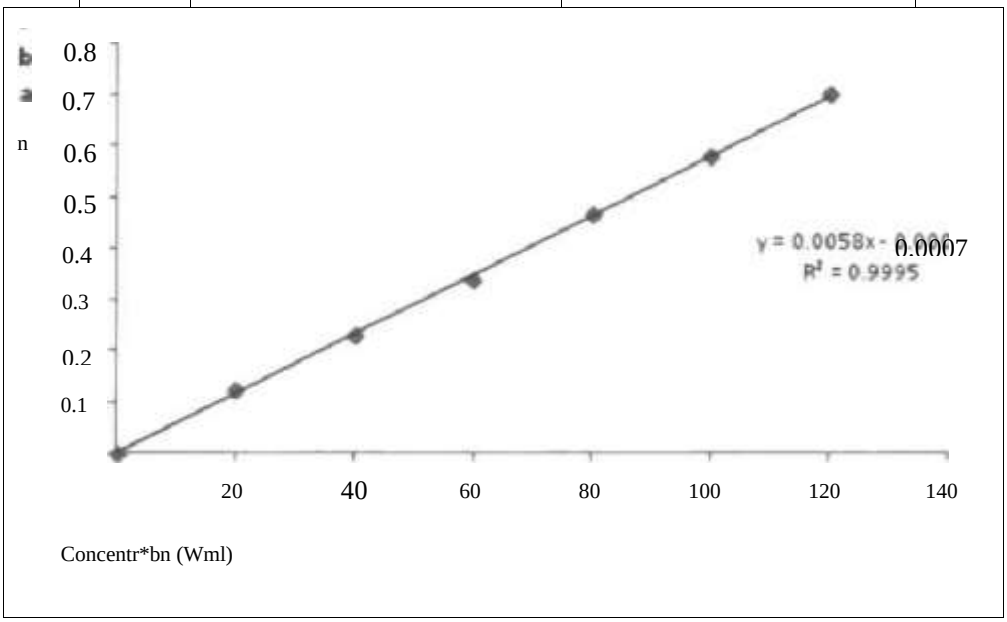

Figure: Calibration Curve of Sitagliptin Phosphate measured using UV

- **In vitro drug release study of solid dispersion containing Drug and carriers for various formulations**

Table: In vitro drug release study of solid dispersion containing Drug and carriers for various formulations

Time (min)	Cumulative Percentage of Drug							
	S.D			S.DP1	S.DP2	S.DP3	P.MI	P.M2

5		12±0.14	12±0.12	10±0.16	10±0.11	11±0.26	10±0.27	10±0.62
10	14±0.23	20±0.36	20±0.32		20±0.54	25±0.42	23±0.32	
15	20±0.15	32±0.21	24±0.62	31±0.34	27=0.22	30±0.26	44±0.32	32±0.24
20	27±0.24	40±0.69	30±0.24	52±0.18	34±0.32	33±0.36	50±0.24	46±0.32
25	32±0.89	53±0.34	35±0.14	6EO.16	45±0.54	36±0.24	51±0.66	54±0.62
30	38±0.56	60±0.54	49±0.34	73±0.14	50±0.36	47±0.26	58±0.62	63±0.34
35	40±0.83	67±0.16	53±0.24	78±0.18	62±0.14	58±0.44	63±0.54	
40	50±0.24	70±0.17	67±0.22	82±0.18	68±0.26	65±0.82	69±0.36	80±0.26
45	63±0.56	7440.18	77±0.26	83±0.16	73±0.16	70±0.56	73±0.42	81±0.38
so	70±0.58	80±0.17	8 .48	84±0.24	84±0.22	85±0.36	78±0.24	83±0.36
55	82±0.87	85±0.19	90±0.18	85±0.22	89±0.42		79±0.34	85±0.62
60	90±0.59	91±0.39	98±0.32	86±0.24	92±0.26	95±0.32	80±0.64	86±0.62

CONCLUSION

Physical appearance, colour, odour and tastes of the Sitagliptin Phosphate and Gliclazide were set up to be complied with the Pharmacopoeial limit. The melting point of Sitagliptin Phosphate were set up to be 200 C independently, which complies with the range specified in literatures indicating that the medicine samples were pure. Sitagliptin Phosphate was observed to dissolve freely in pH 1.2 Hydrochloric acid. therefore, farther studies similar as decomposition, medicine content and in vitro medicine release were carried out in the below specified pH results independently, the maximum absorbance of Sitagliptin Phosphate were set up to be 267nm independently. The results coincide with the reported literatures. From the numbers and the interpretation of the FTIR data which showed that there was no redundant peak or broadening of the peaks, and it indicates that there's no incompatibility between medicine and excipients. Differential Scanning Calorimetry was done for the medicines, solid dissipation and expression. The thermal angles showed a sharp peak at 200.200 C for Sitagliptin Phosphate independently, the results of DSC inferred that there was no commerce between medicines and excipients. Estimation angles were colluded for both Sitagliptin Phosphate grounded on the data attained in UV spectrophotometer and the angles showed a good retrogression measure of 0.999 and 0.999 for the separate medicines.

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