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Formulation and evaluation of sitagliptin phosphate and metformin hydrochloride trilayered tablets

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Abstract

Sitagliptin phosphate when used alone is an oral anti hyperglycemic drug of the dipeptidyl peptidase-4 (DPP-4) inhibitor class. It is available as tablets under trade name JANUVIA. Metformin hydrochloride is used alone in the form of biguanide anti hyperglycemic agent for treating non-insulin-dependent diabetes mellitus (NIDDM) and is available as both conventional and sustained release tablets. The objective of the present study was to develop a trilayered tablet of immediate release Sitagliptin phosphate layer and sustained release Metformin Hydrochloride layer. Apart from the aesthetic appeal this trilayered tablet is expected to improve glucose tolerance in patients with the type 2 diabetes by lowering both basal and postprandial plasma glucose, reducing the dose, reducing frequency of administration and dose related gastrointestinal side effects of metformin and improve its bioavailability thus improving the patient compliance. Metformin Hydrochloride has biological half-life of nearly 6 hours. An attempt was made to sustain its release by using two different polymers in two layers. Preformulation studies including drug excipient compatibility studies were conducted for both drugs. Different formulations of sustained release Metformin HCl tablets were prepared by using a combination of hydrophilic polymers like HPMC K100, HPMC K4M, HPMC K15 M, pH sensitive polymer Carbopol 971P, retarding polymer Ethyl cellulose and Low substituted hydroxy propyl cellulose. Sitagliptin immediate release formulations were prepared using cross povidone, croscarmellose sodium and sodium starch glycolate as super disintegrants. The tablets were evaluated for all physico chemical parameters like angle of repose, bulk density, tapped density, Hausners ratio and carr's index. Based on the invitro dissolution data the formulations SF6, MF9 and MF8 were found to be the optimized formulations for Sitagliptin phosphate and Metformin Hydrochloride formulations respectively. Trilayered tablets were prepared by first preparing Metformin HCl layers namely MF3 and MF8 using lesser compression force. The final compression was made by placing Sitagliptin IR layer (SF6) on the Metformin layers with final hardness of 6.5 kg and evaluated. The IR layer of Sitagliptin phosphate layer disintegrated in 54.67 sec from the trilayered tablet. In vitro dissolution studies of Trilayered tablet were performed in USP type II apparatus. The cumulative % drug release of Sitagliptin phosphate SF6 was found to be 99.65% at 30 min and Metformin HCl MF3 and MF8 was found to be 98.72 % at 12 hrs. From the study it is found that the formulations made from MF3 and MF8 combination of HPMC K15M and HPMC K4M polymers and SF6 Sodium starch glycolate used as super disintegrant was found to show optimum properties of required drug release.

Keywords: Hyperglycemia, Metformin HCl, Sitagliptin Phosphate, Trilayered tablet.

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency and it is often combined with insulin resistance. Non-insulin dependent diabetes mellitus represents a heterogenous group comprising mild form of diabetes that occurs predominantly in adults.

Sitagliptin phosphate (DPP-IV inhibitor) is an oral hypoglycemic agent commonly prescribed drug for the treatment of patients with type II diabetes mellitus [1]. Metformin hydrochloride is used alone in the form of biguanide anti hyperglycemic agent for treating non-insulin-dependent diabetes mellitus [2]. The usual dosage for Metformin is 250–500 mg 3-4 times daily, up to a 2.5 g/day. The absolute bioavailability of Metformin hydrochloride is 50–60% and has biological half-life of 6.2 hrs. Frequent dosing schedule leading to high GI side effects and high daily dose makes its use uncommon. Hence there is a need to formulate SR Metformin tablets to prolong its duration of action and to reduce total dose of drug administered as well as the incidence of adverse side effects.

The combination of a DPP-4 Inhibitor with Metformin allows a broad and complementary spectrum of anti diabetic actions. This combination does not increase the risk of hypoglycemia, does not promote weight gain, and does not cause adverse effect caused by various other oral anti diabetic combinations. Both the drugs have a complimentary and possibly additive effect on glycemic control and reduced glycosylated heamoglobin [3].

Multilayer tablets are gaining importance in oral sustained drug delivery. They consist of an active matrix core and one or more layers applied during tableting which may act as barriers and regulate drug release. This is a best way of combination therapy for treating chronic diseases. These tablets may be designed for different drug release profiles, one layer for the immediate release of the drug and second layer for extended release and third layer for sustained release of the drug thus maintaining a prolonged blood level. Layers may be colored differently to identify the product.

The objective of the present study was to develop a trilayered tablet of immediate release Sitagliptin phosphate layer and sustained release Metformin Hydrochloride layers**.** The formulation and evaluation of trilayered tablets are discussed. The results indicate that the optimized trilayered tablet formulation can be successfully used for treatment of diabetes in chronic patients.

Material and Methods

Materials

Metformin hydrochloride was a kind gift from Gland pharma, Hyd, India. Sitagliptin phosphate was a gift sample provided by Matrix Labs, Hyderabad. HPMC K100, HPMC K4M, HPMC K15M, low substituted hydroxy propyl cellulose, Ethyl cellulose, Carbopol, Microcrystalline cellulose, Starch, Croscarmellose sodium, Sodium starch glycolate, Crospovidone, Sodium bi carbonate, Magnesium stearate, Talc were purchased from S.D Fine Chemicals, Mumbai.

Methods

Preparation of Trilayered tablets

Trilayered tablets of Metformin HCl and Sitagliptin Phosphate were developed in three stages.

Stage-1: Preparation and Optimization of Immediate release layer by wet granulation method.
Stage-2: Preparation and Optimization of Sustained release layers I and II by wet granulation technique.
Stage-3: Compression of Optimized IR layer and SR layers to form Trilayered tablet.

Drug Excipient Compatibility

The compatibility of drugs with their respective excipients was studied by FT-IR spectroscopy. Scanning was performed at a speed of 2 mm/sec with resolution of 4 cm^{-1} over the region 4000-400 cm-1. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction.

Formulation of Sitagliptin phosphate immediate release layer blend of Trilayered tablet

Sitagliptin phosphate immediate release layer was prepared by wet granulation method using varying concentrations of different super disintegrants.

Wet Granulation Technique: It involves many steps such as

1) Sifting: Weighed quantities of Sitagliptin phosphate, SSG, Crospovidone, Cross carmellose sodium and Micro crystalline cellulose, were sifted through sieve # 44.
2) Binder preparation: Starch was dissolved in purified hot water.
3) Dry mixing: The above sieved materials were weighed and mixed thoroughly for 15min.
4) Granulation: Granules were prepared by adding Starch paste (1% solution) to dry blend and make it wet dough, and passed through sieve #18.
5) Drying: The produced Sitagliptin phosphate granules were dried in hot air oven at 50^0C for 15 to 30min.
6) Screening: Dried granules were passed through sieve #22 .
7) Lubrication: Magnesium stearate and Talc were sifted through sieve #44 and added to dried granules and mixed for 2 minutes.
8) Compression: The granules were compressed in Rotary Tablet Compression machine using 6mm deep concave punches plain on both sides at required pressure. [4]

The various formulations (SF1 to SF6) of Sitagliptin phosphate immediate release layer are listed in Table 1

Table 1 Composition of Sitagliptin phosphate immediate release blend using Super disintegrants

Ingredients	SF1(mg)	SF2(mg)	SF3(mg)	SF4(mg)	SF5(mg)	SF6(mg)
Sitagliptin	64.5	64.5	64.5	64.5	64.5	64.5
Cross povidone	10	15	---	---	---	---
Cross carmellose sodium	---	---	10	15	---	---
Sodium starch glycolate	---	---	---	---	10	15
Microcrystalline cellulose	21.5	15.5	21.5	15.5	21.5	15.5
Starch paste-5%	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Avg weight of IR layer	100	100	100	100	100	100

Formulation of Metformin sustained release layers of Trilayered tablets with different concentrations of different polymers

Metformin Hydrochloride sustained release layer containing (250mg dose) were formulated using varying concentrations of different polymers prepared by wet granulation technique.

Wet Granulation Technique

Weighed quantity of drug, polymer (L HPC, Carbopol 971P, Ethyl cellulose, HPMC Grades K100, K15M, and K4M) and micro crystalline cellulose were taken and mixed thoroughly. Granules were prepared using 1% PVP solution as binder and drying at 40^0C for 1 hour. After drying, the granules were screened through sieve no 22. The blend was lubricated using magnesium stearate and talc was finally added and mixed thoroughly. The tablets were compressed in Rotary Tablet Compression machine using 10mm circular flat punches with a break line.

The SR layer with 250mg of Metformin Hydrochloride was formulated using polymers. The quantitative composition of all the formulations MF1 to MF12 is shown in Table 2. [5]

Table 2 Formulation of Metformin Hydrochloride (250mg dose) sustained release blend prepared using individual polymers

INGREDIENTS	MF1 (mg)	MF2 (mg)	MF3 (mg)	MF4 (mg)	MF5 (mg)	MF6 (mg)	MF7 (mg)	MF8 (mg)	MF9 (mg)	MF10 (mg)	MF11 (mg)	MF12 (mg)
Metformin Hydrochloride	250	250	250	250	250	250	250	250	250	250	250	250
L HPC	----	----	----	----	70	77	----	----	----	----	---	---
HPMC K 15M	----	----	52.5	63	----	----	----	----	----	----	---	----
HPMC K100	63	70	----	----	----	----	----	----	----	----	----	----
HPMC K 4M	----	----	----	----	----	----	52.5	63	----	----	----	----
Ethyl cellulose	----	----	----	----	----	----	----	----	----	----	70	77
Carbopol 971	----	----	----	----	----	----	----	----	70	77	----	----
Microcrystalline cellulose	32	25	42.5	32	25	18	42.5	32	25	18	25	18
PVP K-30 (1%)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Avg weight of SR layer	350	350	350	350	350	350	350	350	350	350	350	350

Preparation of sustained release tablets

The sustained release tablet was prepared using different polymers with varying concentrations in two layers to get aesthetic appeal. The SR layer I containing 250mg of Metformin Hydrochloride is placed in 10mm die compressed with low force. The second layer SR layer II was also placed into die and compressed with required pressure. The optimized formulation was compared to the marketed formulation (Glycomet SR®). The quantitative composition of all the formulations CMF1 to CMF6 is shown in Table 3. [6]

Preparation of Trilayered tablets

The granules of Sitagliptin phosphate immediate release layer containing average weight of 100mg was first placed in the 12mm die and compressed at low pressure. Then the SR I layer and SR II layer with average weight of 350mg each were placed into die and compressed at required pressure one upon the other using 12mm capsule shaped punches to form a Trilayered tablets. The different batches of Trilayered tablets were collected and stored in air tight containers. The quantitative composition of all the formulations TF1 to TF6 is shown in Table 4. [7]

Table 3 Formulation of Metformin Hydrochloride (500mg dose) sustained release blend prepared using combination of polymers

Ingredients	CMF1(mg)	CMF2(mg)	CMF3(mg)	CMF4(mg)	CMF5(mg)	CMF6(mg)
Sustained release layer I (SR I)						
Metformin Hydrochloride	250	250	250	250	250	250
HPMC K 15M	---	---	---	52.5	52.5	52.5
LHPC	---	---	77	---	---	---
HPMC K100	70	70	---	---	---	---
PVP (1%)	q.s	q.s	q.s	q.s	q.s	q.s
Microcrystalline cellulose	25	25	18	42.5	42.5	42.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Sustained release layer II (SR II)						
Metformin Hydrochloride	250	250	250	250	250	250
Carbopol	---	77	---	77	---	---
Ethyl cellulose	---	---	---	---	---	77
HPMC K4M	63	---	63	---	63	---
PVP (1%)	q.s	q.s	q.s	q.s	q.s	q.s
Microcrystalline cellulose	32	18	32	18	32	18
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Average weight of SR layers	700	700	700	700	700	700

Preparation of Standard graph of Sitagliptin phosphate and Metformin Hydrochloride

Calibration curve of Sitagliptin Phosphate was constructed by measuring the absorbance of different concentrations of drug in 0.1 N HCl at 267 nm. Calibration curve of Metformin Hydrochloride was constructed by measuring the absorbance of different concentrations of drug in 0.1 N HCl and in pH 6.8 phosphate buffer at 231 nm. A graph was plotted by taking concentration on X axis and absorbance on Y axis.

Physical characterization

Metformin SR granules and Sitagliptin phosphate IR granules were prepared by wet granulation technique. The flow properties of the granules were evaluated by measuring Angle of repose, Bulk density, Tapped density, Carr's index, Hausner's ratio etc. using standard methods as per Indian pharmacopoeia. [8]

Both Sitagliptin phosphate immediate release tablets and Metformin Hydrochloride sustained release tablets were evaluated for post compression parameters like hardness, weight variation, friability, drug content uniformity and in vitro dissolution study. The Optimized formulations were selected and their percentage drug release was compared with that of marketed tablets (Januvia®and Glycomet SR®). [9]

Evaluation of Trilayered tablets

All the post compression parameters like thickness, hardness, weight variation, friability, content uniformity of tablets containing both the drugs were measured.

Invitro dissolution study

The dissolution study of tri layered tablets was performed over a 12 hr period using USP type II (paddle) Dissolution Testing Apparatus (Electro lab) Model. 900ml of 0.1N HCl was used as dissolution

Table 4-Composition of different Trilayered Tablets (TLT)

	INGREDIENTS	TF-1 (SF6+CF1)	TF-2 (SF6+CF2)	TF-3 (SF6+CF3)	TF-4 (SF6+CF4)	TF-5 (SF6+CF5)	TF-6 (SF6+CF6)
IR LAYER	Sitagliptin Phosphate	64.5	64.5	64.5	64.5	64.5	64.5
	Sodium starch glycolate	10	10	10	10	10	10
	Microcrystalline cellulose	21.5	21.5	21.5	21.5	21.5	21.5
	Starch paste (5%)	q.s	q.s	q.s	q.s	q.s	q.s
	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
	Talc	2.5	2.5	2.5	2.5	2.5	2.5
	Colour (poncaeu supra pink)	q.s	q.s	q.s	q.s	q.s	q.s
SR LAYER 1	Metformin Hydrochloride	250	250	250	250	250	250
	HPMC K 15M	---	---	---	52.5	52.5	52.5
	LHPC	---	---	77	---	---	---
	HPMC K100	70	70	---	---	---	---
	PVP (1%)	q.s	q.s	q.s	q.s	q.s	q.s
	Microcrystalline cellulose	25	25	18	42.5	42.5	42.5
	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
	Talc	2.5	2.5	2.5	2.5	2.5	2.5
SR LAYER 2	Metformin Hydrochloride	250	250	250	250	250	250
	Carbopol	---	77	---	77	---	---
	Ethyl cellulose	---	---	---	---	---	77
	HPMC K4M	63	---	63	---	63	---
	PVP (1%)	q.s	q.s	q.s	q.s	q.s	q.s
	Microcrystalline cellulose	32	18	32	18	32	18
	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
	Talc	2.5	2.5	2.5	2.5	2.5	2.5
	Colour(Sunset yellow)	q.s	q.s	q.s	q.s	q.s	q.s
	Avg weight of Trilayered tablet	800mg	800mg	800mg	800mg	800mg	800mg

medium agitated at 100 RPM, at temperature of 37± 0.5^{0}C. 10 ml samples were withdrawn at 5,10,15,20,30,40,60 min for 1 hr to estimate the release of Sitagliptin phosphate, and at 1, 2, 4, 6, 8, 10, 12 hrs for estimating Metformin release. Same volume of dissolution medium was replaced at every time interval. Samples were filtered by Whatman filter paper no. 41. The samples were analyzed for Sitagliptin phosphate and Metformin HCl by UV Spectrophotometry at their respective λ max values 267 nm and 231 nm. The samples collected for first hour were analyzed for Sitagliptin content at 267 nm. The samples collected for 1 - 12 hrs were analyzed for the release of Metformin HCl at 231 nm. From in vitro dissolution study, the percentage drug release of both the drugs was compared with their respective marketed tablets (Januvia for Sitagliptin phosphate and Glycomet SR for Metformin Hydrochloride). [10]

Stability studies

Stability studies were performed for optimized formulations at 40°C at 75% RH for 3 months and analyzed for their physical parameters, drug content and in vitro drug release studies at every one month intervals.

Preparation of tablets for animal studies

The tablets of average weight 50mg using 4mm deep concave punches plain on both sides were prepared for animal studies.

In-vivo pharmacodynamic study

Pharmacodynamic studies were conducted in male wistar rats weighing 200-250gm. Diabetes was induced at a previously standardized dose of 45mg/kg Streptozotocin. The animals were divided into 4 groups. Each group comprised of 3 rats (n=3).GROUP I (Control): Untreated healthy rats.
GROUP II (Diabetic control): Untreated diabetic rats.
GROUP III (Standard): Treated rats with Reference (Marketed tablet).
GROUP IV (Test): Treated rats with optimized test formulation.
After the administration through the oral feeding needle, blood was collected from the retro-orbital plexus using a capillary needle at 0, 1, 2, 4, 5, 6, 8, 10 and 12hrs after oral administration. The blood glucose levels were determined by glucometer (Contour ^{TS}). [11]

Results and discussions

Calibration curve

Calibration curve of both drugs were plotted by measuring absorbance at their respective absorption maxima with 0.1N HCl and Metformin HCl alone with 6.8 pH buffer as solvent. Both the drugs obeyed Beer-Lambert's law by giving good correlation coefficient.

FT-IR study of immediate release layer

From the spectra obtained in Figures 1 and 2 it was observed that characteristic peaks appear with identical or with minor differences. There is no change in shift of major peaks of drug (C=O str, C=N str ,C-F str, NH_2 1^0 amine (N-H)) was observed. From peaks it was evident that there was no chemical interaction between the drug and the superdisintegrant.

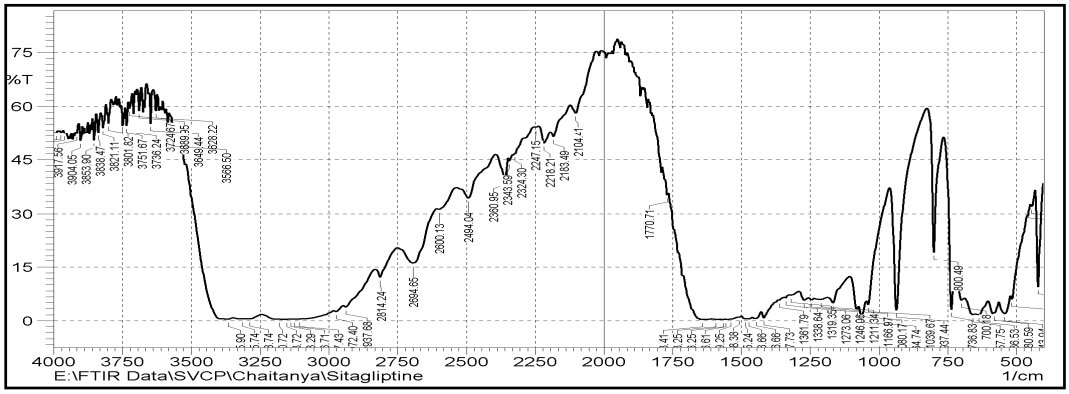

Figure 1: FT-IR spectrum of pure Sitagliptin phosphate

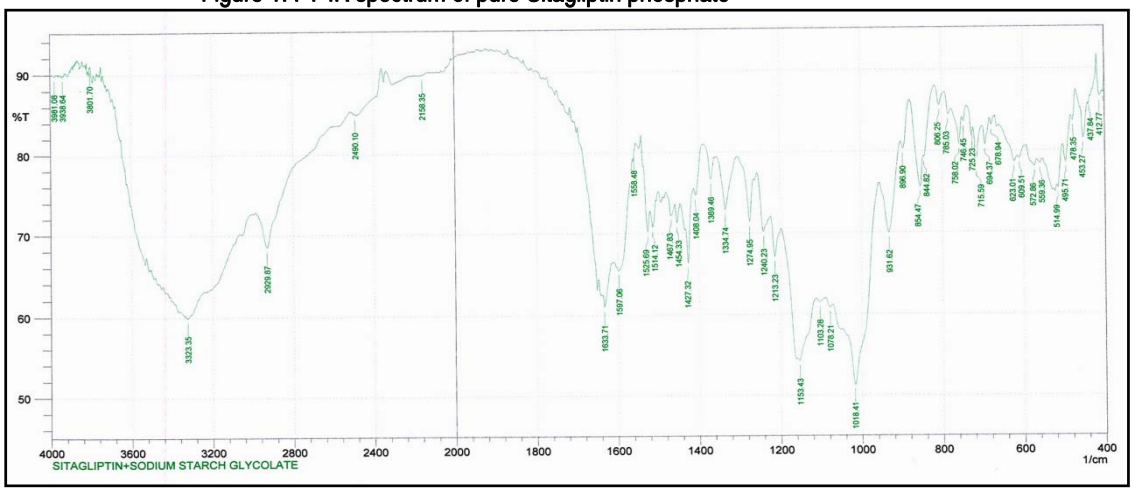

Figure 2: FT-IR spectrum of Sitagliptin phosphate with SSG

FT-IR study of sustained release layer

From the spectra obtained in Figures 3 and 4 it was observed that characteristic peaks appear with identical or with minor differences. There is no change in shift of major peaks of drug (C-N str, C=N str, C-H str, NH_2 1^0 amine (N-H) and N-H (2^0 amine) was observed. From peaks it was evident that there was no chemical interaction between the drug and the polymer

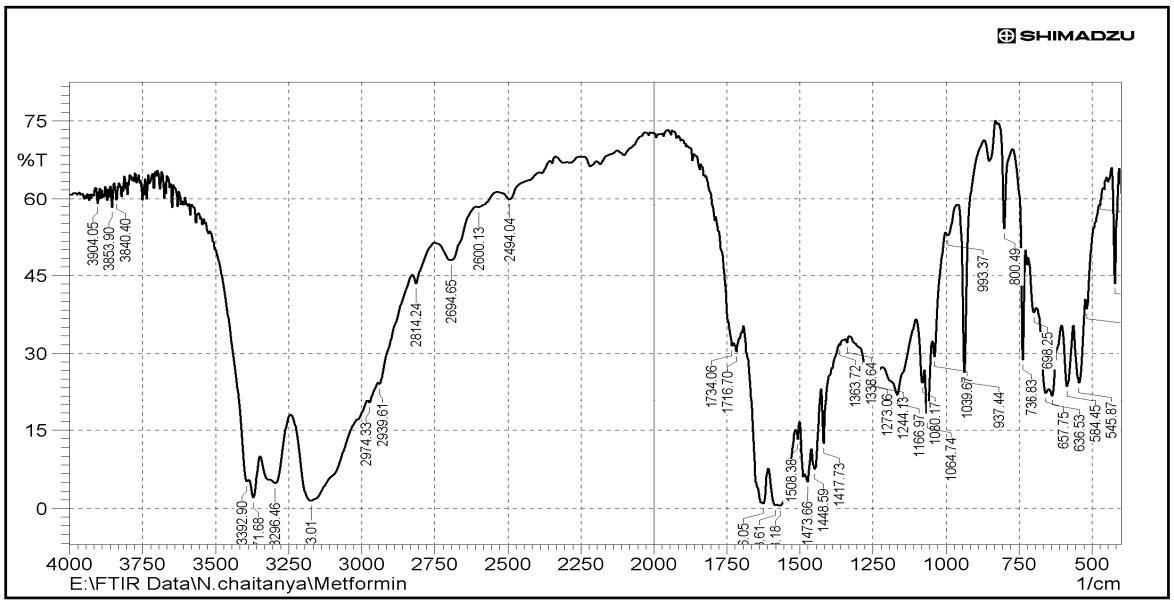

Figure 3: FT-IR spectrum of pure Metformin HCl

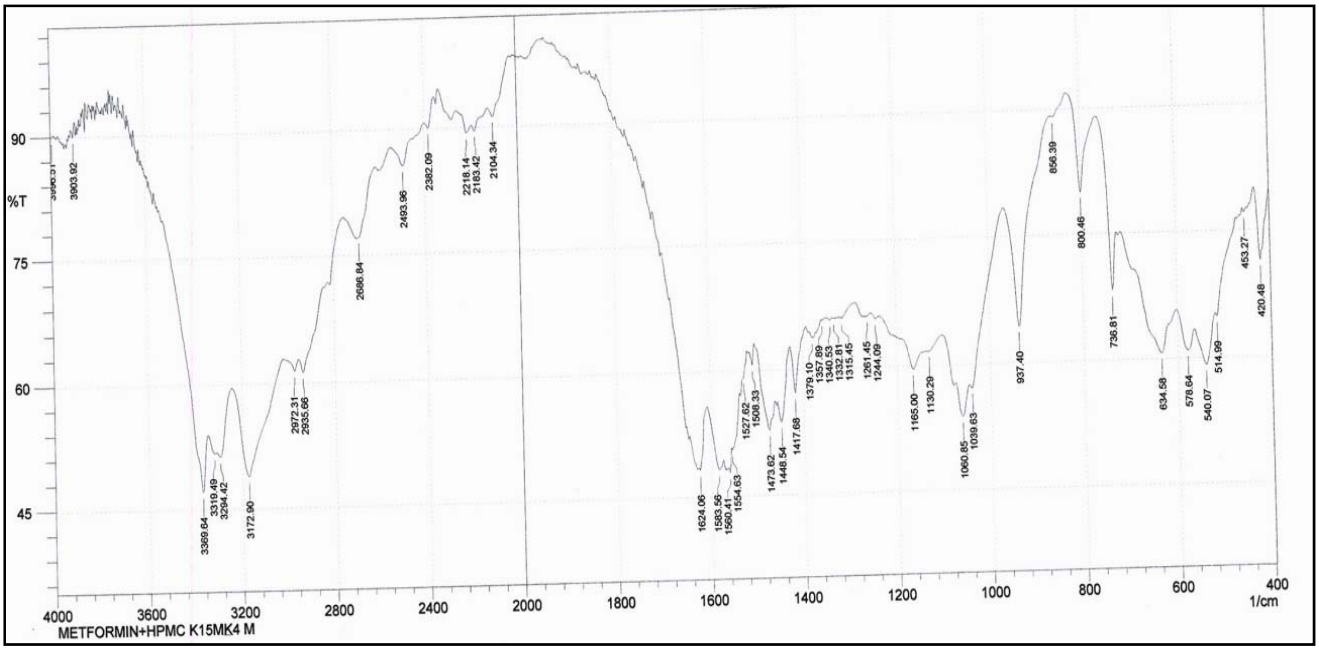

Figure 4: FT-IR spectrum of Metformin HCl with HPMC K15M and HPMC K 4M

Preformulation studies

The Sitagliptin phosphate and Metformin Hydrochloride granules were prepared by wet granulation method. The prepared granules of different batches were evaluated for their angle of repose, bulk density; tapped density, compressibility index and Hausner's ratio are reported in the Table 5.

Table 5 Pre compression parameters of Sitagliptin phosphate immediate release granules and Metformin hydrochloride Sustained release layer I and II granules

Formulations	Bulk density	Tapped density	Angle of repose	Hausner's ratio	Carr's index
SF1	0.296	0.34	28.52	1.16	17.7
SF2	0.38	0.44	26.5	1.15	13.6
SF3	0.31	0.35	29.60	1.13	11.5
SF4	0.353	0.399	27.51	1.13	10.4
SF5	0.43	0.487	23.4	1.12	9.1
SF6	0.39	0.427	29.74	1.10	10.9
Sustained release layer I					
MF1	0.356	0.416	31.1	1.17	14.4
MF2	0.425	0.458	28.8	1.08	7.2
MF3	0.412	0.461	24.2	1.12	10.6
MF4	0.359	0.394	23.7	1.10	8.8
MF5	0.426	0.455	25.7	1.07	6.6
MF6	0.394	0.453	27.9	1.15	13.02
Sustained release layer II					
MF7	0.370	0.392	23.7	1.06	5.6
MF8	0.381	0.422	27.2	1.11	9.7
MF9	0.365	0.405	25.4	1.11	9.8
MF10	0.422	0.476	26.3	1.13	11.3
MF11	0.368	0.441	23.2	1.2	16.5
MF12	0.416	0.465	26.9	1.12	10.5

The bulk densities of the granules were found to be in the range of 0.296 to 0.428 gm/ml. The angle of repose varied from 23.2 to 29.7. The low values of angle of repose indicate the free flowing nature of the granules. The tapped densities ranged 0.34 to 0.487 gm/ml and the Carr's indexes were in the range of 5.6 to 17.7. Hausner's ratio was found in the range of 1.06 to 1.18 and the values showed the low interparticle friction between the granules.

Valuation parameters

The physico-chemical characterization of the individually compressed tablets (immediate release layer, Sustained release layers containing 250mg dose, Combination of sustained release layers containing 500mg dose and optimized trilayered tablet) is shown in the Table 6, 7 and 8. The prepared tablets were evaluated for parameters such as Weight variation, Hardness, Friability, Thickness, drug content and in vitro dissolution profile. From the results reported in Tables 6, 7 and 8. Thickness was found to be in the range of 2.01 to 2.31mm, 5.14 to 5.81mm, 5.91 to 6.20mm and 6.1±0.04 for IR tablet, sustained release tablets containing 250mg dose, Combination of sustain release tablet and Optimized trilayered tablets respectively. Hardness of the tablets was in the range of 3.7 to 4.1 cm^2 for IR tablet, 4.8 to 6.0 kg/cm^2 for SR tablets I and II individually, 5.9 to 6.3 for combination of sustain release tablets and 6.1±0.4 for trilayered tablet which was sufficient for the handling of tablets throughout the shelf life. Percentage % friability was between 0.15–1.87% and complies with pharmacopoeial limit. Weight variation was less than 5% which is a pharmacopoeia limit. Drug content of Metformin HCl found to be in the range of 85.3 %-99.54 %, was within the limit as per I.P and ICH guidelines and Drug content of Sitagliptin phosphate found to be in the range of 91.05 %-96.4 % was within the limit as per I.P and ICH guidelines.

Figure 5: Trilayered tablets

Table 6 Evaluation parameters of Sitagliptin phosphate immediate release tablets and Metformin hydrochloride Sustained release tablets

Formulations	Weight-Variation(n=20)	Hardness Kg/cm^2 (n=3)	Thickness mm (n=3)	Friability % (n=6)	Drug Content(%)
SF1	0.41	3.7	2.01	0.16	95.8
SF2	0.26	4.7	2.13	0.05	96.4
SF3	0.43	4.7	2.01	0.08	91.05
SF4	0.57	4.5	2.31	0.18	93.23
SF5	0.16	3.7	2.25	0.73	91.06
SF6	0.11	4.7	2.14	0.06	93.05
Sustained release I tablets					
MF1	1.05	6.0	5.64	1.10	91.08
MF2	0.95	6.0	5.24	0.84	94.07
MF3	0.92	6.1	5.46	0.98	97.54
MF4	0.68	5.5	5.12	1.89	91.05
MF5	0.16	6.2	5.41	0.96	92.04
MF6	0.91	6.8	5.32	0.84	96.03
Sustained release II tablets					
MF7	1.23	5.8	5.70	0.53	98.54
MF8	0.64	6.2	5.81	1.14	94.05
MF9	1.18	5.5	5.46	1.56	90.21
MF10	1.44	6.0	5.64	1.04	96.70
MF11	0.67	4.8	5.04	0.87	85.3
MF12	0.94	5.9	5.15	1.13	91.64

*SF-Sitagliptin formulations. MF-Metformin formulations

Table 7 Evaluation parameters of Metformin hydrochloride sustained release tablets (500mg dose) prepared using combination of polymers

Formulations	Hardness (Kg/m^2)	Friability (%)	Weight-Variation	Drug content (%)	Thickness in (mm)
CMF1 (MF3+MF8)	6.1	1.24	1.56	96.05	6.18
CMF2(MF2+MF8)	5.9	1.05	0.52	92.05	6.20
CMF3(MF3+MF12)	5.8	0.98	0.63	94.3	6.02
CMF4(MF6+MF8)	6.3	0.86	0.89	91.05	5.91
CMF5(MF2+MF10)	6.0	0.94	1.02	95.61	5.97
CMF6 (MF3+MF10)	5.91	1.85	0.64	93.04	6.04

*CF-Combination of Metformin formulations

Table 8 Evaluation parameters of Optimized Trilayered tablets

Formulation	Weight Variation (n=20)	Hardness (n=3)	Friability (n=20)	Thickness (n=3)	Drug content	
					Sitagliptin Phosphate	Metformin HCl
Trilayered tablet TF5 (SF6+MF3+MF8)	0.53	6.3±0.4	0.91±0.5	6.1±0.04	95.4±1.3	97.1±1.05

*TF-Trilayered formulation

In-vitro dissolution study

The Cumulative % drug release of Sitagliptin phosphate IR tablet (SF1-SF6) formulated using different superdisintegrants (Cros Povidone, Cross Carmellose Sodium and Sodium Starch Glycolate) is graphically represented in Fig 6. From the dissolution studies it was concluded that disintegration activity decreases in the order of Cross Povidone < Cross Carmellose Sodium < Sodium Starch Glycolate i.e. from SF1 to SF6 disintegration time decreases and % cumulative drug release increases.

The percentage drug released for the formulations SF1, SF3 and SF5 was found to be more than 95% after 45 minutes. The increase in concentration of superdisintegrants from 10mg to 15mg a gradual increase in drug release is observed. The percentage drug released formulations SF2, SF4 and SF6 was 98.76, 98.9 and 99.65 respectively after 30 minutes. Therefore SF6 releasing 99.65 % after 30 min was selected as optimized formulation and the drug release is almost similar to the marketed Sitagliptin tablets (Januvia) which is graphically represented in the Fig 7.

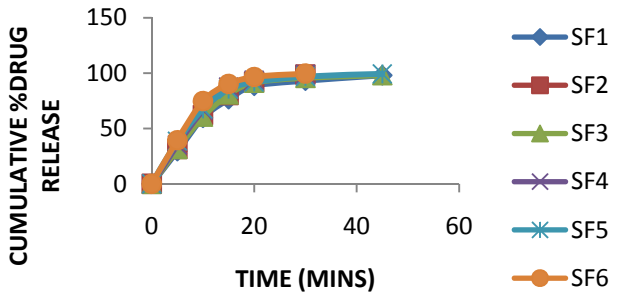

Figure 6: Cumulative % drug release of Sitagliptin phosphate IR tablet formulated using different superdisintegrants

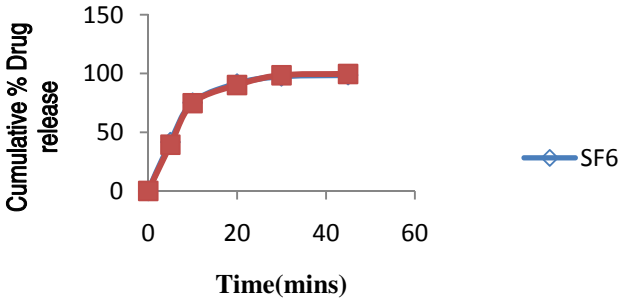

Figure 7: Comparative In-vitro drug release comparison with marketed tablet (Januvia)50mg

From the above comparative drug release profiles of tablets formulated with three super disintegrants, the formulation using SSG (SF6) has shown equivalent drug release profile of Januvia® 50mg marketed tablets. Hence SF6 was selected as optimized formulation.

Cumulative % drug release of Metformin Hydrochloride SR tablet containing 250mg dose

The drug release rate of Metformin HCl was found to be influenced by the concentration of polymer used in the tablet. The influence of polymer concentration on drug release of formulations using different concentrations of L HPC, HPMC K 15M, HPMC K100, HPMC K4M, Ethyl cellulose and Carbopol is represented in Figures 8, 9. With increased polymer concentration further decrease in the drug release was observed.

From the Figures 8 and 9, it can be noted that MF1 and MF2 formulations using LHPC as the release retarding polymer was able to sustain the release of the drug up to 12 hrs. The cumulative % drug release was found to decrease as the concentration of LHPC increased from 70 mg to 77mg. In case of MF1, 98.35% of drug release was observed in 10 hrs.

Further trials were taken by taking HPMC K15M as the rate retarding polymer. Formulation MF4 with 18% of HPMC K15M achieved sustain release of more than 12hrs while MF3 with 15% of HPMC K15M also could sustain drug release up to 12hrs. From MF5 to MF6 as the concentration of HPMC K100 increases from 18% to 20%, the drug release was found to decrease. In these formulations the drug release was not comparable to the marketed tablets at the end of 12 hrs.

In case of formulations MF7 and MF8 high viscosity polymer HPMC K4M was taken in the range of 15%-18% concentration in which MF8 showed sustained drug release. Formulations MF9-MF12 in which Carbopol 20% and Ethyl cellulose 22% were used could sustain drug release up to 12hrs. From these, formulations showing sustained drug release up to 12hrs were taken and combination of any two formulations was prepared in two layers to form bilayer sustained tablet and dissolution study was performed.

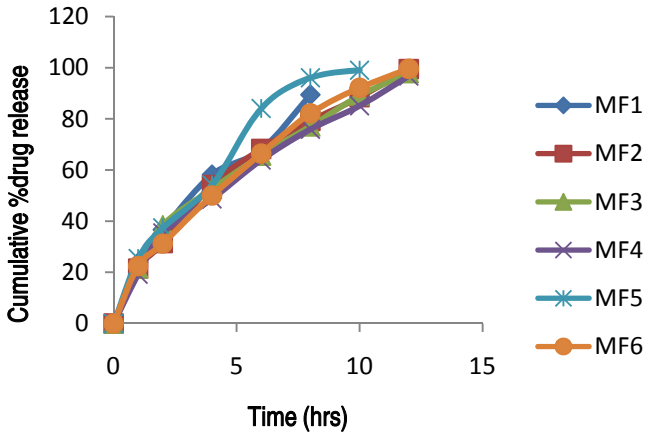

Figure 8: Cumulative % drug release profiles of various formulations of Metformin SR I tablets

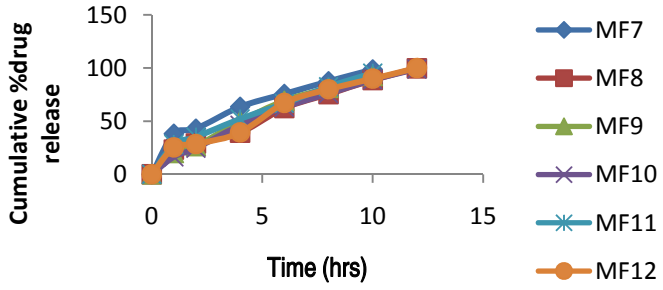

Figure 9: Cumulative % drug release profiles of various formulations of Metformin SR II tablets.

Cumulative % drug release of Metformin Hydrochloride SR tablet containing 500mg dose

Then further trials were taken to determine the effect of combination of polymers in two different layers. Dissolution data of formulations prepared by using combination of SR I and SR II layers containing different polymers with varying concentrations is graphically represented in Figure 10. Formulation CF1 containing 20% of HPMC K 100 and 18% of HPMC K4M drug release is 97.14% at 11hrs. Formulation CF2 containing 20% of HPMC K 100 and 22% of Carbopol drug release is 97.61% at 11hrs. Formulation CF3 containing 22% of LHPC and 18% of HPMC K4M drug release is 97.51% at 11hrs. Formulation CF4 containing 15% of HPMC K 15M and 22% of Carbopol drug release is 98.14% at 12hrs. Formulation CF5 containing 15% of HPMC K 15M and 18% of HPMC K4M drug release is 98.72% at 12hrs. Formulation CF6 containing 15% of HPMC K 15M and 22% of Ethyl cellulose drug release is 99.01% at 12hrs. Therefore CF5 releasing 99.01 % after 12hrs was selected as Optimized formulation and the drug release was compared to the marketed Metformin HCl tablets (Glycomet SR) which is graphically represented in the Fig 11.

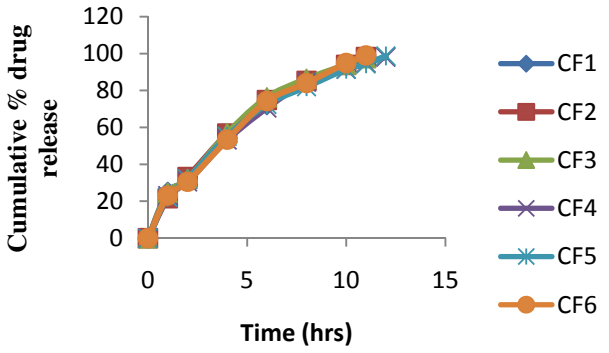

Figure 10: Cumulative % drug release profiles of various formulations of combination of Metformin SR I and II tablets

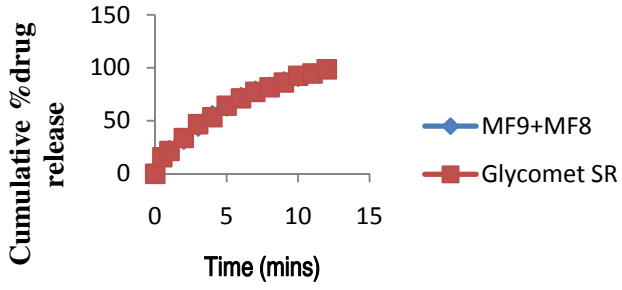

Figure 11: Comparative In-vitro drug release comparison of Metformin HCl sustained release tablet with marketed tablet

From the above comparative drug release profile of tablets formulated with varying concentrations of different polymer, the formulation using HPMC K15M and K4M (MF3+MF8) has shown drug release comparable to the marketed Glycomet® SR 500mg tablets of Metformin HCl. Hence (MF3+MF8) was selected as optimized formulation of Metformin SR Layer.

Drug release profile of Optimized trilayered tablet

The Optimized formulations of IR layer (SF6) and SR layers (MF3+MF8) CF5 are compressed to form a Trilayered tablet (TF5). The dissolution study of Optimized trilayered tablet is performed and graphically represented in Figure 12. The IR layer disintegrated in 54.4 sec and the drug released is 99.65 in 30mins and from the SR layer drug released is 98.72 at 12hrs.

As observed from the data, the % drug release of IR layer released in 30mins in 0.1 N HCl medium and % drug release of SR layers started to release at slow rate in 0.1N HCl medium for 2hrs and released completely for 10hrs in pH 6.8 buffer medium.

The Optimized trilayered tablets, basing on this data were selected for further studies.

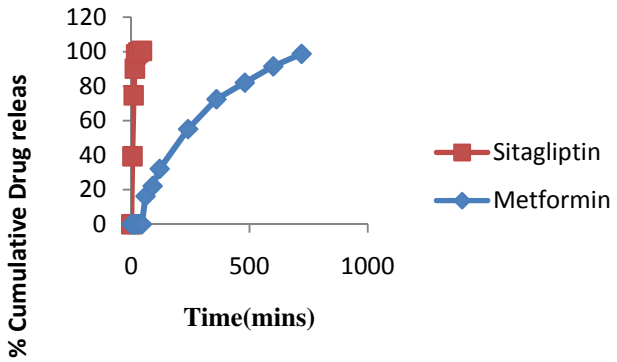

Figure 12: In vitro drug release of Optimized tri layered tablet

Stability studies

The stability studies were performed for Optimized trilayered tablet at elevated temperature (40^{0}C and 75%RH) for three months and

checked for physical characteristics and content uniformity. The stability data containing Hardness and Drug content is depicted in Table 9

Table 9: Stability studies of Trilayered tablets at 40^{0}C and 75%RH

Time interval	Hardness	Drug content	
		Sitagliptin phosphate	Metformin HCl
After 1st month	6.1	95.03	96.51
After 2nd month	6.06	94.67	96.42
After 3rd month	5.79	94.43	96.21

As observed from the data, the formulation shows that there were no significant changes in the hardness and drug content.

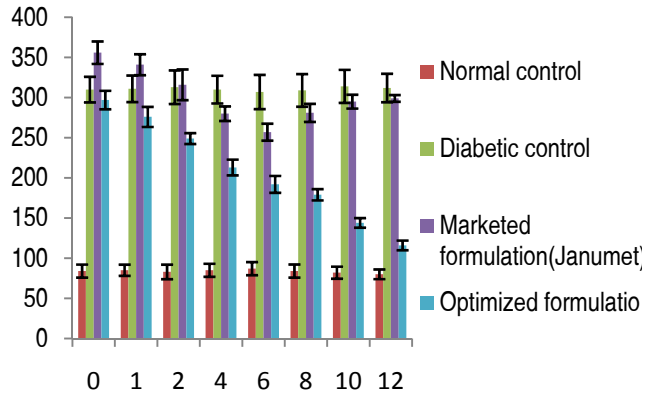

Figure 13: Graphical representation of blood glucose levels (mg/dl) after oral administration of Optimized formulation and Marketed formulation.

In-vivo Pharmacodynamic study

The tablets were prepared with average weight 40mg using 4mm punches plain both sides. The optimized tablet formulation and marketed formulation were administered to diabetes induced rats and the pharmacodynamics activity was compared and graphically represented in Figure 13.

It is clear from the Figure 13 that the blood glucose levels in non-diabetic control group varied from 80 to 87 mg/dl. In diabetic control group, blood glucose levels varied from 307 to 314 mg/dl. From the data it is evident that the marketed tablets showed anti diabetic action up to 6 hrs and after 6 hrs increase in glucose levels was observed. However it is interesting to note that the optimized formulation MF3 and MF8 were able to achieve 12 hrs sustained antidiabetic action in the rats. The study indicates that TLT of Sitagliptin phosphate and Metformin HCl can be successfully for effective treatment of diabetes in chronic patients.

Conclusion

The trilayered tablets of Sitagliptin phosphate and Metformin Hydrochloride can be successfully formulated. Sitagliptin phosphate immediate release layer using different superdisintegrants and Metformin Hydrochloride sustained release layers is formulated using individual and combination of different polymers. All the evaluation parameters were found to be within specified Indian pharmacopoeia limits. The Sitagliptin layer gives the necessary immediate release dose and the two sustained release layers could prolong the release up to 12 hrs. Hence such tablets can be exploited for use in Diabetes treatment.

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