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RESEARCH ARTICLE

Formulation and Evaluation of Sustained Release Tablet of Metformin Hcl and Glimepride

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ABSTRACT

Oral route of drug administration is oldest and safest mode of drug administration. Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries.. The present study was undertaken with an aim to formulate develop and evaluate a combine dosage form of Metformin Hcl and Glimepride Extended Release Tablet using different polymers as release retarding agent. Pre-formulation study was done, Granules were evaluated for tests Loss on drying, Bulk density, tapped density, Angle of Repose, compressibility index, Hausner's ratio before being punched as tablets. IR spectra studies revealed that the drug and polymers used were compatible. Various formulations of extended release tablets of Metformin Hcl and Glimepride were developed using various polymers viz, HPC-HF, HPMC K_4M, HPMC $K_{15}M$ and HPMC $K_{100}M$ in different proportions and combinations by IPA granulation or wet granulation technique. The tablets were evaluated for physical characterization, *in vitro* release study and stability studies. From the above results and discussion it is concluded that formulation of extended release tablet of Batch MHGERT-V containing 40% of HPMC $K_{100}M$ and 4% of DCP and 2% of Povidone K- 30 can be taken as an ideal or optimized formulation of extended release tablets for 10 to 12 hour release as it fulfils all the requirements for extended release tablet.

Key words: Sustained Release, Metformin Hcl and Glimepride, Polymers.

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin or because cells do not respond to the insulin that is produced [1]. Diabetes is one of the major cause of death and disability in the world. World Health Organization estimate for the number of people with diabetes worldwide, in 2000, is 171 million, which is likely to be at least 366 million by 2030. Non-insulin dependent (Type 2) diabetes mellitus is a heterogeneous disorder characterized by an underlying insufficiency of insulin [2].

Combination therapy have various advantages over monotherapy such as problem of dose-dependent side effects is minimized, a low dose combination of two different agents reduces the dose-related risk, the addition of one agent may counteract some deleterious effects of the other. Glimepiride is orally administered sulfonyl urea agent and highly selective agonist for the sulfonyl urea receptors (SUR) are found in pancrease, which are target sites of insulin secretion.

MATERIALS

Table 1: Materials used

S. No	Material Used	Manufacturers	Uses	Specification
1	Metformin Hcl	ALEKHYA DRUGS PVT .LTD	Antidiabetic	USP
	Glimepride	SHARON BIO- MEDICINE LTD	Antidiabetic	BP
2	Hydroxy Propyl Methyl Cellulose K4M	COLORCON ASIA PRINATE LIMITED	Matrix Polymer	BP/USP
3	Hydroxy Propyl Methyl Cellulose K15M	COLORCON ASIA PRINATE LIMITED	Matrix Polymer	BP/USP
4	Hydroxy Propyl Methyl Cellulose K100M	COLORCON ASIA PRINATE LIMITED	Matrix Polymer	BP/USP

Method of Preparation

All ingredients were weighed in specified quantity as given in the formula. Metformin Hydrochloride and Polymer (DCP, HPMC $K_{100}M$,) PVP-K30, were sifted through 40# sieve. The ingredients were then loaded into planetary mixer and mixed

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for 30 minutes. Talc, and Magnesium Stearate was sifted through 40# sieve. Then the granules were prepared by taking the mixture from planatory mixture and put them in Granulator by adding IPA as solvent. After sometime the granules were seemed to be formed and then they are put into tray dryer for drying. After sufficient drying the granules were passed through 14# sieve and now to the granules Glimepride was added with lubrication and the granules are then ready for compression.

Table 2: Proto type Formulations

S. No	Ingredients	Trial-I MHGERT-I (mg)	Trial-II MHGERT-II (mg)	Trial-III MHGERT-III (mg)	Trial-IV MHGERT-IV (mg)	Trial-V MHGERT-V (mg)
1	Metformin Hydrochloride	500	500	500	500	500
2	Dicalcium Phosphate	30.4	45.8	-----	35.8	42.90
3	Microcrystalline Cellulose (Avicel pH-102)	30.4	-----	40.8	-----	-----
4	Gelatin	15	10	10	15	-----
5	Hydroxy Propyl Methyl Cellulose K4M	30	-----	20	150	-----
6	Hydroxy Propyl Methyl Cellulose K15M	100	150	150	-----	-----
7	Hydroxy Propyl Methyl CelluloseK100M	250	240	240	250	400
8	Povidone K-30	-----	-----	-----	-----	20
9	Glimepride	2.2	2.2	2.2	2.2	2.1
10	Purified Talc	10	10	10	10	15
11	Magnesium Stearate	10	10	10	10	15
12	Starch	20	30	35	40	-----
13	Aerosil	2	2	2	2	2
	Total	1000	1000	1000	1000	1000

Evaluation Parameters

Table 3: Pre-compression parameters for granules

Trial	Loss on drying (%)	Bulk density (g/ml)	Angle of repose (%)	Compressibility Index (%)	Hausner's Ratio (%)
MHGERT – 1	1.93	0.3796	31.39	20.59	07742
MHGERT – 2	1.62	0.3836	32.81	20.91	0.7863
MHGERT – 3	1.61	0.3702	32.73	20.18	0.7588
MHGERT – 4	1.60	0.3773	32.98	20.57	0.7924
MHGERT – 5	1.57	0.3802	33.90	20.82	0.7829

Table 4: Physical and chemical parameters for tablets

Trial	Average weight (mg)	Hardness (Kg/cm^2)	Thickness (mm)	Diameter (mm)	Friability (%)
MHGERT – I	1009.32	3	7.26	11.11	0.69
MHGERT – II	998.64	4	7.31	11.11	0.70
MHGERT – III	1002.89	5	7.26	11.11	0.55
MHGERT – IV	999.63	5	7.23	11.11	0.45
MHGERT – V	1006.37	5	7.27	11.11	0.52

Table 5: Assay of the Drugs

Trail	Assay of Metformin Hcl	Assay of Glimepride	Assay of Combined Drug
MHGERT-I	99.60	99.28	99.56
MHGERT-II	98.89	99.56	98.26
MHGERT-III	99.15	98.36	98.32
MHGERT-IV	99.32	98.35	98.46
MHGERT-V	99.89	99.65	99.79

Table 8: *In-vitro* Drug Release (Dissolution) Profile of Prototype Formulations

Time	0 hour	1st hour	3rd hour	10th hour
MHGERT – 1	0	48.95%	75.35%	99.23%
MHGERT – 2	0	40.64%	71.68%	99.39%
MHGERT – 3	0	45.97%	76.03%	99.41%
MHGERT – 4	0	42.93%	78.27%	99.35%
MHGERT – 5	0	31.54%	54.74%	94.45%
Limit (in %)	**0**	**20 – 40%**	**45 – 65%**	**NMT 85%**

Drug Release Profile Comparison of Final Formula

1. Market Sample Details:

Brand Name : Zoryl- M
Manufactured By : IntasPharma
Label Claim : Each Film Coated tablet Contains Metformin Hcl – 500 mg and Glimepride – 2.1mg.
Shelf Life : 2 years
Release Profile : 10 Hrs.

Table 7: Drug Release Profile Comparison of Final Formula with Market Sample

S. No	Time in Hours	Market Sample Drug Release (in %)	Final Formula (FDT-5) Drug Release (in %)	In-House Specification Limit (in %)
1	0	0	0	0
2	1	36.80%	31.54%	20 – 40%
3	4	69.87%	51.74%	45 – 65%
4	8	91.45%	94.45%	NMT 85%

RESULTS AND DISCUSSION

According to the drug excipient compatibility studies shows in the Table: give the inference of selected excipients with drug (Metformin and Glimepride).

Table 8: Trial-I: (Drug Release) *In-vitro* drug release profile I percentage (average of 6 tablet)

Time	0 hour	1st hour	3rd hour	10th hour
MHGERT – 1	0	48.95%	75.35%	99.23%

HPMC K 100 M, K15 M, K 4 M, DCP and MCC used as a Matrix Polymer in trial-I and the result given in the above table.

The result release rate was more, and also sticking of granule on punches and dies. So, glidant and lubricant concentration was increased from 1% to 1.5% in further trials.

Table 9: Trial-II: (Drug Release) *In-vitro* drug release profile I percentage (average of 6 tablet)

Time	0 hour	1st hour	3rd hour	10th hour
MHGERT – 2	0	40.64%	71.68%	99.39%

In trial-II the use of MCC was avoided,. According to the above result the release was more so, further trial was conducted with more concentration of HPMC K_{15}M.

The sticking problem was optimized with 1.5% of lubricants. In this trial also the hardness of the tablet was less concentration of Starch was increased.

Table 10: Trial-III: (Drug Release) *In-vitro* drug release profile I percentage (average of 6 tablet)

Time	0 hour	1st hour	3rd hour	10th hour
MHGERT – 3	0	45.97%	76.03%	99.41%

Trial-III was taken with HPMC K_{100}M and HPMC K_{15}M and MCC instead of DCP, the result of drug release given in above table. According to the release shown in table the further trial planned with HPMC K_{100}M and, HPMC K_4M, with reduced concentration of DCP instead of MCC because the release retardness was still more.

In this trail the hardness of the tablet was also less. which indicates that % of starch should be increased again in further trail.

Table 11: Trial-IV: (Drug Release) *In-vitro* drug release profile I percentage (average of 6 tablet)

Time	0 hour	1st hour	3rd hour	10th hour
MHGERT – 4	0	49.23%	78.27%	99.35%

Based on the trial -III trial-IV was taken with HPMC K_{100}M and HPMC K_4M, the result of drug release in above table.

The release rate was not controlled and satisfactory up to 3rd hour, but after 10th hr the release was match with I.H.S specification, so further trial want to be taken with slight modification . The hardness of the tablet also this time shows some fluctuation so instead of starch and gelatin povidone K 30 will be taken in the next trail.

Table 12: Trial-V: (Drug Release) *In-vitro* drug release profile I percentage (average of 6 tablet)

Time	0 hour	1st hour	3rd hour	10th hour
MHGERT – 5	0	31.54%	54.74%	94.45%

HPMC K_{100}M and DCP was used in this trial, the drug release was controlled and match with In-house specifications. The concordant trial was taken with same formula, the same result got, so this trial formula (MHGERT-V) was considered as Final formula, consequently this batch was planned to go coating.

Stability study was conducted on this formulation as per ICH guidelines.

The hardness of the tablet was very good and satisfactory.

Final Quantitative and Qualitative Formula

Name of the Product :Metformin Hcl and Glimepride ER Tablet

Label Claim : Each Film coated ER tablet contains, Metformin Hcl 500mg And Glimepride 2.1mg.

Average Weight : 1000mg

Punch Size : 19 × 8.8 mm

Table 13: Final Quantitative and Qualitative Formula

S. No	Name of the Ingredients	% Composition	Qty. per Tablet (In mg)	Qty for 1000 Tablets (In gram)
1	Metformin Hcl	50	500	1000
2	Dicalcium phosphate	4.3	42.90	85.80
3	Hydroxy Propyl Methyl Cellulose K100M	40	400	800
4	Isopropyl Alchol	q.s	q.s	q.s
5	Povidone K-30	2	20	40
6	Glimepride	0.2	2.1	4.2
7	Purified Talc	1.5	15	30
8	Magnesium Stearate	1.5	15	30
9	Aerosil	0.5	5	10
	Total	100.00	1000	2000

Table 14: Coating Materials

S. No	Name of Ingredients	Quantity Required for 1000 Tablets
1	Opadry White	14.0 mg
2	Colour Iron Oxide Yellow	0.10 mg
3	Isopropyl Alcohol	50.0 ml
4	Methylene Chloride	50.0 ml

Finished Product Specifications

Product Nam : Metformin Hcl and Glimepride500mg Extended release Tablet

Description : Yellow colour, bi-convexed tablet with plain surface.

Label Claim : Each Film coated Extended Release Tablet contains Metformin Hcl and Glimepride USP is equivalent to Metformin Hcl – 500mg and Glimepride-2.1mg

Punch Dimension: 19×8.8mm

Table 15: Finished Product Specifications

S. No	Compression Parameters	Units	Value	In-process Limits	Final Formulation Parameters
1	Weight of one Tablet	Mg	999.08	990—1010	999
2	Weight of 20 Tablets	g	1998.4	1995--2005	1998.5
3	Thickness	mm	7.27	±0.2	7.25
4	Hardness*	Kg/cm^2	NLT 3	-	-
5	Friability*	%w/w	NMT 1	-	-
6	Assay	%	As per IHS	As per IHS (90—110%)	99.65
7	Dissolution		As per IHS	As per IHS	Complies as per HIS

Note: * - Not applicable for coated tablets

CONCLUSION

Various formulations of extended release tablets of Metformin Hcl and Glimepride were developed using various polymers viz, HPC-HF, HPMC K_4M, HPMC $K_{15}M$ and HPMC $K_{100}M$ in different proportions and combinations by IPA granulation or wet granulation technique. The tablets were evaluated for physical characterization, *in vitro* release study and stability studies..IR spectra studies revealed that the drug and polymers used were compatible. Results of *in vitro* release profile indicated that formulation (MHGERT- V) was the most promising formulation as the extent of drug release from this formulation was optimum and match with the In-house Specification when compared to other formulations.

Stability study was conducted on tablets of Batch MHGERT-V stored at 30°C ± 2°C/65% RH ± 5% RH (Long term) and 40°C ± 2°C/75% RH ± 5% RH (Accelerated) for one month. After one month no significant changes were observed in any of the studied parameters during the study period, thus it could be concluded that formulation of Batch MHGERT-V was stable. It was concluded that the tablets of Batch MHGERT-V had considerable *in vitro* drug release. It was observed that tablets of Batch MHGERT-V followed the Zero order release profiles.

From the above results and discussion it is concluded that of Batch MHGERT-V containing 40% of HPMC $K_{100}M$ and 4% of DCP and 2% of Povidone K- 30 can be taken as an ideal or optimized formulation of extended release tablets for 10 to 12 hour release as it fulfills all the requirements for extended release tablet.

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