International Journal of Early Childhood Special Education (INT-JECSE)
DOI: 10.9756/INT-JECSE/V14I1.418 ISSN: 1308-5581 Vol 14, Issue 01 2022 PP:3461-3470

Formulation and Evaluation of Metformin and Glimepiride Fast Dissolving Tablet

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ABSTRACT:
Metformin hydrochloride and Glimepiride are orally active hypoglycaemic substance these are used in non-insulin dependent (type 2) diabetes mellitus.Metformin is slowly and incompletely absorbed from the GI tract, mainly absorbed from upper GI tract.Glimepiride is less soluble and is BCS class II drug. Hence to improve absorption and solubility Fast Dissolving Tabletof Metformin hydrochloride and Glimepiride combination is developed which may have better patient palatability, especially in case of geriatric and paediatric patients.
Fast dissolving tablets of Metformin hydrochloride and Glimepiride were developed using simple wet mixing approach. Drug excipients compatibility was performedforall selected excipients as per Carstensen approach as dry and with 5 % moisture at 55^0C to observe any incompatibility within drug and excipients.Glimepiride is less soluble and is BCS class II drug; hence initially solubility enhancement study was carried outusingsimple physical mixture withPolyvinylpyrrolidone K30with various ratios to get better dissolution ofGlimepiride. Further Polyvinylpyrrolidone K30 was used in formulation of fast dissolving tablets.
Fast dissolving tablets were prepared using wet mixing approach using microcrystalline cellulose, crospovidone, polyvinyl pyrrolidone K30, shellac, croscarmellose, aspartame and magnesium stearate. Furtherfast dissolving tablets are evaluated for description, average weight, friability, hardness, disintegration time, wetting time and dissolution.Optimizedformulation was subjected to stability study at accelerated condition of 40^0C/75 % RH and long term condition of 30^0C/75 % Rh (Zone IVb) as per ICH recommendation. Parameters evaluated for stability were description, hardness, disintegration time, dissolution, assay and related substances. UV spectrophotometric method was used for dissolution study and high performance liquid chromatographic method was used for related substance test. Stability study indicates that all parameters observed were well within proposed limit.
Based on this study it can be concluded that fast dissolving tablets of metformin hydrochloride and Glimepiride can be used alternatively instead of conventional tablets for better patient palatability.

KEYWORDS: Metformin Hydrochloride, Glimepiride,fastdissolving tablets, solubility enhancement, wet granulation,simultaneous estimation, UV spectrophotometer, high performance liquid chromatography.

ABBREVIATIONS:
ICH: International Council of Harmonization
BCS: Biopharmaceutical classification system
USP: United States Pharmacopoeia
FDA: Food drug administration
C_{max}: Maximum plasma concentration
t_{max}: Time for maximum plasma concentration
UV spectrophotometer: Ultraviolet spectrophotometer.

INTRODUCTION:

Metformin is the most common oral hypoglycemic agent to be prescribed followed by glimepiride[1].The two principal defects in type 2 diabetes are insulin deficiency and insulin resistance. Therefore, combining an insulin-

providing agent with an insulin sensitizing agent will augment the efficacy of current anti- hyperglycaemic agents. This is the general rational for the development and marketing of sulfonylurea/metformin combination tablets [2]. Study conducted by Manuel et al demonstrated that Glimepiride/metformin are more efficacious than glibenclamide/metformin atreaching the glycemic control goals with less hypoglycemic events in patients with uncontrolled type 2 diabetes mellitus [3]. Fixed combination of glimepiride/metformin is as effective and safe therapy as free combination in type 2 diabetes patients[4].

Metformin was first approved in Canada in 1972, followed by 1995 in the USA Metformin is an antihyperglycemic agent of the biguanide class, used for the management of type II diabetes[5]. Chemically Metformin hydrochloride is identified as 3-(diaminomethylidene)-1,1-dimethylguanidine;hydrochloride with molecular weight of 165.62 g/mol[6]. It is currently the drug of first choice for the treatment of type II diabetes, it is prescribed to at least 120 million people worldwide[7].Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The p^{Ka} of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68[8].Metformin is BCS class III agent *i.e.* with high solubility and low permeability[9]. Slowly absorbed after oral administration, about 30 to 50% of an oral dose is excreted in the urine as unchanged drug in 24 h, and about 30% of the dose is eliminated unchanged in the faeces[10].Active tubular secretion in the kidney is the principal route of metformin elimination[11]. Maximum plasma concentration (C_{max}) is reached in approximately 2.5 hours (t_{max}). After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear[12].

Glimepiride is an oral antidiabetic drug which belongs to the sulfonylurea group and usually given as an oral antidiabetic therapy for patients with type-2 diabetes mellitus. Glimepiride acts to lower blood glucose by stimulating the release of insulin from pancreatic β-cells[13].Glimepiride, which is sometimes referred to as a third-generation agent, was released in 1995[14]. Chemically it is identified as 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)ureawith molecular weight of 490.62. Glimepiride is practically insoluble in water[15]. Glimepiride belongs to BCS II drug with low solubility and high permeability[16].The bioavailability of Glimepiride after oral administration is complete. Maximum serum concentrations (C_{max}) are reached approx. 2.5 hours after oral intake (mean 0.3 µg/ml during multiple dosing of 4 mg daily) and there is a linear relationship between dose and both C_{max} and AUC (area under the time/concentration curve)[17].Less solubleover Physiological pH range [18].

Fast dissolving tablets termed as Orodispersible tablets in British Pharmacopoeia and orally disintegrating tablets in United StatesPharmacopoeia.Fast dissolving tablets/Orodispersible tablets are uncoated tablets intended to be placed in mouth where they disperse rapidly before being swallowed.Orodispersible tablets disintegrate within 3 minutes, using water R as the liquid medium[19]. Characteristics that were exhibited by the initial products include low tablet weight, small tablet size, highly soluble components, and rapid disintegration. Such characteristics supported the intended uses of these products.This mode of administration was initially expected to be beneficial to pediatric and geriatric patients, to people with conditions related to impaired swallowing, and for treatment of patients when compliance may be difficult[20].

USPharmacopoeia recommends pH 6.8 phosphate buffer for dissolution testing of Metformin hydrochloride tablets[21] and pH 7.8 phosphate buffer for dissolution testing of Glimepiride tablets[22].

MATERIAL AND METHODS:

MATERIALS:

Metformin Hydrochloride and Glimepiride were received as gift sample. Crospovidone, povidone (k 30), shellac, isopropyl alcohol, croscarmellose sodium, aspartame, trusilraspberry flavor, magnesium stearate were of Loba ChemiePvt. Ltd., Mumbai.

Potassium dihydrogen phosphate, dipotassium hydrogen phosphate and sodium chloride and water used were of analytical grade (LobaChemie Pvt. Ltd., Mumbai).All other chemicals and reagents used were analytical grade unless otherwise indicated.

INSTRUMENTS:

The proposed work was carried out using lab model tablet press, USP dissolution apparatus Type II of TDT-08L Electrolab, UV-visible spectrophotometer of Jasco, Japan (model V-630). All weighing was done on electronic balance (Shimadzu, Japan). A Labhosp, India was used for degassing the physiological media and pH meter of Chemline, India was used to adjust pH. Stability chamber of Remi motors, Mumbai, India.

METHODS:

Maximum allowable limit for excipients

All excipients used in this study are well FDA recommendation for inactive ingredient. List of excipients along with maximum allowable limit is included inbelowTable 1[23].

Table 1: IIG limits for selected Excipients

Sr. No.	Name of excipient	IIG limit for oral use
1.	Crospovidone	280 mg
2.	Croscarmellose sodium	48 mg
3.	Microcrystalline cellulose	415.92 mg
4.	Povidone PVP-K30	35.71mg
5.	Bleached Shellac	28.35 mg
6.	Magnesium stearate	71.43 mg
7.	Aspartame	40 mg
8.	Trusil Raspberry Flavor	5 mg

Solubility enhancement for Glimepiride
Polyethylene glycol 6000 and Polyvinylpyrrolidone K30 have been reported to enhance solubility of Glimepiride. Considering formulation approach Polyvinyl pyrrolidone K30 studied for solubility enhancement at various concentration ratios as stated in Table 5below.
Physical mixture of drug and carrier (Polyvinyl pyrrolidone K30) is mixed and then triturated further and used checked for solubility enhancement.

Drug: Excipientscompatibility
All excipients used in this study are well known tabletting excipients and are used in preparation of immediate release formulation since long time. No novel excipient is used in manufacturing of fast dissolving tablets.As per recommendation drug excipients compatibility is required to be performed for novel excipients. Since excipients used in this study are reported to be used in reference products of Metformin hydrochloride and Glimepiride, hence physical compatibility was observed.
Carstensen approach with samples as dry and with 5 % moisture at 55^0C were charged to observe compatibility[24].The physical interaction between API (Metformin hydrochloride and Glimepiride) and crospovidone, croscarmellose sodium, Microcrystalline cellulose, Povidone PVP-K30, Bleached Shellac, Aspartame and Trusil Raspberry Flavor was studied in the stability chamber at temperature 55± 2 ^{0}C at dry and with 5 % moisture for period of two weeks. Samples were observed for physical interaction at 7^{th} day and 15^{th} day. These samples were kept for compatibility study and observed for caking, liquefaction, color change or any other physical incompatibility. Details of samples kept for drug excipients compatibility are presented in Table 6 below.

Preparation of mouth dissolving tablet:
Dry mixing -Sift Glimepiride, microcrystalline cellulose, povidone (PVP K-30), crospovidone through sieve # 40 ASTM (425 µm) and mix.
Granulation -Dissolve bleached shellac in isopropyl alcohol under continuous stirring and filter further carry out granulation to get suitable sized granules. Air dry granulesinitially and then at 50^0C. Pass through suitable mesh.
Pre-lubrication -Sift Metformin hydrochloride, crospovidone, croscarmellose sodium, microcrystalline cellulose, aspartame, flavour raspberry. Mix these with above granules.
Lubrication -Sift magnesium stearate and mix with above blend.
Compression -Carry our compression.
Different trials are as per table 2 below.

Table 2: Formulation and development trials

Sr. No.	Ingredients	Quantity (in mg/Tablet)						
		Trial I	Trial II	Trial III	Trial IV	Trial V	Trial VI	Trial VII
Granulation								
1.	Metformin hydrochloride	500.0	--	--	--	--	--	--
2.	Glimepiride	4.0	4.0	4.0	4.0	4.0	4.0	4.0
3.	Microcrystalline cellulose	54.0	59.5	56.0	56.0	51.0	43.0	34.0
4.	Crospovidone	4.0	8.0	8.0	8.0	8.0	8.0	10.0
5.	Povidone (k 30)	1.0	2.5	3.0	3.0	3.0	3.0	5.0
Binder								
1.	Shellac	15.0	5.0	4.0	2.0	2.0	2.0	2.0
2.	Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Pre-Lubrication								
1.	Metformin hydrochloride	--	500.0	500.0	500.0	500.0	500.0	500.0
2.	Croscarmellose sodium	--	5.0	6.0	6.0	8.0	10.0	12.0
3.	Crospovidone	--	5.0	8.0	10.0	15.0	20.0	25.0
4.	Microcrystalline Cellulose	--	15.0	15.0	15.0	15.0	15.0	15.0
5.	Aspartame	--	3.0	3.0	3.0	3.0	3.5	3.5
6.	Trusil Raspberry Flavor	--	3.0	3.0	3.0	3.0	3.5	3.5
Lubrication								
1.	Magnesium Stearate	--	10.0	10.0	10.0	8.0	8.0	6.0
Total weight of the Tablets		--	620.0	620.0	620.0	620.0	620.0	620.0

q.s.: Quantity sufficient.

Evaluation parameters:

Appearance: Take five tablets on a clean and dry petri dish against white background and observeagainst specification.

*Average weight:*Weigh 10 tablets selected and calculate the average weight.

Calculation Average weight (mg)=W/10;Where,W = Weight of 20 tablets in mg.Acceptance criteria – Average weight ± 5 %

*Friability:*Take a sample of 6.5 g of whole tablets. The tablets are carefully dedusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum of friability apparatus 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh. Acceptance criteria – Not more than 1 % (British Pharmacopoeia, 2019)

Hardness:

Place the tablet between the jaws, taking into account the shape, the break-mark and the inscription; for each measurement orient the tablet in the same way with respect to the direction of application of the force. Carry out the measurement on 10 tablets, taking care that all fragments of tablets have been removed before each determination. Acceptance criteria – Not less than 2 kg/cm^2[19].

Disintegration time:

Place 1 dosage unit in each of the 6 tubes of the basket and, if prescribed, add a disc. Operate the apparatus using the specified medium, maintained at 37 ± 2°C, as the immersion fluid. At the end of the specified time, lift the basket from the fluid and observe the dosage units: all of the dosage units have disintegrated completely. If 1 or 2 dosage units fail to disintegrate, repeat the test on 12 additional dosage units. The requirements of the test are met if not less than 16 of the 18 dosage units tested have disintegrated.Acceptance criteria – Not more than 60 seconds.[19].

Wetting time:

Two circular tissue papers of 10 cm diameter are placed in a petridish having the same inner diameter. Ten ml of phosphate buffer solution, 1.2 pH containing Eosin, a water soluble dye, is added to petridish. A tablet is carefully

placed on the surface of the tissue paper so that complete tablet was not immersed in the solution. Then, the time required for buffer to reach upper surface of the tablet is noted as wetting time [25].

Dissolution method:

Selection of dissolution media -

USP recommends pH 6.8 phosphate buffer for dissolution testing of Metformin hydrochloride tablets and pH 7.8 phosphate buffer for dissolution testing of Glimepiride tablets. As per recommendation of fixed dose combination medicineless rigorous condition should be selected for dissolution. Hence pH 6.8 phosphate buffer is selected as media for dissolution study of combination of Metformin hydrochloride and Glimepiride.

Dissolution Media- pH 6.8 phosphate buffer (at 37 °C ± 0.5 °C)

Apparatus type II paddle, 50 rpm

Diluent - pH 6.8 phosphate buffer

Wavelength: 226 nm and 233 nm using Blank as dissolution media (pH 6.8 phosphate buffer)

UV spectrophometric method with 1 cm cell in

Acceptance criteria – Not less than 80 % (Q) of labeled amount of Metformin and Glimepiride.

Related substances and assay method

Column - lnertsil ODS 3V, (250 mm x 4.6 mm), 5 µ

Mode – Gradient

Injection volume – 10 µl

Wavelength – UV, 218 nm

Flow rate – 1 ml/ minutes

Gradient flow:As per table 3

Mobile phase A: Phase, prepare a mixture of buffer pH 3.0 and methanol (94: 6 *v/v*), degas

Mobile Phase B:Use methanol

Table 3: Gradient program for related substance and assay

Time (Minutes)	**Mobile phase A (% *v/v*)**	**Mobile phase B (% *v/v*)**
0	100	00
50	100	00
51	40	60
65	40	60
66	100	00
85	100	00

Acceptance criteria for related substances

- Any single unknown impurity: Not more than 0.2 % (ICH recommendation, Q3(B), 2006).
- Total impurity: Not more than 1.0 % (British Pharmacopoeia, 2019).

Acceptance criteria:

- Not less than 95 % of labeled amount at release.

Not less than 90 % of labeled amount at shelf life[26].

Note:This test for related substance and assay is performed only on optimized formulation.

Stability study[27]

Stability study is performed as per ICH recommendation, in line with stability protocol stated in table4 at accelerated condition of 40^0C/75 % RH and long term condition of 30^0C/75 % Rh (Zone IVb).

Table 4: Stability study protocol

Tests	**Acceptance criteria**	**Long term stability at 30 ± 2°C / 75 ± 5 % RH**						**Accelerated condition at 40 ± 2°C / 75 ± 5 % RH**		
		3 M	**6 M**	**9 M**	**12 M**	**18 M**	**24 M**	**1 M**	**3 M**	**6 M**
Description	White to off white tablet	√	√	√	√	√	√	√	√	√
Disintegration time	Not more than 60 seconds	√	√	√	√	√	√	√	√	√
Dissolution	Not less than 80 % (Q) of labeled amount in 15	√	√	√	√	√	√	√	√	√

Tests	**Acceptance criteria**	**Long term stability at 30 ± 2°C / 75 ± 5 % RH**						**Accelerated condition at 40 ± 2°C / 75 ± 5 % RH**		
		3 M	**6 M**	**9 M**	**12 M**	**18 M**	**24 M**	**1 M**	**3 M**	**6 M**
	minutes.									
Related substances	Any single unknown impurity: Not more than 0.2 % Total impurity: Not more than 1.0 %	√	√	√	√	√	√	√	√	√
Assay	Not less than 90 % of labeled amount	√	√	√	√	√	√	√	√	√
Wetting time	To record	X	X	X	√	X	√	X	X	√

√ - Testing to be performed
X - Testing not to be performed

RESULTS

*Solubility enhancement for Glimepiride:*Based on dissolution results of solid dispersion of Glimepiride and PVP K-30it can be concluded that 1:1 and 1:2 drug: carrier ratio of significantly increases solubility of Glimepiride. Hence this PVP K-30 1:1 to 1:2 is further used in manufacturing of tablets to enhance solubility of Glimepiride, which will result in desired dissolution. Results are provided in table 5.

Table 5: Dissolution of Glimepiride with Povidone PVP-K30

Drug:Carrier Ratio (Glimepiide /Povidone PVP-K30)	**Dissolution (%)**
1 : 0	65 %
1 : 0.5	74 %
1 : 1	84 %
1 : 2	88 %
1 : 3	90 %

*Drug-excipients compatibility:*Physical mixtures were placed in dry and with 5 % moisture at 55°C. It was observed for cacking, discoloration, liquefaction and other physical changes for 15 days. It was observed that, there was no presence of any physical incompatibility like cacking, discoloration and liquefaction this shows that all excipients are compatible with each other. Results of physical observation are as shown in Table 6 below.

Table 6: Physical observation of drug excipients compatibility for Metformin Hydrochloride and Glimepiride

Sample No	**Sample content (Proportion)**	**Observation at 55 ^{0}C with 5 % moisture**		
		Initial	**7 day**	**15 day**
1.	Metformin Hydrochloride : Crospovidone (1:1)	Almost white powder	No change	No change
2.	Metformin Hydrochloride : Croscarmellose sodium (1:1)	Almost white powder	No change	No change
3.	Metformin Hydrochloride : Microcrystalline cellulose (1:1)	White powder	No change	No change
4.	Metformin Hydrochloride : Povidone PVP-K30 (1:1)	White to slightly yellowish powder	No change	No change
5.	Metformin Hydrochloride : Bleached Shellac (1:1)	Slightly brown coloured powder	No change	No change
6.	Metformin Hydrochloride : Magnesium stearate(1:1)	Almost white powder	No change	No change

Sample No	**Sample content (Proportion)**	**Observation at 55 ^{0}C with 5 % moisture**		
		Initial	**7 day**	**15 day**
7.	Metformin Hydrochloride : Aspartame (1:1)	White powder	No change	No change
8.	Metformin Hydrochloride : Trusil Raspberry Flavor (1:1)	Almost brown coloured powder.	No change	No change
9.	Glimepiride: Crospovidone (1:1)	Almost white powder	No change	No change
10.	Glimepiride: Croscarmellose sodium (1:1)	Almost white powder	No change	No change
11.	Glimepiride : Microcrystalline cellulose (1:1)	White powder	No change	No change
12.	Glimepiride : Povidone PVP-K30 (1:1)	White to slightly yellowish powder	No change	No change
13.	Glimepiride: Bleached Shellac (1:1)	Slightly brown coloured powder	No change	No change
14.	Glimepiride: Magnesium stearate(1:1)	Almost white powder	No change	No change
15.	Glimepiride: Aspartame (1:1)	White powder	No change	No change
16.	Glimepiride: Trusil Raspberry Flavor (1:1)	Almost brown coloured powder.	No change	No change
17.	Metformin Hydrochloride : Glimepiride : excipients (1:1:1)	White to off white powder	No change	No change

Preparation and evaluation of mouth dissolving tablet:

Trials with wet granulation approach were taken. **Trial I** was taken with Metformin hydrochloride as granulation part. But granules were formed with difficulty without suitable consistency, even after addition of additional quantity of granulating aid. This may be due to additional quantity of blend that which is formed due to high dose of Metformin hydrochloride.

Hence Metformin hydrochloride is included in extra-granular part in further trial.

Trial II was taken with Metformin in extra-granular part; procedure is followed as presented above. Granules were formed; further tablets evaluation shows that it takes too long to disintegrate which led to slower dissolution. Additionally hardness of tablets observed was high which may be the reason for high disintegration time, hence further binder concentration was reduced and disintegrant concentration was increased.

Trial III, in this binder concentration was reduced and disintegrant concentration was increased along with concentration of Povidone (k 30)in order to overcome disintegration and dissolution issues. Selected binder concentration was sufficient to form Granules and further lubricated and compressed. Evaluation shows higher results for disintegration time, wetting time and which results in less dissolution.

Trial IVwas taken by further reducing concentration of binder to minimum and increasing concentration of disintegrant. Reduction in binder does not have impact on formation of granules. These granules were further lubricated and compressed. Evaluation shows higher disintegration time and slow dissolution of Metformin and Glimepiride.

Trial Vwas taken with increased concentration of disintegrant for improvement in disintegration and dissolution. Compressed tablets were evaluated. It shows significant improvement in disintegration and dissolution of Metformin which further needs to be improvised for dissolution of Glimepiride. This is planned with increasing concentration of disintegrant (Trial VI) and increasing concentration of Povidone (k 30)(Trial VII).

Trial VIwas taken with further increasing disintegrant concentration. Further for improvement in Glimepiride dissolution mixing time of Glimepiride and Povidone (k 30) is increased. Tablets were compressed and evaluated which shows that all (disintegration, friability, hardness, wetting time) parameters are well within proposed limit. Further dissolution of Metformin hydrochloride was well within proposed limit however dissolution of Glimepirideneedsto be improved further. Further Povidone (k 30) which is used as solubility enhancer for Glimepiride is increased which may lead to improvement in dissolution of Glimepiride.

Trial VIIwas taken with increasing concentration of Povidone (k 30) which is solubility enhancer for Glimepiride, in addition mixing time of Glimepiride and Povidone (k 30) is increased to form proper mixture. Tablets were compressed and evaluated further. All parameters were well within proposed specification. Dissolution of Glimepiride is improved to acceptable limit of not less than 80 % (Q) of labeled amount in 15 minutes.
Hence formulation of Trial VII was selected as optimized formulation and reproduced further. This was charged on stability at per zone IVb condition [accelerated conditions (40 ± 2°C / 75 ± 5 % RH) and 9 months long term conditions (30 ± 2°C /75 ± 5 % RH)] as a worst case scenario, stability protocol provided in table 7 below.

Table 7: Results of evaluation of formulated preparations

Test	**Limit/ Specification**	**Observation**						
		Trial I	**Trial II**	**Trial III**	**Trial IV**	**Trial V**	**Trial VI**	**Trial VII**
Appearance	To record results	--	White to off white powder	White to off white powder	White to off white powder	White to off white powder	White to off white powder	White to off white powder
Average weight	Mean ± 5 %	--	618.5	615.0	612.3	621.3	625.2	622.3
Friability	Not more than 1.0 %	--	0.25	0.29	0.32	0.35	0.40	0.45
Hardness	Not less than 2 kg/cm^2	--	7.2	6.8	6.2	5.6	6.0	4.8
Disintegration time (Seconds)	Not more than 60	--	365	312	125	45	39	25
Wetting time(Seconds)	To record in seconds	--	510	508	210	65	58	43
Dissolution	Not less than 80 % (Q) of labeled amount in 15 minutes.							
For Metformin hydrochloride		--	82	83	89	92	88	96
For Glimepiride		--	69	70	69	70	75	95

Stability study:
As per ICH recommention, the test parameters that may change over time were evaluated during the stability testing such as description, disintegration time, dissolution, related substances, Assay and wetting time. The acceptance criteria for these test parameters during release and stability is given in the table 8 below. Samples were charged on stability by packing in HDPE container pack closed with child resistant closure. Silica gel of 1 g is inserted in HDPE conainer. In addition to above parameters samples were observed for any physical defect or change.
Six months stability data at accelerated conditions (40 ± 2°C / 75 ± 5 % RH) and 9 months long term conditions (30 ± 2°C /75 ± 5 % RH) indicates that all the test parameters monitored during the stability study are well within the proposed specifications. The detailed results of stability studies are presented in table 8.
Accelerated stability data is evaluated for any significant change in assay and related substane test. As per ICH recommendation any out of specification of related substance test and deviation of more than 5 % from initial assay value is considered as significant change which further needs to be evaluated at intermendiate or condition. Stability data at accelerated condition shows that there is no significant change in assay or related substance test. Further no test parameter evaltaed is out of specification.
Long term stability data is performed shows that description observed shows that there is no change in description of tablets. Disintegration tie is incresed upto 29 seconds at 9 month interval. Further there is no significant change in dissolution and related substances of tablets. Assay results of Glimepiride is not varied by significant value whereasassay value for Metformin hydrochloiride is dropped from 100.2 % to 97.2 % however it is well within acceptace criteria of $\pm$10 %
Based on the results obtained after 9 months of stability at long term condition of 30 ± 2°C /75 ± 5 % RH and 6 months accelerated condition of 40 ± 2°C /75 ± 5 % RH and as per ICH recommendatuon a shelf life of 24 months and storage condition ‘Store at or below 30°C’ can be proposed for developed optimized formulation.

Table 8: Stability study results for optimized formulation

Tests	**Acceptance criteria**	**Long term stability at 30 ± 2°C / 75 ± 5 % RH**				**Accelerated condition at 40 ± 2°C / 75 ± 5 % RH**			
		Initial	**3 M**	**6 M**	**9 M**	**Initial**	**1 M**	**3 M**	**6 M**
Description	White to off white tablet	Complies				Complies			
Disintegration time	Not more than 60 seconds	20	25	23	29	20	22	21	29
Dissolution									
For Metformin	Not less than 80 % (Q) of labeled amount in 15 minutes.	95	92	91	92	95	94	92	90
For Glimepiride		90	92	94	89	90	92	89	88
Related substances									
Any single unknown impurity	Not more than 0.2 %	0.09	0.12	0.11	0.10	0.09	0.15	0.12	0.16
Total impurity	Not more than 1.0 %	0.23	0.32	0.35	0.42	0.23	0.35	0.61	0.8
Assay									
For Metformin	Not less than 90 % of labeled amount	100.2	98.8	99.0	97.2	100.2	99.1	98.6	96.2
For Glimepiride		99.6	98.4	98.2	97.5	99.6	98.5	97.6	96.8
Wetting time	To record results	45	X	X	X	45	X	X	60

X - Testing not to be performed.

DISCUSSION

Polyvinyl pyrrolidone (PVP K-30) is useful in enhancing solubility of Glimepiride. This is further used as one of component of formulation of fastdissolving tablet of Metformin hydrochloride and Glimepiride.

Considering API characteristics wet granulation approach is selected for preparation of fast dissolving tablets. Results in present study shows that optimum binder concentration and super disintegrant concentration are required for preparation of fast dissolving tablets. Higher concentration of binder results in difficulty in granulation and produces tablets with high hardness which in turn results in high disintegration and dissolution time. Metformin hydrochloride forms extra-granular part of formulation as its concentration is about 80 % *w/w*of total formulation. Further PVP K-30 is used in dry mix with Glimepiride results in better dissolution characteristics.

Hence it can be concluded that fast dissolving tablets of Metformin hydrochloride and Glimepiride can be prepared by using simple wet granulation approach for faster action in diabetic patients.

ACKNOWLEDGEMENT:

The authors are grateful to the authorities of Department of Pharmaceutics, Shri. Vivekanand Nursing Home Trust's College of B. Pharmacy, Shrishivajinagar, Rahuri Factory, Dist-Ahmednagar for providing facilities to carry our research activities.

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