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FORMULATION AND DEVELOPMENT STUDIES OF SUSTAINED RELEASE DOSAGE FORM OF METFORMIN HYDROCHLORIDE USING HYDROPHILLIC POLYMERS

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ABSTRACT

Metformin hydrochloride, the only available biguanide, remains the first line therapy for treating type 2 diabetes mellitus acts by decreasing hepatic glucose output and peripheral insulin resistance. It has relatively short plasma half life, low absolute bioavailability. The need for the administration for two to three times a day when larger doses are required can decrease the patient compliance. Sustained release formulations that would maintain plasma level for 8-12 hrs might sufficient for daily dose Metformin HCL presents significant challenges due to its poor inherent compressibility, high dose and high water solubility. The present study was to design metformin extended release by using hydrophilic controlled release polymers polyvinyl pyrrolidone, sodium carboxymethyl cellulose, polyoxrs301, carbopol 971P by wet granulation method. The formulated granules blend was evaluated for flow property parameters. *In-vitro* dissolution studies were carried out in pH 6.8 phosphate buffer using the apparatus type 2 paddle type described in the USP monograph. From the different formulation and its data's we find the optimized formula which is similar to the innovator product. From the stability data analysis the optimized formula complies with that of innovator.

Key Words:- Metformin hydrochloride, Controlled release tablets, In-vitro dissolution studies.

INTRODUCTION

Diabetes is one of the major causes of death and disability in the world. The latest, WHO 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.The focus of medical community is on the prevention and treatment of the disease, as is evident from the rising number of research papers every day on this subject. A plethora of ant diabetic drugs are used in clinic, of which Metformin HCl is a widely accepted drug.

Metformin HCl is an anti-hyperglycemic agent, which improves the glucose tolerance in Type 2 diabetes. According to BCS classification metformin is considered as Class-III drug i.e., High solubility and low permeability. The absolute bioavailability of metformin HCl is 50-60% & its Biological half-life is 1.5-3 hrs. The high solubility, short biological half-life and dosing frequency more than once per a day make metformin HCl as an ideal candidate for extended release. To reduce the

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frequency of administration and to improve patient compliance, it is aimed to formulate extended release tablets of metformin HCl.

Sustained Release Dosage Forms

Sustained released means that the drug will be released under first order kinetics. Therefore if a drug starts out at 100 mg and releases at a rate of 10% per unit time (Lordi *et al.,* 1986; Stepensky *et al.,* 2001; Merkus *et al.,* 1986).

100mg --> 90mg --> 81mg --> 72.9 mg.

Site Specific Targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

Receptor targeting

These systems refer to targeting of drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial of drug delivery and are also considered to be controlled drug delivery systems.

A. Modifying drug dissolution by controlling access of biological fluids to the drug through the use of barrier coatings.

B. Controlling drug diffusion rates from dosage forms.

C. Chemical reaction or interaction between the drug substance and its pharmaceutical barrier and site specific biological fluids.

Oral Sustained and Controlled Release System

Types of oral controlled release systems are,

- Dissolution controlled release system
- Diffusion controlled release system
- Bio-erodible and combination diffusion and dissolution systems
- Osmotically controlled release systems
- Ion exchange systems (Chien *et al*., 1992; Pawar *et al*., 2005; Robinson *et al*., 2005)

Monolithic Matrix System

In pharmaceutical CRDDS, matrix based systems are the most commonly used type of release controlling methodology owing to their simple manufacturing process. The preparation of a tablet with the matrix involves the direct compression of the blends of drug, release retardant and other additives, in which the drug is uniformly distribute throughout the matrix core of the release retardant. Alternatively, drug release retardant blends may be granulated to make the mix suitable for the preparation of tablets by wet granulation or beads.

To characterize and define the matrix systems the following properties of the matrix are considered,

Chemical nature of the support.

- The physical state of the drug.
- The matrix and alteration in volume as the function of the time.
- The routes of administration.
- The release kinetics model (in accordance with Higuchi's equation, these system considered to release the drug as a function of square root of time).are made by employing the conventional wet granulation method to achieve continuous and prolonged release of the medicament (Higuchi *et al*., 1963; Korsmeyer *et al*.,1983).

MATERIALS AND METHODS

Metformin hydrochloride was purchased from wanburry. Polyvinyl pyrolidine K-90 was purchased from ISP Technologies. PolyethyleneoxideWsr 301 from colrcon. Carbopol 971 P was obtained from Lubrizolo. Carboxy methylcellulose sodium 50cps was obtained from Aqualon-Hercules. All other ingredients used were of laboratory reagents and used as such further testing.

Methodology

Different metformin hydrochloride (F1- F8) formulations were prepared by wet granulation technique. First metformin was weighed accurately and shifted through 20# mesh. Then polymer was taken and binder was prepared to the accurate purified water. The granules was prepared by hand granulation method. Where in case of combination one polymer was binding agent the other was used in extra granulation. If necessary sufficient purified water or isopropyl alcohol was used. The granules were dried at 60^{o}c in an oven and the moisture content was be 1.5 to 2.5%.Then the granules were passed through 20# mesh and then the prelubricants and lubricants were added and mixed for two to five minutes. The granules were compressed by using punch size length 18 mm & 8 mm width. Different metformin hydrochloride formulations were prepared by wet granulation process.

Compatibility study of drug and Excipient

The drug and excipient compatibility was done at 25^{0}C / 60% ± 5% RH, 30^{0}C / 65% ±5%RH and 40^{0}C / 75% ±5% RH. Open and closed vial methods were used. The result does not show any physical change to the mixture after 4 weeks. Chemical compatibility was analyzed by UV method as per IP specification. This fact concluded that the drug and excipients are compatible with each other. The calibration graph of metformin performed

in Phosphate buffer PH 6.8 and it shows regression value 0.997 and shows the linearity

Dissolution studies

The in-vitro release of Metformin HCl from formulated tablets was carried out for 10 hours in 6.8 phosphate buffer. The studies were performed in USP dissolution apparatus II (Electro lab, Mumbai, India) at 37 ±0.5°C and 100 rpm speed. Samples were taken at1, 3, 5 & 10 hours and diluted to suitable concentration and analyzed for Metformin HCl content at 233.0 nm by using UV–visible spectrophotometer. Yield a straight line with a slope equal to *K0* and intercept the origin of the axes.

OBSERVATION

Formulations of metformin hydrochloride was prepared with polymers Polyvinyl pyrollidone, poly ethylene oxide, Carbopol and carboxy ethyl cellulose sodium individual and combination of polymers by wet granulation technique and direct compression technique.

In F1 formulation polyvinyl pyrrolidine k-90 was used as a binder in granulation process. In the dissolution process the percentage of polymer was not maintained.

Table 1. Formulation chart of metformin hydrochloride extended release tablets

S.NO	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Metformin	500	500	500	500	500	500	500	500
2	MCC PH101	200	172	92	172	92	200	92	200
3	PVP K90	92	-----	----	-----	----	40	-----	40
4	PEO wsr 301	----	-----	----	120	200	----	----	-----
5	Carbopol 971p	----	120	200	-----	-----	52	-----	------
6	CECS 50cps	----	-----	-----	----	-----	-----	200	52
7	IPA	QS	QS	QS	QS	QS	QS	QS	QS
8	Magnesium sterate	8	8	8	8	8	8	8	8
9	Total weight[mg]	800	800	800	800	800	800	800	800

Table 2. Physicochemical properties of metformin Hydrochloride blend

S.No	Description	Result
1	Colour	White
2	Odor	Odourless
3	Appearance	Crystalline powder
4	Melting point	222-226 ^{o}C
5	Solubility	Freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride
6	Log P	1.254
7	Ph	1% aqueous solution of metformin hydrochloride is 6.68.
8	Loss on drying	Maximum 2.0% w/w
9	Residue on ignition	Maximum of 0.1%w/w
10	Identification by FTIR	Complied

Table 3. Evaluation of the Formulation [F1 to F8]

S.No	Formulation Trials	Bulk density	Tapped density	Carr's index	Hausner"s Ratio
1	F1	0.596	0.785	24.07	1.31
2	F2	0.581	0.714	18.60	1.22
3	F3	0.654	0.802	18.45	1.22
4	F4	0.694	0.834	16.67	1.2
5	F5	0.480	0.625	23.07	1.30
6	F6	0.582	0.714	18.60	1.443
7	F7	0.583	0.745	21.74	1.277
8	F8	0.582	0.714	18.60	1.22

Table 4. Evaluation of Tablets formulations (F1 to F8)

Formulations code	F1	F2	F3	F4	F5	F6	F7	F8
Thickness [mm]	5.49	5.51	5.45	5.53	5.55	5.51	5.49	5.53
Hardness [kg/cm^2	20	21	18	20	19	21	20	20
Friability [%]	Nil	0.52	0.54	0.52	0.51	0.52	Nil	0.52
Wt. variation [mg]	Pass	Pass	pass	Pass	Pass	Pass	Pass	pass
Drug content [%]	101	99.2	99.8	102	100	99.2	99.2	100

Table 5. Calibration curve of metformin in PH 6.8 Phosphate buffer

S. No	Concentration [mcg/ml]	Absorbance [nm]
1	2	0.216
2	4	0.368
3	6	0.547
4	8	0.764
5	10	0.953

Table 6. Cumulative drug release profile of the tablet formulations

Time [Hrs]	Innovator product	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0	0
1	35	37	35.5	25.5	28.7	24.6	36.4	34.5	27.4
3	59	75.6	68.5	45.8	55.4	55.3	61.3	67.4	65.2
5	81	97.8	85.5	68.5	75.7	62.6	82.5	72.6	72.5
10	96	----	98.9	78.8	98.6	82.2	97.5	81.6	98.6

Table 7. Estimation of similarity difference factors

S.No	RT-Tt	]RT-Tt]^2	Similarity factor [f2]	Difference factor [f1]
1	13	169	53.5	4.8
2	12.8	163.84	53.4	4.7
3	49	2401	54.08	18.0
4	11.5	132.25	53.45	4.24
5	51	2631.69	54.1	18.9
6	6.4	40.96	53.2	2.36
7	17.1	292.41	53.62	6.31
8	24.9	620.21	53.79	9.19

Table 8. *In vitro* drug release kinetics for the optimized formula

Zero oreder data		First order data	Higuchi's data		Peppa's data	
Time [hrs]	Cumulative % release	Log cumulative % drug released remained	√t	CDR%	Log time	Log CDR%
0	0	2	0	0		
1	36.4	1.803	1	36.4	0	1.2
3	61.3	1.587	1.732	61.3	0.477	1.42
5	82.5	1.143	2.236	82.5	0.698	1.57
10	97.2	0.447	3.162	97.2	0.90	1.71

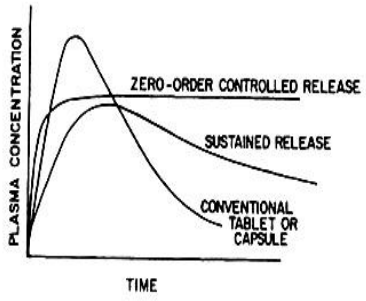


Fig. 1 Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero-order controlled release formulation.

Fig 1. FTIR of Metformin Pure drug

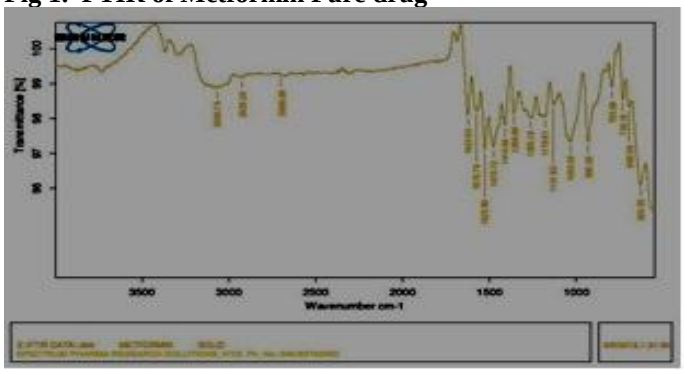


Fig 2. FTIR of Metformin Formulations

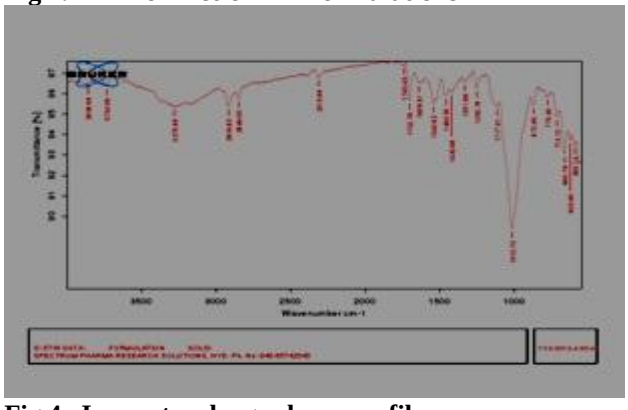


Fig 3. Calibration graph of Metrformin

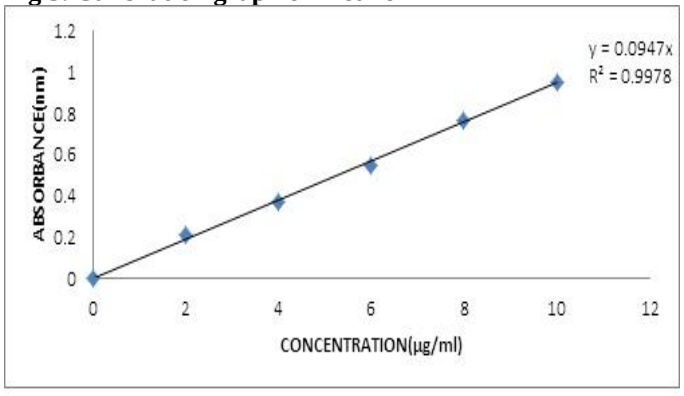


Fig 4. Innovator drug release profile

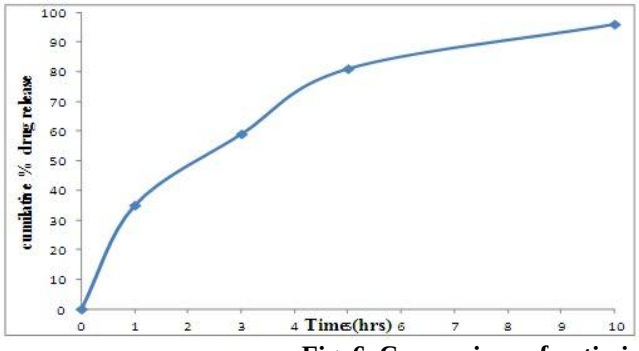


Fig 5. Drug release profile of the formulations (F1 to F8)

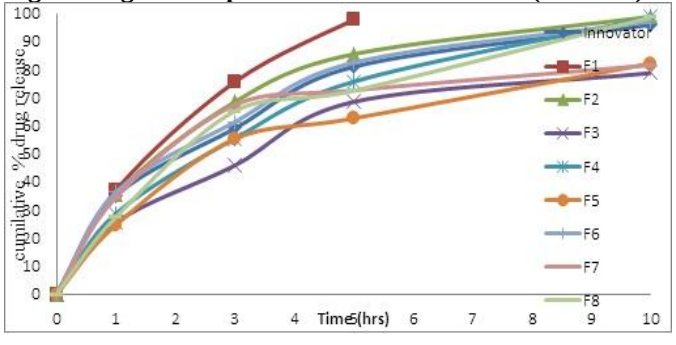
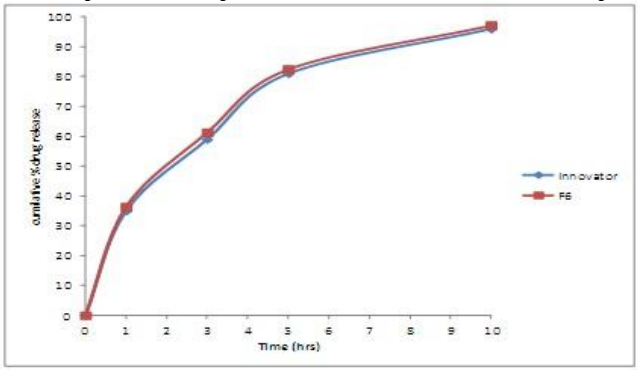
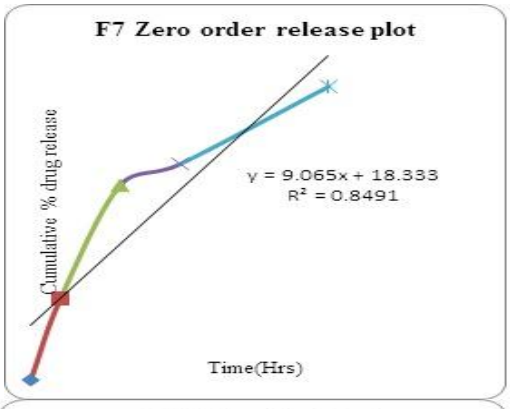
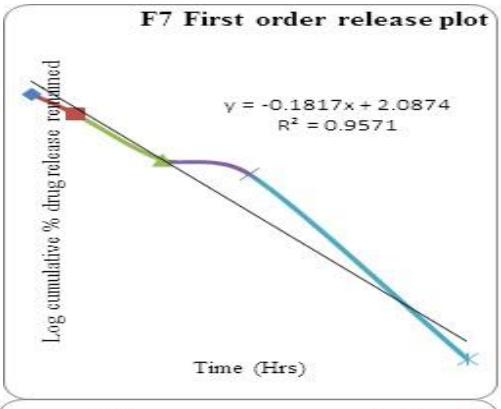
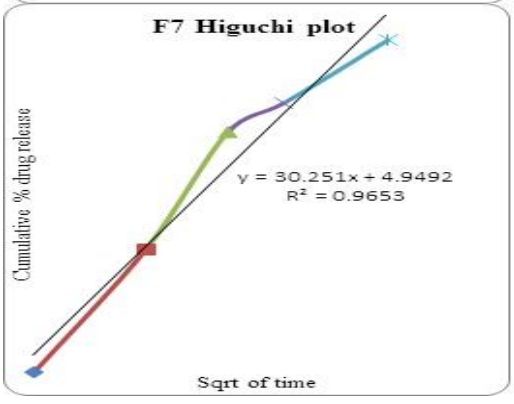


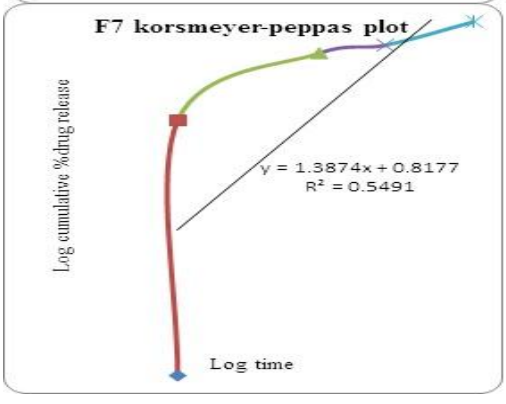
Fig 6. Comparison of optimized formula with innovator product











In F2-F3 formulation the percentage of polymer was increased where the release of the drug was retained and conformed the percentage of polymer was maintained at 25-30%. In F2-F3 the Carbopol was used as binder where that Carbopol has gel forming and swelling nature was observed when both purified water and IPA was used as a binder solution, where the physic chemical properties were not satisfied.

In F4 formulations polyethylene oxide was used as a direct compression process where the hardness of granules was vary and not satisfied in dissolution parameters and in F5 formulation polyethylene oxide was used as binder where the granules hardness was satisfied with dissolution parameters.

In F6 formulation combination of polymers polyvinyl pyrollidone k90 was used as a intra granulation process and Carbopol was used as a extra granulation process where the drug release profile was satisfied with the innovator drug release profile and the process of drug release was observed with official pharmacokinetic parameters where Higuchi process where the drug release was diffusion and dissolution process.

In F7 process sodium carboxy methylcellulose was used as a binder. Where the physical and chemical properties were satisfied. In dissolution process drug release undergoes diffusion process and swelling property was observed and it was retained upon eight hours. In F8 process combination of polymers was used where the drug release was slow and it was not satisfied with the physical and chemical properties. Upon all above formulations F6 was satisfied with the physical and chemical properties and it was release of drug from the polymer was follow first order process and dissolution and diffusion process matched with the Higuchi process.

Stability studies

The stability studies were carried out according to ICH guidelines for optimized formulation i.e. F6. The stability studies were carried out under Accelerated stability studies (40 ± 2^0C/75% ±5% RH).Samples were collected at an interval of zero time and 6^{th} months and evaluated.

CONCLUSION

Extended release tablets of metformin hydrochloride were prepared by wet granulation method using carbopol 971P, sodium carboxy methyl cellulose, poly vinyl pyrrolidine (K-90), polyox. The drug and excipients compatability was studied by FT-IR which showed no physico-chemical interaction. The combination

of polymers used as carbopol 971 P and hydroxy propyl ethyl cellulose was granular blend. Also it is concluded that it improves the drug release at 10th hour. The kinetic treatment of the drug release data of the prepared formulations followed zero order drug release the prepared formulations followed higuchi profile. It indicated that drug release was diffusion controlled and directly proportional to squar root of time. On comparing equation of line and regression coefficient (r^2) with Innovator, the formulation F6 shows similarity of results with innovator, hence F6 was considered as formulation extending 89.4% of drug was released at the end of 10 hrs. The stability studies were carried out for period of 6 months as per ICH guidelines, there is no significant change in dissolution profile and other parameters of the optimized formulation F6 were in acceptable limits.

REFERENCES

Chien CE. Novel Drug Delivery Systems 2nd edition Marcel Dekker, New York, 1992.

Higuchi T. Mechanism of sustained-action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *Journal of Pharmaceutical Sciences*, 52, 1963, 1145 -1149.

Korsmeyer RW, Gurny R, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *International Journal of Pharmacetics*, 15, 1983, 25-35.

Lordi N. Sustained release dosage forms. In: Lachman L, Lieberman HA, Kanig LJ. The Theory and Practice of Industrial Pharmacy. Philadelphia, Lea and Febiger, 1986, 430–478.

Merkus FW. Controlled and rate-controlled drug delivery, principal characteristics possibilities and limitations, In Struyker-Boudier HA. eds, Rate- Controlled Drug Administration and Action, CRC Press, Boca Raton, FL, USA, 1986, 15-47.

Pawar AP, Nishad D. Modern dispensing Pharmacy, 2nd ed., 2005, 327-374.

Robinson JR, Lee VH. Controlled Drug Delivery: Fundamentals and Applications, 2nd edition. Marcel Dekker, NewYork, 1987.

Stepensky D, Friedman M, Srour W *et al*., Preclinical evaluation of pharmacokinetic- pharmacodynamic rationale for oral CR metformin formulation. *Journal of Controlled Release*, 71, 2001, 107–115.