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Design and evaluation of extended release metformin hydrochloride tablets for type II diabetis mellitus

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ABSTRACT

Metformin hydrochloride tablets intended for extended release were prepared using Eudragit L 100, Eudragit NE 30 D and Hydroxy Propyl Methyl Cellulose(HPMC)/Ethyl cellulose (EC) combination. The technique employed was wet granulation followed by compression. The in vitro release profile of the resulting tablets was evaluated in 0.1N Hcl for 2 hrs and pH 6.8 phosphate buffers for remaining hrs. Preliminary data suggested that the HPMC/EC combination of polymer showed a great promising retardant release. The other in process quality parameters were also studied for the batch tablets, which gave in vitro profiles in accordance with the theoretical release profiles for, sustained release. The release kinetics has been examined for the tablets, which obeyed the stability study, and *in vitro* profile limits from the standard point of diffusion controlled process (higuchi profile) and that of a first order kinetics. The release pattern of the drugs is uniform throughout and is reproducible. Batches 7-10 of metformin ER tablets were formulated using varying proportions of drug and HPMC K4M ratios keeping a constant ratio of ethyl cellulose. The drug is primarily granulated with ethyl cellulose and again re-granulated with HPMC K4M for maximum sustained release. This formulation was done with easily available & low cost polymers, which can effectively reduce the cost of formulated product.

KEYWORDS

Eudragit;
Metformin hydrochloride;
Extended release;
In vitro study.

INTRODUCTION

Metformin hydrochloride(metformin), an oral hypoglycemic agent belonging to the biguanide group is widely used throughout the world[1]. Significant hypolipidemic effect and of changes in the lipoprotein structure, and metabolism in both experimental animal and in man has stimulated the interest in the use of metformin. The drug is neither metabolized nor protein bound[2]. It has a biological half life (=3.5h) and rapid elimination through kidney prevents its accumulation[3]. It is given in dose of 500mg, 850mg tablets 3 times daily and even in 1000mg tablets. Metformin is a relatively strong diacid biguanide base (pKa_1 2.8, pka_2 11.5)

this ensures free solubility during its transit in the whole GIT on the other hand, binding of drug to the intestinal wall was also observed in the animals and in clinical study[4]. This was perhaps due to the rapid build up of molecules in contact with the mucosa[5]. There are only few trials to prolong the release of biguanide anti diabetics (especially metformin). All the presiding points justify the clear need to formulate metformin in the form of extended release tablets.

EXPERIMENTAL

Metformin Hcl (290-310μm, the Madras pharmaceuticals, Chennai, India), Eudragit-L100 and NE 30D (Rohm Pharma, GmbH, chemische fabrik, Darmstadt, Germany), HPMC (Dow chemicals, India), Ethyl cellulose (colorcon, India), polyvinyl pyrrolidine (PVP K 30) (plaskol, China), magnesium stearate (Sinai Pharma, India), microcrystalline cellulose(singha chemicals, Medak, India). Hydrochloric acid, the ingredients of phosphate buffer and all the other chemicals used were of analytical grade.

Tablets containing 850mg of metformin (dosage calculated based on the clinical pharmacokinetic parameters of metformin. Hcl for 8hr release was as follows. Total dose=initial dose+maintanence dose=343+469mg=812mg=850mg). With respect to polymers, the additives were prepared by wet granulation technique[6] followed by compression using Erweka single punch tablet machine. The prepared tablets were of hardness greater than 9 kg/cm^2 which was tested using Monsanto hardness tester. Three polymers were used as a trial for preparation of matrix tablets and those were Eudragit L 100, NE 30 D and HPMC/EC blend.

Particle size and compressibility

The particle size of the metformin tablets were determined by sieving method[7] and compressibility was computed from powder density.

Formulation of metformin ER tablets using different drugs: EUD L 100 ratios:

The metformin ER tablets were prepared by wet granulation techniques with various ratios of EUD L 100 as per TABLE 1.

Metformin Hcl was passed through sieve #40 and EUDL 100, starch and Microcrystalline Cellulose (M.C.C) were passed separately through sieve #40. EUDL 100 in isopropyl alcohol (IPA) was used as a primary binding agent. Metformin Hcl and starch were mixed with the binder solution and granules were made. The wet granules were dried at 40^{0}C . After adequate drying, required quantity of M.C.C was added and again regranulated with PVP K 30 in IPA as binding agent. The granules were obtained by passing through sieve #14 and were dried to 40^{o}C. The granules so obtained were lubricated with magnesium stearate and compressed (Erweka Clit Rotary press) using double strength caplet punch to get the required tablets.

TABLE 1 : Formulation of metformin ER tablets using different drug: EUD L100 ratios (quantities expressed in mg per tablet)

Ingredients	Formulation batches			
	Batch 1	Batch 2	Batch 3	Batch 4
Metformin.Hcl	850	850	850	850
EUD L100	106.25	127.50	150	170
Starch	170	170	170	170
MCC	60	60	60	60
PVP K30	60	60	60	60
Magnesium stearate	50	30	30	30

Batch (B)→ B2 →15%(Polymer% w.r.t. the drug) ; B4→20%

TABLE 2 : Formulations of metformin ER tablets using different drug: EUD NE 30D ratios (quantities expressed in mg per tablet)

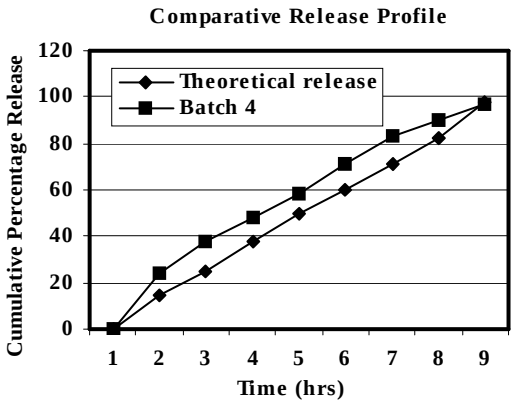
Ingredients	Formulation batches	
	Batch 5	Batch 6
Metformin.Hcl	850	850
EUD NE 30D	127.5	170
Starch	50	50
PVPK30	45	45
Talc	21	21
Magnesium stearate	2	2

B5-15% EUD NE 30D(Polymer % w.r.t. the drug); B6-20% EUD NE 30D

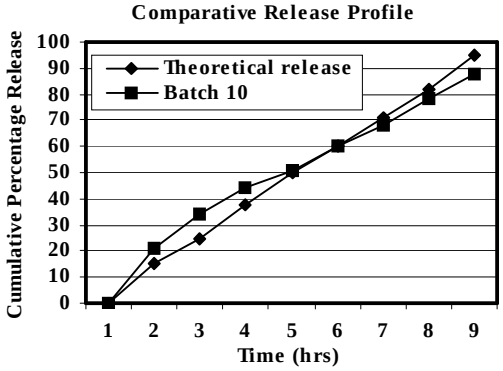
Formulation of metformin ER tablets using different drugs : NE30D ratios

The metformin ER tablets were prepared by wet granulation techniques with different ratios of EUD NE 30D as per TABLES 2-4.

Metformin Hcl and starch were passed through sieve #40 and mixed thoroughly. Polyvinyl pyrrolidine (PVP K30) in IPA was used as binding agent. EUD NE 30 D is mixed with the binder and paste was prepared. Half the quantity of the above paste was mixed with metformin and starch and mixed well. This mass is



Graph 1 : *In vitro* release profile of metformin. Hcl from matrix tablet (batch 4) compared with the theoretical release. Each point represents mean ± s.d. of 6 experiments



Graph 2 : *In vitro* release profile of metformin. Hcl from matrix tablet (batch 10) compared with the theoretical release. Each point represents mean ± SD of 6 experiments

TABLE 3: Formulations of metformin ER tablets using different drug: HPMC K4 M ratios (quantities expressed in mg per tablet)

Ingredients	Formulation batches			
	Batch 7	Batch 8	Batch 9	Batch 10
Metformin.Hcl	850	850	850	850
Ethyl cellulose	85	85	85	85
Methocel K4M	187	210	240	260
M.C.C.	40	40	40	40
PVPK 30	80	80	80	80
Magnesium stearate	20	20	20	20

(Polymer % w.r.t. the drug); Batch-(B7) 10% EC, 20% HPMC; B10 -10% EC, 28% HPMC; B8-0% EC, 22% HPMC; B9 -10% EC, 26% HPMC

subjected to drying (primary drying) at 40^{0}C. After adequate drying, the remaining amount of paste was added, mixed and subjected to drying. The granules were prepared by passing through sieve # 14, dried at 40^{0}C and lubricated with talc and magnesium stearate. Lubricated granules were subjected to tablet punching using double strength caplet punch to get the tablets. For the entire batch formulated, parameters like average weight, hardness and friability were checked during compression as in process quality measures. The moisture content of granules of all batches were also determined as per KFR method and reported.

In vitro dissolution studies

The *in vitro* studies were carried out for all the batches at 0.1N Hcl medium for two hours (to stimulate gastric media condition) and the medium was changed to pH 6.8 phosphate buffer medium (to stimulate intestinal media condition). USP dissolution apparatus (basket type-USP XXIII programmable TDT-06T, electrolab) was used at 50 rpm at 37^{0}C ± 2^{0}C . The volume of the dissolution medium was 900ml and the samples were withdrawn every hour. Equal amount of respective medium is replaced to maintain sink condition.

Stability study

The formulated metformin ER tablets of batch 10 which gave *in vitro* drug release complying the calculated theoretical release limits, as well as complying assay limits and other physical and chemical parameters were kept for a short term accelerated stability study in high density polyethylene sealed covers at different temperatures (40^{0}C, 50^{0}C, and 70^{0}C) for 3 months. Samples were withdrawn every 15 days of storage and evaluated for the following parameters (a) appearance (b) hardness, (c) assay and the samples were analyzed once every month for its dissolution release.

TABLE 4: Physical and chemical parameters of formulated metformin ER tablets

Parameters	Formulation batches									
	1	2	3	4	5	6	7	8	9	10
Average weight (gm)	1.260	1.290	1.310	1.340	1.090	1.120	1.260	1.385	1.310	1.330
Friability (%)	0.81	0.95	0.85	0.94	0.76	0.84	0.69	0.79	0.91	0.73
Thickness (mm)	5.8	5.9	6.1	6.1	5.6	5.7	6.2	6.2	6.3	6.3
Hardness (kg/cm^2)	8	8	8	8	8-9	8-9	9	9	9	9
Assay (%)	98.13	94.19	98.01	94.67	97.58	96.81	98.56	99.25	97.56	99.41
Moisture content	2.4	2.2	1.9	2.2	2.3	2	2.1	2.3	2.5	2.1

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RESULTS AND DISCUSSION

In vitro dissolution data

The dissolution was carried out in varying pH conditions to stimulate in vivo conditions (pH 1.2 & phosphate buffer pH 6.8). The dissolution profiles of metformin from batch 4 tablets (Graph 1) obeyed the theoretical release limit, which was formulated using EUD L100 polymer. The cumulative percentage release was 98% at the 8th hour. Similarly dissolution profiles of batch 10(Graph 2) formulated with EC/HPMC combination obeyed more precisely with the theoretical release limits. The cumulative percentage release was 90.16% at the 8th hour. Therefore batch 10 tablets were subjected to further characterization tests and stability studies. The mechanism of release rate from the matrix tablet was also analyzed for batch 10 ER tablets.

Release kinetics

To explore more precisely the mechanism of release from the batch 10 formulated metformin ER tablet, the release kinetics was assumed to be and correlated with relationship expressed by the higuchi equation and first order equation (profile). The release profile of ER tablets showed a release rate of 10.59% per hour with R=0.9881, R^2=0.9764. The higuchi profile & first order plot are as shown in the graph 3 and graph 4 respectively.

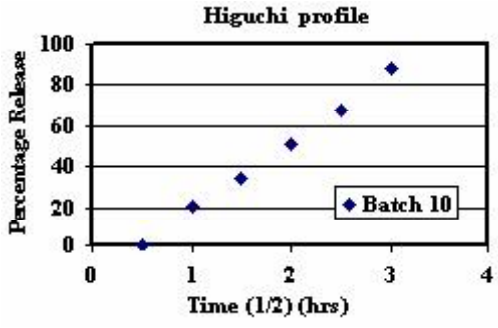
The release profile was found to follow higuchi profile (r^2=0.9894) than first order profile (r^2=0.9164) (TABLE 5)

Stability studies

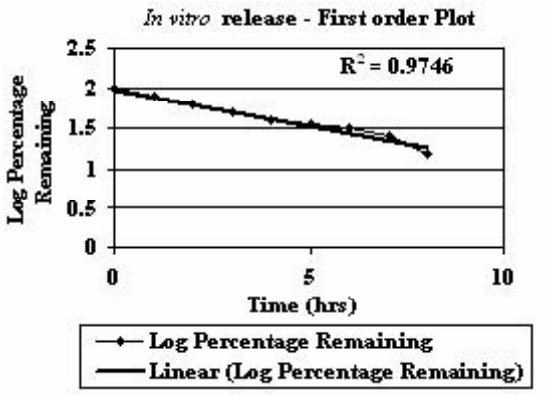
Stability studies were performed on batch 10 tablets, which were in accordance with the theoretical drug release limits. Once every month drug dissolution study was performed and once every 15 days friability, appearance, hardness and assay were performed. All these parameters were compared with the initial parameters and were found that the batch under stability testing did not show much variation during the stability studies.The shelf life of the batch was found to 1.7 years. EUD L100 is an anionic polymer[8] that was expected to give a complex of low solubility with the cationic metformin molecules. 1-4 batches of metformin tablet were formulated using various metformin: EUD L100 proportions to study the effect of polymer concentration on drug release profile.

TABLE 5: Analyses of release data

Parameter	Higuchi equation	First order model
Regression coefficient (R)	0.9894	0.9742
Determination coefficient (R^2)	0.9789	0.9490
Release rate (K)	9.86%h^{-1}?	0.14%h^{-1}
Correlation coefficient (r)	0.9894	0.9164



Graph 3 : Higuchi profile



Graph 4 : *In vitro* release-first order plot

EUD NE 30D is a 30% aqueous dispersion (neutral ester dispersion) used in manufacture of matrix tablets. Due to its high cost, its usage is often restricted. The neutral polymer is independent of the pH of the dissolution medium and therefore provides sustainability in drug release. Batches 5 & 6 of metformin ER tablets were formulated using various metformin: EUD NE30D proportions(TABLE 5).

Methocel is an inert polymer and formation of matrix tablet is compatible and easy. The release pattern of drugs is uniform throughout and reproducible. Batches 7-10 of metformin ER tablets were formulated using varying proportions of drug and HPMC K4M ratios keeping

a constant ratio of ethyl cellulose . The drug is pri-

marily granulated with ethyl cellulose and again re-granulated with HPMC K4M for maximum sustained release. This formulation was done with easily available & low cost polymers, which can effectively reduce the cost of formulated product.

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