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Formulation and Evaluation of Sustained Release DOSAGE Form of Metformin Hydrochloride using A Combined Hydrophobic and Hydrophilic Matrix

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ABSTRACT

Combination of ethyl cellulose and hydroxyl propyl methyl cellulose and investigated as a sustained release matrix. Metformin hydrochloride is used as a model for evaluating the matrix system .Ethyl cellulose and hydroxyl propyl methyl cellulose used in different proportions i.e., 1:1, 2:2 3:3 and 3:4 along with usual tablet additives, microcrystalline cellulose, magnesium stearate and colloidal silicon dioxide. The matrix component was varied from20 ,40,60and 80%w/w of total tablet weight. The in vitro release data showed that 80%w/w total matrix component gave sustained release of metformin hydrochloride for more than 12 h. Tablets were prepared by direct compression. The resulting formulation produced robust tablets with optimum hardness, low friability and consistent weight variation. Before tablets compression the formulations blend were studied DSC analysis, angle of repose, true volume, bulk density and percentage porosity. All tablets but one exhibited gradual and near –completion sustained release for metformin hydrochloride 98-100% released at the end of 10h. Short term in vitro release stability studies on formulations F4 was carried out. Formulations F4 was selected on the basis of Invitro and invivo studies compared with marketed sustained release.

Keywords: Metformin hydrochloride; Matrix tablets; Sustained release; Hydroxy propyl methyl cellulose and ethyl cellulose.

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INTRODUCTION

Metformin hydrochloride, an anti-diabetic drug lowers both basal and postprandial-elevated blood glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM or type II diabetes) whose hyperglycemia cannot be satisfactorily managed by diet alone. Some high incidence of concomitant GI symptoms, such as abdominal discomfort, nausea and diarrhoea, may occur during the treatment. Administration of a sustained release, once-a-day metformin hydrochloride dosage form could reduce the dosing frequency and improve patient compliance [1-2].

Inspite of its favorable clinical response and lack of significant drawbacks, chronic therapy with metformin hydrochloride suffers from certain specific problems of which the most prominent is the high dose (1.5-2.0 g/day) low bio-availability (60%) and high incidence of gastrointestinal tract [GIT] side effects (30% cases). Therefore, there were continued efforts to improve the pharmaceutical formulation of metformin hydrochloride in order to achieve an optimal therapy. These efforts mainly focus on sustained release of the drug including the sophisticated gastroretentive system. [3-9]

Numerous studies have been reported in literature investigating the HPMC matrices to control the release of variety of drug from matrices [10-16]. Several authors have reported the use of ethyl cellulose microcapsules for the encapsulation of a variety of drugs such as zidovudine [14], cimetidine [15], potassium chloride [16], isosorbide dinitrate [17], theophylline [18] etc for a variety of reasons. Therefore, in this study, the hydrophobic (EC) and hydrophilic polymer [HPMC] alone/in combination has been used as matrix material in order to get the required theoretical release profile of metformin hydrochloride.

MATERIALS AND METHODS

Materials

Metformin hyohochloride – USP was a gift sample from Wokhardt Pharmaceuticals (Mumbai, India).Hydroxy propyl methyl cellulose ($K_{100}M$) – USP was obtained from Shin, Etsu. Chemicals Co.Ltd.(Tokyo, Japan). Ethylcellulose (18 cps) was procured from SD Fine Chemicals Ltd(Mumbai,India). Microcrystaline cellulose powder I.P was obtained from Sigha Ehichlro Chemicals Pvt. Ltd. (India). All other chemicals and reagents used were of high analytical grade. Double distilled water was used for evaluation studies.

Machineries

Machineries and equipment used were Tablet compression machine, (Cadmach Machinery Co. Pvt. Ltd), UV Visible Spectrophotometer, (Shimazu 1700), Six stage dissolution rate test apparatus IP / BP/USP, (Tab-machines). Friability Test Apparatus, (Remi Equipments, Pvt. Ltd), Monsanto Hardness Test Apparatus, (Rollex, Pvt. Ltd.), India. B.S. Sieves, (Jayant Scientific), Granulator, (Kevin Engineers) and Tray Drier (Bombay Engineering Works), Differential scanning calorimetry (Perkin Elmer DSC-7 model)

Methods

Preparation of Metformin Hydrochloride Sustained Release Matrix Tablets

Different tablet formulations (F1 to F4) were prepared by direct compression technique [19-22] Ingredients required for 1000 tablets are given in Table 1 and tableted as follows. The metformin hydrochloride, HPMC, EC and MCC powders were separately passed through 44 mesh. The drug HPMC, EC and MCC powders were uniformly mixed in a double cone blender for 5 mins (Formulations F1, F2' F3 and F4 separately). Then the dried powders were lubricated with magnesium stearate and aerosil by mixing in a rapid mixer granulator at slow speed for 5 mins and compressed using 16/32 flat punches in Cadmach tablet compression machine to get tablets.

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Table 1: Composition of Metformin Hydrochloride Tablet Formulations with Polymers F_1 To F_4

Ingredients per tablet	Formulations **(mg / tab)**			
	F1	F2	F3	F4
Metformin hydrochloride	500	500	500	500
Hydroxy propyl methyl cellulose (K100 M)	**50**	**100**	**150**	**200**
Ethyl cellulose (18 centipoise)	**50**	**100**	**150**	**200**
Microcrystalline cellulose	75	75	75	75
Colloidal silicone dioxide	0.006	0.006	0.006	0.006
Magnesium stearate	0.012	0.012	0.012	0.012

Evaluation of powders blend

The formulated powders were evaluated for DSC analysis [23], angle of repose, bulk density, true volume and total % porosity [24 -26]. Drug content was determined on an accurately weighed amounts of powdered formulation of metformin hydrochloride (500 mg). The formulation powders were dissolved in 900 ml. of distilled water and filtered through 0.45µ membrane filter (Nunc, New Delhi, India). The absorbance was measured at 230 nm. The amount of drug was calculated by using standard curve.

Evaluation of Tablets.

The formulated tablets were tested for weight variation, friability, hardness [22, 27] and the drug content (ten tablets were weighed individually and the drug was extracted using distilled water) was determined as described above.

In-Vitro Release Studies

The in vitro dissolution studies were carried out [28] using six stage dissolution rate test apparatus IP/BP/USP at 50 rpm. The dissolution medium consisted of simulated gastric fluid (pH. 1.2-acid buffer) for the first 2 hours and followed by the simulated intestinal fluid (pH 7.2- phosphate buffer) [29] from 2 to 12 hours (900 ml), maintained at $37^{o}C \pm 0.5^{o}C$. Samples were taken at predetermined time intervals and analysed for metformin hychloride content at 227.5 nm and 230 nm respectively and compared with the blank. The same procedure was followed to study the in vitro release of metformin hydrochloride sustained release (SR) for a marketed product. All the release studies were conducted in triplicate and the mean values were plotted versus time with standard deviations less than 3, indicating the reproductibility of the results.

Stability Studies

The formulation (F4) which gave an in vitro drug release complying with the calculated limits was kept for a short term accelerated stability studies in high density polyethylene sealed cover at room temperature ($25\text{-}30^{0}C$) and elevated temperature (at $40^{0}C$ with 75RH) [30]. Samples were withdrawn for everyone, three and six month of storage and evaluated for appearance hardness, drug content. Friability and rate of in vitro drug release.

***Invivo* release studies**

Diabetes was induced in healthy Wistar albino rats of either sex weighing (200-250gm) by injecting a single intraperitoneal injection of 150 mg/kg body weight of Streptozocin. Blood glucose level was checked after 48h. Animal with blood glucose level greater than 250mg/dl were considered diabetic and were selected for our further study[25-27].

The rats were divided into 4 groups of rats each group having 6 rats and group-I animal served as normal control, they were not given any drug. The groups II, III and IV were diabetic rats. From the groups (II to IV), group II animal are diabetic control rats. The groups III and IV were given formulated metformin hydrochloride matrix tablet formulation F_4 and reference standard (FM) respectively in the form of suspension orally at a dose level of 450 mg/ kg body weight. On fasting blood samples were collected from the tail vein on 3rd day of each groups (I to IV) at 0, 1, 2, 4, 6, 8, 10 h, intervals. Glucose levels were estimated by using glucosemeter. Statistical comparisons with animal of non-treated groups of control I and II with drug treated groups were performed with student's t-test. Data's were expressed as mean ± standard error mean.

RESULTS AND DISCUSSION

An ideal sustained release metformin hydrochloride matrix tablets should release the required quantity of drug with predetermined kinetics in order to maintain effective drug plasma concentration. To achieve this tablets were formulated in such a way as to release the drug in a predetermined and reproducible manner. The tablet showed the release of the drug as per the predetermined rate even under storage conditions.

It belongs to the class of biguanides. It is freely soluble in water. Metformin hydrochloride is sensitive to moisture, heat and light. Generally capsules, tablets and drug powder should be stored at 25-30°C in a dry and cool place[31]. In the present work, we tried to develop HPMC and EC based metformin hydrochloride tablets, which could release the drug in a predetermined rate for 12 hrs. Three formulations were formulated by changing the polymers combination.

Formulations F1, F2. F3 and F4 were formulated by using various combination of metformin hydrochloride EC and HPMC as per formula given in Table I in order to study the effect of EC and HPMC on drug release profile and it shows the mean cumulative percentage of metformin hydrochloride released versus time for tablets formulated with various percentage of EC , HPMC and marketed sustained release tablet F4. All the batches showed a release time of 6-12 hrs. As expected the release rate was slower with higher quantity of ECand HPMC. Among the three formulations the formulation F4 showed the optimum release profile.

All other evaluation parameters like angle of repose, bulk density, true density, true volume, percentage porosity, drug content, hardness, friability, weight variations were studied for all the formulations. All formulations passed the acceptable limits of their respective parameters [22-27] (Table 2 to 4). DSC results shows the DSC curve for the interaction analysis [23] of metformin hydrochloride with HPMC and EC. The in vitro release data obtained for formulations (F1 to F4) and with marketed sustained release tablet (F_4) were given in Table 5 and 6.

Table 2: Physical and Chemical Parameters of Formulated Metformin Hydrochloride Powder Blends With Polymers (F_{13} To F_{24})

Evaluation parameters	Formulations			
	F1	F2	F3	F4
Angle of repose (degree)	29.5	30.43	25.02	22.94
Bulk density (gm/ml)	0.66	0.67	0.63	0.54
Compressibility Index (%)	16.01	15.93	16.67	12.68
Porosity (%)	28.01	27.26	22.68	18.33

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Table 3: Data of absorbance of metformin hydrochloride in pH 1.2 and pH 7.2 measured at 227.5 nm and 230nm respectively

S.no	pH1.2 (Acid buffer)		pH 7.2 (Phosphate buffer)	
	Concentration (mcg/ml)	Absorbance	Concentration (mcg/ml)	Absorbance
1	2.5	0.123	1.25	0.097
2	5	0.222	2.5	0.203
3	10	0.431	5	0.389
4	15	0.607	7.5	0.579
5	20	0.824	10	0.722
6	25	1.006	12.5	0.907
7	30	1.198	15	1.080

Table 4: Physical and Chemical Parameters of Formulated Metformin Hydrochloride Compressed Tablet Formulations (F_1 To F_4) And Marketed Formulation (Fm)*

Evaluation parameters	Formulations				
	F1	F2	F3	F	FM
Hardness (kg/cm^2)	7.2	8.67	7.67	8.67	8.00
Friability (%)	0.67	0.53	0.41	0.38	0.39
Weight variation (%)	0.81	0.79	0.79	0.73	0.51
Drug content (%)	0. 72	99.10	99.40	100.20	100.4

Table 5: Comparative % *in vitro* release profile of metformin hydrochloride formulations ($F_1$to F_4) and marketed formulation (FM)*

Time (mins)	pH	F_1	F_2	F_3	F_4	F M
30	pH 1.2 (Simulated gastric fluid)	40.59±2.11	38.60±2.13	30.49±1.35	14.10±1.11	19.98±0.02
60		49.11±2.22	43.86±1.71	40.95±2.32	22.78±0.52	28.86±1.40
90		62.22±4.12	53.08±1.47	46.68±2.36	28.60±0.95	38.36±1.75
120		73.10±3.13	60.25±0.55	53.59±3.46	35.53±0.79	43.90±2.69
150	pH 7.2 (Simulated intestinal fluid)	87.29±4.81	76.08±3.38	59.79±1.91	43.49±0.67	52.51±1.32
180		99.72±3.66	84.4±2.77	70.73±1.66	48.85±0.44	58.27±2.12
240		-	90.26±1.46	81.95±3.37	56.86±1.14	67.72±2.69
360		-	99.62±0.62	90.85±2.22	71.43±0.79	79.90±0.78
480		-	-	99.57±0.57	76.03±1.67	89.32±2.12
600		-	-	-	88.48±1.92	100.01±0.45
720		-	-	-	99.78±0.17	-

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Table 6: Regression coefficient values (R2) of selected sustained release matrix tablets of Metformin Hydrochloride (Formulations F4 and FM)

Formulations	O order	1st order	Higuchi model	Korsemeyer and Peppas model
F4	0.8231	0.7471	0.9923	0.9907
FM	0.8723	0.6911	0.9948	0.9920

Accelerated stability studies were performed on formulation F_3 tablet. The in vitro release was studied at periodic intervals and the results shown in Table 7 to 11. The change of in vitro release profile was observed during stability studies. All the other tested parameters of formulation F_4 were within acceptable limits as given in Table 7 to 11. The formulation F_4 among threee formulations was found to be suitable formulation for metformin hydrochloride matrix sustained release tablet based on t_{25} (time of 25% drug release), t_{50} (time of 50% drug release) and t_{90} (time of 90% drug release) Table-7 to 11.

Table 7: Percentage *in vitro* release profile of metformin hydrochloride tablet formulation F_4 at 25°C ± 2°c at 60% ±5% RH for the period of twelve months*

Time (mins)	pH	0th Month	1st Month	3rd Month	6th Month	9th Month	12th Month
30	pH 1.2 (Simulated gastric fluid)	17.09±0.37	16.02±0.75	16.42±1.95	15.97±2.90	15.93±1.63	16.89±1.89
60		25.65±1.24	25.07±1.46	23.80±2.11	22.06±2.21	22.90±2.39	22.75±1.19
90		31.51±0.95	31.55±1.22	31.07±1.34	30.71±2.17	29.37±1.78	30.56±0.56
120		37.00±0.96	31.55±1.22	36.95±1.25	37.09±1.38	36.07±2.28	35.88±0.91
150	pH 7.2 (Simulated intestinal fluid)	42.67±0.81	45.63±1.27	43.28±2.18	43.22±2.99	43.25±1.35	43.95±1.71
180		46.84±1.80	47.95±1.08	49.16±1.33	50.77±1.80	49.26±1.31	49.72±2.21
240		54.56±1.21	53.82±1.79	54.86±2.39	55.62±1.17	54.63±1.92	53.97±1.80
360		70.67±1.40	76.61±2.10	68.72±2.42	62.64±2.69	65.48±2.43	67.74±3.11
180		80.56±1.30	81.35±1.11	77.69±3.41	74.99±4.65	77.19±3.32	75.83±1.75
600		89.97±0.80	87.63±0.93	88.79±3.42	88.48±2.86	89.01±1.63	89.39±3.77
720		99.74±0.72	99.52±0.65	99.35±0.31	98.02±0.56	97.65±0.70	96.74±0.33

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Table 8: Percentage *in vitro* release profile of metformin hydrochloride tablet formulation f_4 at accelerated condition (40°C± 2°c at 75% ±5% RH) for the period of six months*

Time (mins)	pH	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month
30	pH 1.2 (Simulated gastric fluid)	17.21±3.02	15.86±1.64	17.64±2.00	15.32±1.33	15.22±2.69	15.7±2.69
60		22.65±3.56	21.98±3.00	22.56±1.30	21.51±1.04	21.91±2.51	21.50±1.03
90		27.88±1.65	29.56±1.73	29.16±1.11	28.16±0.41	25.31±1.21	29.68±1.19
120		36.26±2.08	36.58±3.02	35.85±1.66	35.33±1.67	37.02±2.39	36.42±1.90
150	pH 7.2 (Simulated intestinal fluid)	42.64±2.99	40.84±1.50	43.23±2.07	42.98±3.71	42.60±2.19	44.42±2.95
180		49.18±2.12	51.58±3.00	48.67±1.49	49.24±1.74	49.89±1.14	50.53±2.70
240		56.85±2.33	58.11±2.19	56.21±3.31	59.2±4.38	57.7±1.08	60.27±2.63
360		69.31±2.31	72.11±1.84	70.44±2.19	70.60±1.91	68.02±2.10	67.97±3.49
450		74.76±3.67	78.22±1.49	78.78±1.74	76.86±2.19	77.85±3.05	78.60±4.07
600		84.83±1.38	87.75±4.02	87.11±3.29	88.25±2.98	90.80±1.49	91.79±1.78
720		99.87±0.39	99.48±0.67	99.41±0.43	97.69±0.44	97.29±0.87	96.46±0.34

Table 9: Stability studies on percentage *in vitro* release data of t_{25}, t_{50}, and t_{90} on formulation F_4

Period in Month	Room temperature (25°C±2°C at 60%±5% RH)			Period in Month	Accelerated temperature (40°C±2°C at 75%±5% RH)		
	t_{25} (h)	t_{50} (h)	t_{90} (h)		t_{25} (h)	t_{50} (h)	t_{90} (h)
0 Month	0.56	3.12	10.01	1st Month	1.12	3.09	10.45
1st Month	0.58	3.25	10.22	2nd Month	1.26	2.57	10.18
3rd Month	1.06	2.59	10.18	3rd Month	1.16	3.09	10.20
6th Month	1.08	2.58	10.26	4th Month	1.28	3.08	10.20
9th Month	1.13	3.04	10.06	5th Month	1.27	3.06	9.58
12th Month	1.12	3.09	10.08	6th Month	1.18	2.59	9.15

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Table 10: Regression coefficient values (R2) of selected sustained release matrix tablets of Metformin Hydrochloride (Formulations F4 & FM) after 12 month of stability studies at 25°C ±2°C at 60%±5%RH

Formulations	0 order	1st order	Higuchi model	Korsemeyer and Peppas model
F4	0.8992	0.9360	0.9957	0.9934
FM	0.9675	0.9528	0.9950	0.9912

Table 11: Regression coefficient values (R2) of selected sustained release matrix tablets of Metformin Hydrochloride (Formulations F4 & FM) after 6 month of stability studies at 40°C ±2°C at 75%±5%RH

Formulations	0 order	1st order	Higuchi model	Korsemeyer and Peppas model
F4	0.9651	0.9610	0.9920	0.9868
FM	0.9576	0.9921	0.9896	0.9860

Table 12: *In vivo* studies for determination of blood glucose level in albino rats for metformin hydrochloride tablet formulation F_4 and marketed formulation (FM)

Group	Treatment	Mean (Blood sugar in mg/dl) ±SEM						
		0 (h)	1 (h)	2 (h)	4 (h)	6 (h)	8 (h)	10 (h)
I	Normal (control)	99.67 ±2.26	100.12 ±2.02	97.13 ±1.89	102.44 2.10±	110.39 ±2.31	95.91 ±1.76	103.33 ±1.74
II	Diabetic control (Streptozocin)	502.17 ±1.38	509.40 ±1.42	517.77 ±1.33	522.88 ±1.02	531.12 ±1.18	536.46 ±1.21	544.12 ±0.99
V	**Formulation F_4** (Diabetic)	494.83 ±3.16	484.00 ±3.38	458.00 ±3.46	427.33 ±3.14	378.50 ±4.03	321.67 ±3.76	**291.33 ±2.01**
VI	Reference Standard FM (Diabetic)	499.83 ±1.66	492.17 ±2.01	469.17 ±2.55	436.50 ±3.91	390.33 ±3.19	333.00 ±3.76	339.62 ±3.95

Table 13: Paired t- test for determination of reduction of blood glucose level in albino rats

Formulations	Average	S.D.	D f	t calculated value	t table value	P value
F4	407.62	79.67	10	2.38	2.34	P<0.001
FM	422.80	69.75	--	--	--	--

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Table 14: Mean plasma drug concentration of metformin hydrochloride matrix tablet formulation of reference standard, FM, and F4

Time (h)	Mean Plasma drug concentration ±Standard deviation (ng/ml)		
	RS	**FM**	**F4**
0	0	0	0
0.5	1.26 ± 0.09	1.24 ±0.14	1.14 ±0.11
1	1.47 ±0.08	1.31 ±0.13	1.38 ±0.08
2	2.15 ±0.15	1.69 ±0.04	1.75 ± 0.06
4	0.91 ± 0.11	0.95 ±0.06	1.02 ± 0.15
6	0.05 ±0.01	0.70± 0.06	0.79 ± 0.12
8	0.05 ±0.02	0.34 ±0.07	0.40 ± 0.03

***Invivo* release studies**

From the t-test, comparision of F_4 and reference standard (FM), t calculated value < t table value (0.001 <2.34). Therefore accepted the null hypothesis. There is no difference between F_4 and FM. So the formulation F_4 was similar as reference standard (FM) to produced extended release to lower the blood glucose level in animal at tested dose level. (Table No:12 & 13) [25-27]. The pharmacokinetic studies results were shown in table 14 and figure No,5.

CONCLUSION

Based on in vitro t_{25} .t_{50} and t_{90} drug release formulation F4 was found to have a selective drug release pattern among the formulations prepared,. The values were compared with marketed sustained release tablet(FM) and was subjected to pharmacodynamic and Pharmacokinetic study. The also includes short term stability study at cool temperature, room temperature and elevated temperature to find the effect of aging on release pattern. The result of all evaluated parameters does not indicate any significant alteration in the in-vitro release pattern and invivo release pattern of the drug from the matrix tablet. Formulation F4 was found to be stable on storage and does not exhibit any alteration in its release pattern.

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