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Comparative Study of Sustained Release Matrix Tablets Containing Metformin Hydrochloride Prepared By Various Techniques

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A B S T R A C T

Diabetes Mellitus, a metabolic disorder of multiple etiologies, is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism that results from imperfections in insulin secretion, insulin action or both. Metformin Hydrochloride Fourteen formulations (WG1, WG2, WG3, WG4, WG5, WG6, WG7, DC1, DC2, DC3, DC4, DC5, DC6 and DC7) of varying constituents were prepared. The formulations were evaluated for precompression and post compression properties. The similarity factor of WG1 is high when comparing to other formulations so, it is more similar to that of marketed formulation. The study reveals that the extended release of Metformin Hydrochlorideis possible for choosing the xanthan gum (natural polymer) as matrix former also shows anomalous diffusion.

Keywords: Diabetes Mellitus, Metformin hydrochloride, hyperglycemia and xanthan gum

A R T I C L E I N F O

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1. Introduction

Diabetes: Diabetes Mellitus, a metabolic disorder of multiple etiologies, is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism that results from imperfections in

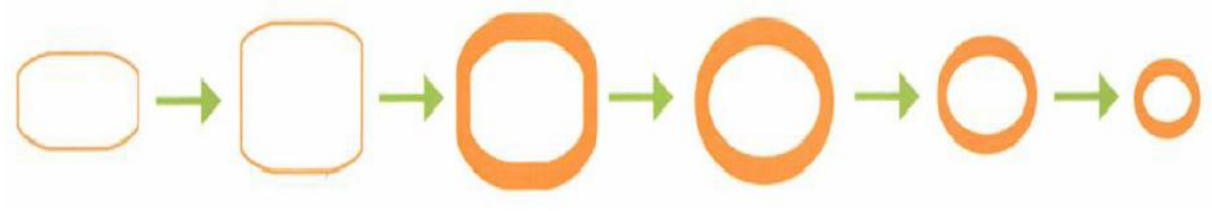
insulin secretion, insulin action or both [1]. The dosage of metformin is from 500 mg to a maximum of 2.55 g daily, with the lowest effective dose being recommended.

Sustained-Release Drug Delivery Systems (SRDDS):

The sustained release dosage form is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug". Sustained-release technologies can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, thereby reducing both the size and number of doses required [2, 3].

Matrix System [4]:

The matrix system is commonly used for manufacturing dosage forms because it makes manufacturing easy. Sustained release tablets are formulated so that the active ingredient is embedded in the matrix insoluble substance. So, that the dissolving drug has to find its way out through the holes in the matrix. In some sustained release formulation the matrix physically swell up, to form gel, so that the drug has first dissolve in matrix, then exit through the outer surface.



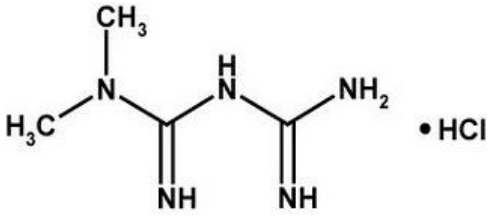
Initial swelling Expansion Dissolution Erosion

First stage **Second stage**

Figure 1: Schematic dissolution profile of the matrix tablet

Drug Profile

Metformin Hydrochloride [4]:



Metformin Hydrochloride

Figure 2

Molecular formula: $C_4H_{11}N_5$. Hcl
Molecular weight : 165.63 g/mol
Solubility : freely soluble in water
Chemical name : 3-(diaminomethylidene)-1, 1-dimethylguanidine hydrochloride

2. Materials and Methods

Preparation of Metformin Hydrochloride Extended Release Matrix Tablets [5]:

Fourteen formulations (WG_1, WG_2, WG_3, WG_4, WG_5, WG_6, WG_7, DC_1, DC_2, DC_3, DC_4, DC_5,DC_6, DC_7) of varying constituents were prepared. First seven formulations (WG_1-WG_7) was prepared by the wet granulation process and consists of Xanthan Gum and guar gum with other polymers like micro crystalline cellulose and magnesium stearate etc. Other seven formulations (D_{C1}-D_{C7}) were prepared by the direct compression process and consist of xanthane gum (or) guar gum (or) both in different compositions.

Table 1: Composition of Formulations (Wg_1-Wg_7) Of Metformin Hydrochloride Granules By Wet Granulation Method

S.No	Name of Batch	Metformin Hydrochloride (mg)	Xanthan Gum (mg)	Guar Gum (mg)	PVP K 30 (mg)	Magnesium Stearate (mg)
1	WG-1	500	250	-	30	10
2	WG-2	500	200	50	30	10
3	WG-3	500	150	100	30	10
4	WG-4	500	100	150	30	10
5	WG-5	500	50	200	30	10
6	WG-6	500	-	250	30	10
7	WG-7	500	125	125	30	10

Table 2: Composition of Formulations of Metformin Hydro Chloride Tablets (Dc-1 -Dc-7) By Direct Compression Method

S.No.	Name of Batch	Metformin Hydrochloride (mg)	Xanthan Gum (mg)	Guar Gum (mg)	Micro Crystalline Cellulose (mg)	Magnesium Stearate (mg)
1	DC-1	500	250	-	30	10
2	DC-2	500	200	50	30	10
3	DC-3	500	150	100	30	10
4	DC-4	500	100	150	30	10
5	DC-5	500	50	200	30	10
6	DC-6	500	-	250	30	10
7	DC-7	500	125	125	30	10

Characterization of Metformin Hydrochloride Granules (Pre Compression Properties): The Angle of repose, Bulk density, Tapped density, Compressibility Index, Hausner ratio, % LOD and sieve analysis was calculated for granules.

3. Results and Discussion

Characterization of Metformin Hydrochloride Granule (Pre Compression Properties):

Table 3: Pre compression properties of Metformin hydrochloride Granules

S.no	Formulations	Angle of Repose	Bulk density(g/c.c)	Tapped density(g/c.c)	Compressibility index (%)	Hausner's ratio	% loss on drying
1	W_1	28.38 ± 0.21	0.64 ± 0.01	0.72 ± 0.01	14.28 ± 0.3	1.16 ± 0.04	0.64 ± 0.02
2	W_2	26.45 ± 0.48	0.66 ± 0.03	0.71 ± 0.01	13.88 ± 0.6	1.37 ± 0.16	0.82 ± 0.36
3	W_3	27.31 ± 0.17	0.66 ± 0.02	0.74 ± 0.02	15.14 ± 0.6	1.29 ± 0.05	1.06 ± 0.41
4	W_4	27.08 ± 1.06	0.65 ± 0.02	0.74 ± 0.01	15.31 ± 0.08	1.32 ± 0.02	0.96 ± 0.58
5	W_5	26.64 ± 0.43	0.63 ± 0.01	0.74 ± 0.03	14.46 ± 0.4	1.32 ± 0.02	0.62 ± 0.02
6	W_6	27.48 ± 0.71	0.64 ± 0.01	0.73 ± 0.03	14.34 ± 0.02	1.36 ± 0.07	0.88 ± 0.37
7	W_7	27.24 ± 0.17	0.66 ± 0.03	0.73 ± 0.03	14.60 ± 0.24	1.29 ± 0.05	1.15 ± 0.51

* Each reading is an average of three determinations

Characterization of Metformin Hydrochloride Powder Mixtures: (Pre Compression Properties):

Table 4: .Pre compression properties of Metformin hydrochloride powder mixtures

S.no	Formulations	Angle of repose	Bulk Density(g/c.c)	Tapped Density(g/c.c)	Compressibility Index (%)	Hausner's Ratio
1	DC_1	26.25 ± 0.11	0.68 ± 0.01	0.76 ±0.01	15.39 ± 0.21	1.16 ±0.04
2	DC_2	25.13 ± 0.01	0.68 ± 0.01	0.74 ± 0.01	15.39 ± 0.21	1.37 ±0.16
3	DC_3	27.43 ± 0.50	0.65 ± 0.02	0.74 ± 0.03	13.31 ± 0.08	1.30 ±0.05
4	DC_4	29.38 ± 0.26	0.63 ± 0.02	0.72 ± 0.01	14.34 ± 0.02	1.33 ± 0.02
5	DC_5	28.40 ± 0.25	0.63 ± 0.01	0.73 ± 0.02	14.43 ± 0.38	1.33 ±0.02
6	DC_6	27.13 ± 0.01	0.65 ± 0.02	0.73 ± 0.01	13.31 ± 0.08	1.36 ±0.07
7	DC_7	27.38 ± 0.24	0.66 ± 0.02	0.72 ± 0.01	15.09 ± 0.39	1.29 ±0.05

Note: +- Presence, – - Absence, *Each reading is an average of three determinations.

Characterization of Metformin Hydrochloride Granules (Post Compression Properties):

Table 5: Post compression properties of Wet Granulation and Direct Compression matrix tablets

S.No	Formulations	Thickness (mm)	Weight Variation (mg)	Hardness(kg/cm2)	Friability (%)	Assay (%)
1	**WG_1**	6.52 ± 0.11	790.00 ± 1	5.53 ±0.11	1.31 ± 0.10	100.19 ± 0.97
2	**WG_2**	6.57 ± 0.13	791 ± 2.08	5.50 ± 0.17	1.24 ± 0.15	99.19 ± 0.51
3	**WG_3**	6.35 ± 0.17	793 ± 2	5.47 ± 0.30	1.15 ± 0.07	98.42 ± 1.01
4	**WG_4**	6.15 ± 0.05	791 ±2.51	5.40 ± 0.17	1.35 ±0.05	97.77 ± 1.26
5	**WG_5**	6.48 ± 0.05	791.33 ± 2.30	5.20 ± 0.26	1.44 ± 0.02	97.53 ± 1.82
6	**WG_6**	6.53 ± 0.28	792 ± 1.52	5.37 ± 0.20	1.38 ± 0.06	99.82 ± 0.33
7	**WG_7**	6.54 ± 0.18	792.1 ± 1.15	5.13 ± 0.05	1.30 ± 0.12	100.55 ± 0.58

8	**DC_1**	6.60 ± 0.19	352.33 ± 1.52	5.57 ± 0.25	1.31 ±0.10	100.49 ± 2.40
9	**DC_2**	6.64 ± 0.01	349.00 ± 1.73	5.33 ± 0.05	1.28 ± 0.15	98.53 ± 1.91
10	**DC_3**	6.58 ± 0.11	352.33 ± 1.52	5.23 ± 0.35	1.14 ± 0.07	101.23 ± 0.09
11	**DC_4**	6.40 ± 0.26	348.33 ± 1.5	5.33 ± 0.25	1.32 ±0.18	99.60 ± 0.04
12	**DC_5**	6.58 ± 0.10	350.67 ± 1.15	5.10 ± 0.1	1.32 ± 0.17	100.44 ± 0.94
13	**DC_6**	6.67 ± 0.05	349.67 ± 2.08	5.23 ± 0.20	1.33 ±0.12	99.91 ±1.44
14	**DC**	6.47 ± 0.22	351.33 ± 1.52	5.33 ± 0.05	1.30 ± 0.16	98.63 ± 1.46

***n=3, the values are mean ± S.D, p < 0.001**

In vitro Drug Release–Tablets Prepared By Wet Granulation: The *In-vitro* drug release was studied in USP XXII dissolution apparatus both 0.1 N Hcl for 2 hrs and up to 10 hrs in phosphate buffer pH 6.8. The results shown that the some of the formulations of wet granulation and direct compression matrix tablets shown the good release of the drug from the formulations. In case of wet granulation matrix tablets WG_2 ,the release of drug shows 99.46 ± 0.36% and in case of WG_1 the release is 96.01% and controlled the drug release, but WG_2 is not suitable for the sustained release action because the drug release in the the 0.1 N Hcl is more. So, the formulation WG_1 is suited for the extended release of Metformin Hydrochloride in the treatment of Diabetes. In release kinetic study the 'n' value ranges from 1.0994 to 1.4103 for all formulations, these values are characteristic of super case II transport, suggesting that more than one mechanism may be involved in release kinetics. High the value of 'n' high is the polymer relaxation and swelling / erosion and drug is release in this fashion. For **WG_1** the 'n' value is high shows that drug is released by high polymer relaxation and swelling / erosion.

Comparision of Selected Formulation WG_1 (Drug: Polymer 2:1 Ratio) With Marketed Formulation (Mf)

Table 6: Comparitive *in-vitro* drug release of WG-1 with MF in SGF AND SIF

S.No	Time (hrs)	WG-1	Marketed Formulation
1	0	0	0
2	1	13.37333	14.01
3	2	25.36333	24.96
4	4	45.93	45.14
5	6	64.40667	63.465
6	8	77.99	78.06
7	10	96.01	96.12

Simlarity Factor (f2):

On comparison with marketed formulation the invitro drug release of Metformin Hydrochloride of best formulation WG_1 is slightly similar to that of marketed formulation.

4. Conclusion

The study reveals that the extended release of Metformin Hydrochlorideis possible for choosing the xanthan gum (natural polymer) as matrix former also shows anomalous diffusion. Hence by the use of the xanthan gum polymer as matrix once daily dose of Metformin Hydrochloride (500mg) is achieved.

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