Original Research Article

EFFECT OF SUPERDISINTEGRATING AGENTS ON THE RELEASE OF METFORMIN HCl FROM RAPID RELEASE TABLETS

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ABSTRACT:

Immediate release tablet of Metformin HCl (MET) requires to formulate for emergency urgent treatment of type- II diabetes. The prime objective of the present research work was to formulate fast release tablet of metformin for prompt action by using SSG (Sodium starch glycolate), kollidon CL (Crospovidone) and Sodium carboxymethyl cellulose (Crosscarmellose Na) as super disintegrants. Wet granulation technique/method was performed for the tablet preparation, maize starch was used as a diluent, Povidone k-30 (PVK) as a binder, SSG, kollidon CL and Na-CMC as super disintegrants in different concentration (3-6%). Aerosol-200 (Colloidal silicon dioxide) to offer proper flow characteristics and magnesium salt of stearic acid called magnesium stearate as a lubricant. Formulations were prepared and evaluated for hardness pattern, thickness of tablet, diameter, friability, weight variation of tablet, disintegration time (DT) and *in-vitro* drug release profile. All the prepared formulations were compared for disintegration time (DT) and % drug release. All formulations are assessed for pre-compression and post-compression parameters. The outcome indicated that the prepared batch of metformin formulations containing SSG provides a short DT between 42 to 24 seconds, with adequate friability and satisfactory crushing strength.

***Key words*:** Super disintegration, Fast DT, Immediate release tablet

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INTRODUCTION:

Most common tablets are those intended to be swallowed whole and to disintegrate and release their API rapidly in the GIT [1]. The appropriate choice of disintegrant agents and its consistency of performance are of critical significance to the formulation development of such tablets [1]. The bioavailability of a API is dependent on in vivo disintegration time, dissolution, and various other physiological factors [2]. Superdisintegrants provide quick disintegration (DT) due to the combined effect of swelling and water absorption of the formulation. Due to swelling of superdisintegrant agents, the wetted surface of the carrier increases, which promotes/helps the wettability and dispersibility of the system, thus enhancing the disintegration, dissolution profile and oral bioavailability [3].

Metformin (MET) is an orally administered antihyperglycemic agent, used in the treatment of type II diabetes (NIDDM) and type I diabetes [4]. It is a very unpleasant API and highly aqueous soluble [4]. This work aims at the design a formulation with the immediate/rapid

release of Metformin. Different types of disintigrating agents (Sodium starch glycolate (SSG), Collidon CL, and Crosscarmellose Na) were investigated and evaluated for their efficacy in formulating such kind of dosage form. Metformin (500mg) was used as a model drug.

MATERIAL AND METHOD:

Materials:

Metformin Hydrochloride (MET), Povidon k -30, Na-Starch glycolate, kollidon CL (Crospovidone) Mg-stearate, Crosscarmallose-na/Sodium carboxymethyl cellulose, Starch, Aerosil-200 purchased from local vendor. Monopotassium phosphate and Disodium hydrogen phosphate heptahydrate collected from local vendor.

Formulations:

In this research work, few feasible formulations were prepared to take MET as a model drug and containing three super disintegrants such as SSG, crospovidone (kollidon CL), Sodium carboxymethyl cellulose formulation design summarized as table 1.

Table 1: Formulations of Metformin HCL Rapid release tablets.

Ingredients (mg)	Formulations								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Metformin	500	500	500	500	500	500	500	500	500
Starch	28	24	20	28	24	20	28	24	20
Povidon K30	32	32	32	32	32	32	32	32	32
SSG	10	14	18						
kollidon CL (Crospovidone)				10	14	18			
Sodium carboxymethyl cellulose							10	14	18
Aerosol 200	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mg. stearate	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5

Preparation of Metformin granules: [5, 7]

Granules preparation is done in a series of steps in the laboratory. At first the active drug (MET), diluent (starch) and exact amount of superdisintegrants are passed through a 40 mesh sieve to obtain uniform particles. Then, the API, superdisintegrants and the diluent under current investigation are appropriately weighed and mixed together for 15 minutes in a mortar and pestle. Then the binder solution is prepared by dissolving the above stated amount of

povidone k-30 in sufficient amount of distilled water. This solution is then added drop by drop to the mixture in the mortar. The mixture was constantly mixed in a clockwise direction. This mixing process is continued for a further 15 minutes until all the binding solution has been added. A uniform mixture of wet mass was obtained. Then the wet mass was then passed through16 mesh sieve to attain granules. The granules were dried in an oven to get dry granules at 55-60^0 C. Finally, these granules are mixed with the aerosil-200, superdisintegrant and magnesium stearate to obtain granules with the pre-requisite flow properties. The API and all the other excipients were taken in such amounts that at least 20 tablets of each formulation could be prepared.

Pre-compression Study/ Evaluation of Prepared Metformin Granules: [5, 7]

After preparation of granules pre-compression study like the angle of repose, bulk and tapped densities, compressibility index, Hausner ratio was performed.

Post-compression Study/ Assessment of some Physical Parameters of MET Tablet: [5, 7]

Post compression evaluation like diameter measurement, hardness, thickness, friability test, weight variation test and *in-vitro* dissolution study was performed.

In-vitro Dissolution Assay: **[5, 6, 7]**

Dissolution studies were carried out according to the USP method (USP XXII) using apparatus 2. In all cases the conditions were maintained to be exactly the same, i.e. the RPM was maintained at 90 while the temperature maintained always at 37^0±0.5C. Dissolution medium 900 ml of the prepared buffer was used. The dissolution was then set up with paddles and the tablets directly placed in the dissolution vessel. The example, 5 min, 10 min, 15 min, etc, 10 ml of sample was then withdrawn, at each withdrawal, 10ml of fresh dissolution medium (prepared buffer) was immediately added to maintain the sink condition. The dissolution study was carried out for one hour. This was performed to obtain a simulated picture of drug release profile in the in-vivo condition. The sample that was collected and filtered being assayed at 237 nm using a UV spectrophotometer. The amount of drug released was calculated with the help of a straight line equation obtained from the standard curve of Metformin at the same λmax 237 nm the percentage (%) of drug released in then calculated and plotted against time. This drug release profile was fitted into several mathematical models to get an idea of the release mechanism of the drug from the dosage form.

Model Dependent Analysis of the Dissolution data of the different MET formulations: [6]

Several kinetic models have been used to describe the release characteristics of a drug from a dosageform [6]. The dissolution release data of all the formulations are treated in these various pharmacokinetic models to find the probable mechanism of release of the drug from the dosage form. The dissolution release data's were fitted in the following four models like zero order kinetics, first order kinetics, higuchi plotting, korsmeyer plotting etc [6].

RESULT AND DISCUSSION:

Evaluation of Metformin granules*:* Granules are formulated by wet granules method and all the granules formulations were evaluated and assessed on different parameters and results are summarized as table 2. It is evident that all the formulations quite readily meet prerequisite criteria for showing good flow ability. Formulation F-4 and F-6 showed higher angle of repose, and lower compressibility index and Hausner ratio. The lowest value of bulk and tapped (0.374)

densities were shown for F-6, the lowest value of compressibility index and Hausner ratio was for F-5 and the lowest (26.571) value of angle of repose was given by F-7.

Table 2: Evaluation of formulated MET granules (during pre-formulation study) [7].

Formulation	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility Index (%)	Hausner ratio	Angle of Repose (Degrees)
F-1	0.408	0.523	21.81	1.32	28.247
F-2	0.389	0.522	22.69	1.35	31.588
F-3	0.379	0.547	28.59	1.39	29.955
F-4	0.384	0.479	19.85	1.27	33.28
F-5	0.315	0.395	19.95	1.21	32.79
F-6	0.276	0.374	26.92	1.34	33.49
F-7	0.409	0.539	21.88	1.32	26.571
F-8	0.413	0.508	20.82	1.25	28.239
F-9	0.399	0.515	22.60	1.29	28.257

Evaluation of tablets: All the formulated granules were compressed into tablets and tables are assessed for different acceptable parameters and all the outcomes are summarized as table 3.

Table 3: Evaluation of final MET tablets (Post Compression Study) [7].

Formulations	Average weight (gm.)	Average diameter (mm.)	Average thickness (mm.)	Average Friability (%)	Hardness (kg)
F-1	577.2	12.96	3.15	0.24	8.1
F-2	579.1	12.89	3.28	0.31	7.55
F-3	576.2	13.12	3.37	0.27	7.45
F-4	577.38	13.10	3.35	0.19	7.69
F-5	578.5	12.93	3.66	0.12	8.12
F-6	577.6	13.19	3.39	0.19	7.75
F-7	579.05	12.98	3.42	0.31	7.52
F-8	577.72	13.12	3.48	0.36	7.49
F-9	579.01	13.21	3.72	0.30	7.86

Theoretically the average weight of the formulated tablets of the different formulations should be 578±2 mg. Average weight and weight variation of MET tablets analysis follows the standard of pharmacopoeia [5, 7]. The average diameter was also found to be pretty much consistent varying insignificantly between the ranges of (12.89-13.21) mm. The average thickness of the prepared tablets also ranged within the acceptable range between (3.15-3.72) mm. On the contrary, friability of the MET tablets of different formulations varied greatly range from (0.12-0.36) % but in pharmacopoeial range [5, 7]. The friability was found to be the greatest for formulations F-8. This indicates maximum loss of tablets upon attrition. According to some authentic references the maximum friability range should be in between (0.5-1) % [5, 7]. As the friability values for none of the tablets exceed more than 1%, it does not pose any serious complications. Hardness of the tablets were varied widely ranging from (7.45-8.1) kg. Since hardness greater than 5.10 kg is considered acceptable, all the tablet formulations are therefore thought to show the desired requisite hardness [5, 7].

Disintegration test: After the above study tablet of all formulations were tested for disintegration and mean dissolution time. Results are summarized as table 4.

Table 4: Disintegration and Successive Mean DT (Disintegration Time) [5, 7]

Formulation		Amount (mg)	DT (Sec.)	$T_{25\%}$	$T_{50\%}$	$T_{80\%}$	MDT
SSG	F-1	10	2.3	0.51837	2.9804	15.5436	7.8562
	F-2	14	2.1	0.26127	2.32175	13.4805	8.1548
	F-3	18	1.94	0.11315	1.50425	8.40065	3.42658
Kollidon CL	F-4	10	2.58	1.17529	6.9545	21.7785	12.0356
	F-5	14	2.39	0.65126	4.90298	18.7658	10.8752
	F-6	18	2.29	0.45133	3.85215	17.3546	7.6585
Na CMC	F-8	10	2.75	2.23895	9.52356	24.4433	12.8464
	F-9	14	2.7	1.40344	6.76548	22.2175	11.0152
	F-9	18	2.46	1.22222	5.85356	18.4567	8.9658

From the table 4, it was seen that the lowest disintegration time (1.94) was found when SSG was used as a disintegrant and the highest disintegration time (2.75) was found when sodium CMC was used as a disintegrant. All disintegrating agents enhanced disintegration time. With respect to disintegration time, the following trend is observed amongst the disintegrants, SSG > Collidon CL > sodium CMC.

Dissolution and Drug Release Profile: Dissolution and total drug release profile was presented in figure 1 and table 5.

Table 5: Dissolution (%) and Release Profile of prepared MET tablets [7]

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	37.41	41.93	41.37	26.33	31.22	34.25	28.12	24.45	28.4
10	54.29	59.96	62.31	47.69	53.98	55.74	49.80	51.41	53.75
15	64.28	66.68	70.57	54.67	60.75	62.52	57.23	57.20	60.35
20	69.89	67.87	70.85	59.75	61.27	64.84	66.78	60.66	65.35
25	70.96	69.68	72.33	62.72	65.69	67.81	68.48	63.14	68.72
30	71.55	70.43	74.51	63.32	66.82	68.65	69.52	65.35	71.18
35	77.63	78.41	80.42	73.89	89.02	78.22	72.85	75.59	76.11
40	80.79	82.72	83.47	76.87	81.24	81.41	75.28	76.36	78.41
45	85.38	86.49	85.12	79.58	82.98	84.48	76.01	77.96	79.75
50	89.66	90.7	91.32	82.39	86.54	87.64	76.96	78.89	82.10
55	90.66	91.98	92.58	86.55	89.6	91.78	77.81	79.52	82.81
60	92.29	93.04	92.95	88.25	90.5	92.01	78.88	81.06	83.12

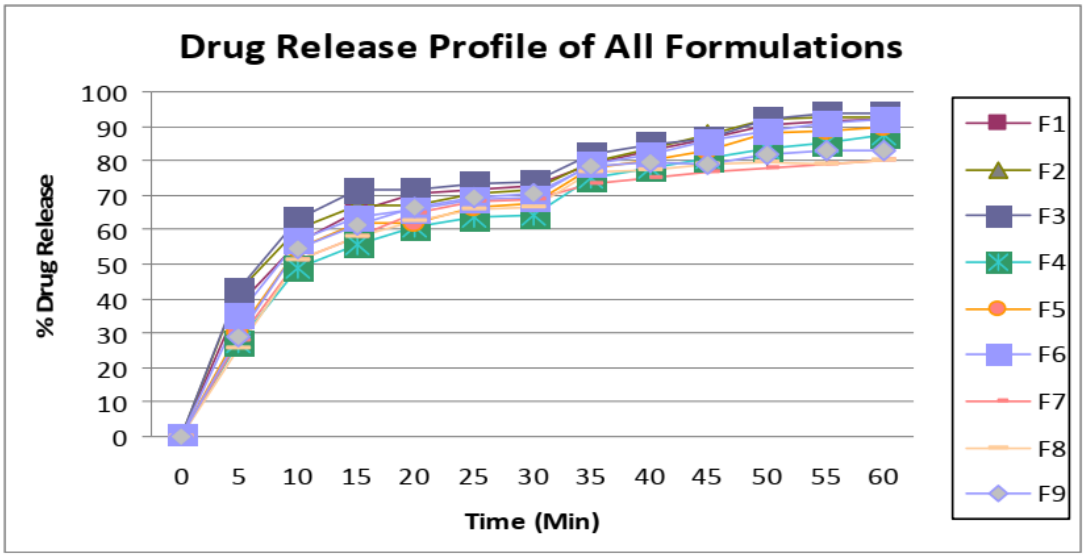

Figure 1: Drug release pattern of all formulations.

From the figure 1 and table 5, it was seen that the highest % of drug release (93.04) was found when Sodium Starch Glycolate(SSG) was used as a disintegrant and the lowest % of drug release

(78.88) was found when crosscarmellose sodium was used as a disintegrant. With respect to % of drug release, same trend like disintegration is observed amongst the disintegrants, SSG > Kollidon CL (Crospovidone) > Crosscarmellose sodium.

Model dependent drug release kinetics analysis was performed and findings are given as table 6. The tablet dissolution data's were fitted in the following four models like zero order kinetics, first order kinetics, higuchi plotting, korsmeyer poling etc.

Table 6: Summery of Drug (MET) Release Model kinetics [6]

Formulation	Zero Order		Higuchi		First Order		Korsmeyer	
	Ko	R^2	Kh	R^2	K1	R^2	n	R^2
F-1	2.56	0.698	15.88	0.937	-0.038	0.952	0.289	0.987
F-2	2.51	0.765	15.67	0.925	-0.029	0.923	0.263	0.985
F-3	2.49	0.682	15.96	0.845	-0.039	0.879	0.248	0.965
F-4	2.39	0.765	15.88	0.898	-0.029	0.928	0.372	0.935
F-5	2.48	0.698	15.97	0.975	-0.031	0.954	0.352	0.896
F-6	2.52	0.726	16.44	0.934	-0.032	0.983	0.339	0.936
F-7	2.37	0.786	14.96	0.972	-0.024	0.928	0.487	0.865
F-8	2.52	0.798	16.38	0.982	-0.032	0.962	0.426	0.896
F-9	2.67	0.763	16.69	0.938	-0.029	0.939	0.466	0.859

Formulation F1, F2, F3, F4, F5, F6 and F9 best fits with Higuchi (R^2) and First order (R^2) kinetic models near to identical magnitude and then with Korsmeyer (R^2) model. The value of release exponent obtained from Korsmeyer model, which indicates that the release pattern of MET from F1, F2, F3, F4, F5, F6 and F9 was followed Fickian diffusion/transport mechanism, which appears to indicate a Class 01 diffusion mechanism (Higuchi) [6, 7].

Formulation F7 best fits with Higuchi (R^2 = 0.954) and First order (R^2 = 0.907) kinetic models to same extent and then with Korsmeyer (R^2 = 0.887) model [6]. The value of release exponent obtained from Korsmeyer model is 0.487which indicates that the release pattern of MET from this formulation was followed Anomalous/non-Fickian transport mechanism [6]. Whereas F8 follows Higuchi model (R^2 = 0.982). The value of n for Korsmeyer release is 0.426. This value indicates that the drug was released by Anomalous/non-Fickian transport mechanism [6].

CONCLUSION

The *in-vitro* drug release profile of all prepared formulations was assessed and this *in-vitro* release studies demonstrated that, the release of Metformin HCL from all tablet formulations was generally fast. The prepared tablets conforming to good quality, displayed various drug release mechanisms. High concentration of superdisintegrants were used in the formulations caused high percent release of drug, while lower concentration caused low MET release. Thus, the release characteristics were significantly influenced by the characteristics and concentration of super disintegrants used. The release profile was also influenced by altering the type of disintegrants. Most release mechanism could be well illustrated by the Higuchi model with the release from tablets being class1 diffusion. Disintegration time (DT), % of in vitro drug release and dissolution time was also assessed/tested for all formulations. Again, the various mechanical and physical parameters of granules and formulated tablets such as the friability, flow properties, hardness, etc. were found to comply with the standards set by the different international organizations e.g. pharmacopeias. Thus the granules and tablets characteristics were satisfactory in terms of its physical parameters as well as the in vitro drug release profile from the instant release tablets.

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