

Original Research Article**EFFECT OF SUPERDISINTEGRATING AGENT ON THE RELEASE OF METFORMIN HCl FROM IMMEDIATE RELEASE TABLETS**

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ABSTRACT:

Immediate release tablet of Metformin HCl needs to formulate for emergency treatment of type-II diabetes. The prime objective of the present research was to formulate immediate release tablet of Metformin HCL for rapid action by using Sodium starch glycolate, Collidon CL and Crosscarmellose Na as super disintegrants. Wet granulation method was adapted for the tablet preparation, maize starch used as a diluent, Povidone k-30 as a binder, sodium starch glycolate, collidon CL and crosscarmellose Na as super disintegrants in different concentration (2-5%). Aerosol -200 to provide proper flow characteristics and magnesium stearate as a lubricant. Total nine formulations were prepared and evaluated for hardness, thickness, diameter, friability, weight variation, disintegration time and *in-vitro* drug release. All the formulations were compared for disintegration time and % drug release. All formulations are evaluated for pre-compression and post-compression parameters. The result obtained showed that the selected batch of tablet formulations containing sodium starch glycolate provides a short DT between 40 to 22 seconds, with sufficient crushing strength and acceptable friability.

Key words: Super disintegration, Metformin, Immediate release tablet

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INTRODUCTION:

Most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract (GIT). The proper choice of disintegrant and its consistency of performance are of critical importance to the formulation development of such tablets [1]. The bioavailability of a drug is dependent on *in vivo* disintegration, dissolution, and various physiological factors [2]. Superdisintegrants provide quick disintegration due to the combined effect of swelling and water absorption of the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system, thus enhancing the disintegration, dissolution and bioavailability [3].

Metformin hydrochloride is an orally administered antihyperglycemic agent, used in the management of type II diabetes (NIDDM) and type I diabetes (IDDM). It is a very bitter drug and highly soluble in water [4]. This work aims at the design a formulation with the immediate

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

MATERIAL AND METHOD:

Materials:

Metformin Hydrochloride, Starch, Povidon k -30, Na-Starch glycolate, Collidon CL, Crosscarmallose-na, Aerosil -200 and Mg-stearate from ACI pharmaceuticals limited, Bangladesh. Potassium Di-hydrogen orthophosphate and Di-Sodium hydrogen orthophosphate collected from UAP laboratories.

Formulations:

In this research work, nine (09) probable formulations were designed to take Metformin Hydrochloride as a model drug and containing three super disintegrants such as Na-starch glycolate, Collidon CL, Crosscarmallose sodium formulation design summarized as table 1.

Table 1: Formulations of Metformin HCL immediate release tablets.

Ingredients (mg)	Formulations								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Metformin HCl	500	500	500	500	500	500	500	500	500
Starch	27.2	23.2	19.2	27.2	23.2	19.2	27.2	23.2	19.2
Povidon K30	30	30	30	30	30	30	30	30	30
Na. Starch Glycolate	12	16	20						
Collidon CL				12	16	20			
Crosscarmallose Na.							12	16	20
Aerosol 200	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8
Mg. stearate	6	6	6	6	6	6	6	6	6
Total (mg)	578	578	578	578	578	578	578	578	578

Preparation of granules: [5]

Granules preparation is done in a series of steps in the laboratory. At first the active drug (Metformin HCl), diluent (Starch) and $\frac{3}{4}$ of stated amount of superdisintegrants are passed through a 40 mesh sieve to obtain fine particles. Then, the active drug, superdisintegrants and the diluent under current investigation are appropriately weighed and mixed together for 10 minutes in a mortar. Then the binder solution is prepared by dissolving the above stated amount of

povidone k-30 in sufficient amount of water. This solution is then added drop by drop to the dry mixture in the mortar. During this addition the mixture is continuously mixed in a clockwise direction, an action. This mixing process is continued for a further 10 minutes until all the binding solution has been added. At the end of this mixing, a uniform mixture of wet mass is obtained. Then the wet mass is then passed through a 16 mesh sieve to obtain granules. The granules were dried in an oven to get dry granules at 60⁰ C. Finally, these granules are mixed with the above declared quantities of aerosil-200, 1/4 superdisintegrant and magnesium stearate to obtain granules with the pre-requisite flow properties. The active drug and all the other excipients were taken in such amounts that at least 40 tablets of each formulation could be prepared.

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

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

Post-compression Study/ Measurement of some Physical Parameters: [5, 7]

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

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

Dissolution studies were conducted 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 100 while the temperature maintained always at 37⁰±0.5C. Dissolution medium 900 ml of the prepared buffer was poured. 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, 10ml of sample was then withdrawn, at each withdrawal, 10ml of fresh dissolution medium was immediately added to maintain the sink condition. The dissolution was carried out for one hour. This was done to get a simulated picture of drug release in the in-vivo condition. The sample that was collected was first filtered, and then diluted, being assayed at 233 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 HCL at the same λ_{max} the percentage of drug released in thus 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 formulations: [6]

Several kinetic models have been proposed to describe the release characteristics of a drug from a dosage form. The dissolution data of all the formulations are treated in these various pharmacokinetic models to identify the probable mechanism of release of the drug from the dosage form. The dissolution data's were fitted in the following four models like zero order kinetics, first order kinetics, Higuchi plotting, Korsmeyer plotting etc.

RESULT AND DISCUSSION:

Evaluation of granules: Granules are prepared by wet granules method and all the granules of 09 formulations were evaluated on different parameters and results are summarized as table 2. It is evident from the table 2, that all the above formulations quite readily meet prerequisite criteria for showing good flowability. Formulation F 04 and F 06 showed higher angle of repose, and lower compressibility index and Hausner ratio. The lowest value of bulk and tapped

densities was given by F 06, the lowest value of compressibility index and Hausner ratio was given by F 05 and the lowest value of angle of repose was given by F 07.

Table 2: Evaluation of granules (during pre-formulation study).

Formulation	Bulk density (gm/cm ³)	Tapped density (gm/cm ³)	Compressibility Index (%)	Hausner ratio	Angle of Repose (Degrees)
F 01	0.412	0.533	22.70	1.29	29.248
F 02	0.396	0.519	23.70	1.31	32.619
F 03	0.381	0.54	29.63	1.42	30.963
F 04	0.380	0.476	20.17	1.25	34.25
F 05	0.317	0.397	20.15	1.25	33.89
F 06	0.272	0.37	27.03	1.37	34.56
F 07	0.412	0.533	22.70	1.29	27.474
F 08	0.411	0.512	21.88	1.28	29.248
F 09	0.396	0.519	23.70	1.31	29.248

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

Table 3: Post Compression Study/Evaluation of tablets.

Formulations	Average weight (gm.)	Average diameter (mm.)	Average thickness (mm.)	Average Friability (%)	Hardness (kg)
F 01	578	13.05	3.22	0.26	7.93
F 02	576	13.04	3.3	0.26	7.63
F 03	578	13.27	3.41	0.25	7.53
F 04	576	13.05	3.42	0.17	7.42
F 05	579	13.22	3.69	0.14	7.53
F 06	579	13.2	3.46	0.15	7.63
F 07	576	13.06	3.36	0.24	7.42
F 08	579	13.2	3.46	0.32	7.53
F 09	578	13.18	3.67	0.27	7.63

Theoretically the average weight of the tablets of the different formulations should be 578 mg. Average weight and weight variation analysis follows the standard of pharmacopoeia. The average diameter was also found to be pretty much consistent varying insignificantly between the ranges of (13.04-13.27)mm. The average thickness of the tablets also ranged between (3.22-3.69)mm; however the variations were not alarming, result remained within the acceptable range. On the contrary, friability of the tablets of different formulations varied greatly range from (0.14-0.32) % but in pharmacopoeial range. The friability was found to be the greatest for formulations F 09. This indicates maximum loss of tablets upon attrition. According to some authentic references the maximum friability range should be in between (0.5-1)%. As the friability values for none of the formulations exceed 1%, it does not pose any serious problems. Hardness of the tablets of the different formulations varied widely ranging from (8.42-8.93)kg. Since hardness greater than 5.10 kg is considered acceptable, all the formulations are therefore thought to show the desired requisite hardness.

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 Disintegration Time

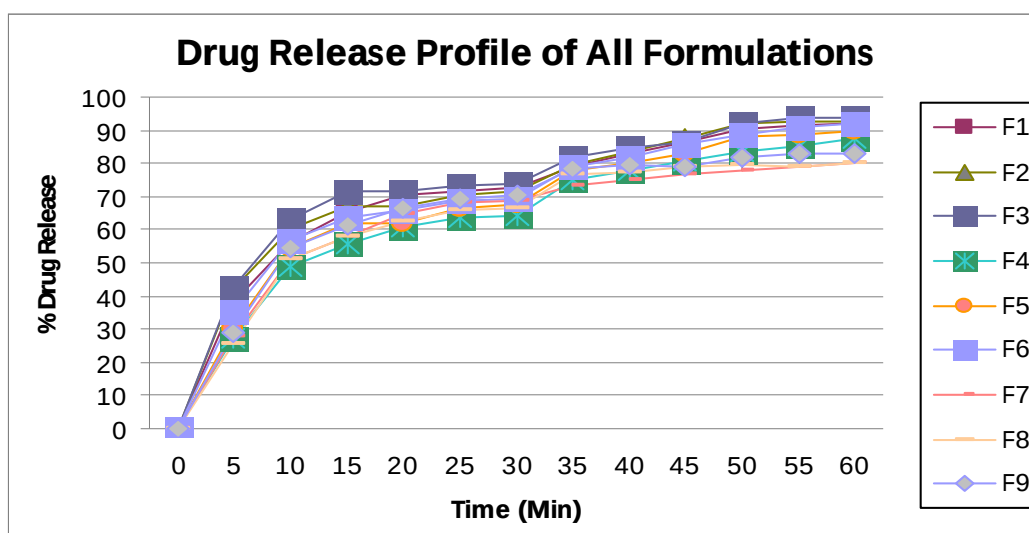
Formulation		Amount	DT	T _{25%}	T _{50%}	T _{80%}	MDT
		(mg)	(Sec.)				
Sodium starch glycolate	F01	12	2.2	0.41938	3.7604	16.6412	8.09641
	F 02	16	2	0.16019	2.35189	14.5405	7.08173
	F 03	20	1.9	0.10426	1.51496	9.30054	4.52848
Collidon CL	F 04	12	2.6	1.18329	6.9035	22.8275	11.3629
	F 05	16	2.4	0.64628	4.96364	19.7767	9.6729
	F06	20	2.3	0.47039	4.13163	18.0311	8.77679
Crosscarmellose sodium	F 08	12	2.8	2.25705	9.53637	25.3366	13.0862
	F 09	16	2.6	1.43441	7.16339	21.3165	10.7746
	F09	20	2.4	1.23111	6.36263	19.3791	9.75866

From the table 4, it was seen that the lowest disintegration time (1.90) was found when sodium starch glycolate was used as a disintegrant and the highest disintegration time (2.60) was found when Crosscarmellose sodium was used as a disintegrant. All disintegrating agents enhanced disintegration time. With respect to disintegration time, the following trend is observed amongst the disintegrants, Sodium starch Glycolate > Collidon CL > Crosscarmellose sodium.

Dissolution and Drug release Profile: Dissolution and total drug release profile summerized in figure 1 and table 5.

Table 5: Dissolution and Drug Release Profile

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	38.23	41.93	42.48	27.24	30.21	35.05	27.61	25.75	29.1
10	56.31	60.06	63.23	48.74	54.72	56.63	50.97	50.95	54.34
15	65.3	67.23	71.55	55.78	61.83	63.77	58.04	58.02	61.45
20	70.32	67.23	71.36	60.8	62.02	65.63	64.92	62.67	66.47
25	71.8	70.56	73.11	63.76	66.72	68.72	67.95	66.04	69.54
30	72.57	71.31	73.89	64.44	67.62	69.45	68.68	66.75	70.29
35	78.73	79.32	81.55	74.98	77.64	79.11	73.31	76.57	78.66
40	82.84	83.74	84.44	77.92	80.16	82.02	75.08	77.27	79.37
45	86.45	87.55	86.08	80.69	83.22	85.66	76.67	78.88	79.01
50	90.12	91.8	92.27	83.28	87.83	88.48	77.89	79.49	81.97
55	91.7	92.86	93.68	85.49	88.7	90.89	78.91	79.1	82.76
60	91.9	92.86	93.81	87.49	89.7	91.89	79.91	80.1	82.76

**Figure 1: Drug release pattern of all formulations.**

From the figure 1 and table 5, it was seen that the highest % of drug release (93.81) was found when sodium starch glycolate was used as a disintegrant and the lowest % of drug release

(79.91) 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, Sodium starch Glycolate > Collidon CL > Crosscarmellose sodium.

Model dependent drug release kinetics analysis was performed and results are summarized as table 6. The dissolution data were fitted in the following four models like zero order kinetics, first order kinetics, Higuchi plotting, Korsmeyer plotting etc.

Table 5: Summary of Drug Release Model kinetics

Formulation	Zero Order		Higuchi		First Order		Korsmeyer	
	Ko	R ²	Kh	R ²	K1	R ²	n	R ²
F 01	2.58	0.724	16.87	0.935	-0.034	0.931	0.316	0.923
F 02	2.48	0.666	16.64	0.902	-0.032	0.875	0.258	0.894
F 03	2.52	0.648	16.98	0.889	-0.035	0.829	0.259	0.843
F 04	2.45	0.772	15.68	0.955	-0.025	0.918	0.393	0.917
F 05	2.46	0.724	16.04	0.931	-0.027	0.889	0.34	0.882
F 06	2.49	0.712	16.35	0.927	-0.029	0.895	0.319	0.89
F 07	2.4	0.796	15.08	0.954	-0.021	0.907	0.481	0.887
F 08	2.56	0.779	16.27	0.952	-0.027	0.925	0.431	0.893
F 09	2.63	0.773	16.78	0.951	-0.03	0.934	0.422	0.891

Formulation F 01, F02, F03, F04, F05, F06 and F09 best fits with Higuchi (R^2) and First order (R^2) kinetic models near to same extent and then with Korsmeyer (R^2) model. The value of release exponent obtained from Korsmeyer model, which indicates that the release pattern of Metformin HCL from F 01, F02, F03, F04, F05, F06 and F09 was followed Fickian transport mechanism, which appears to indicate a Class 01 diffusion mechanism (Higuchi).

F 07 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. The value of release exponent obtained from Korsmeyer model is 0.481 which indicates that the release pattern of Metformin HCL from F 07 was followed Anomalous/non-Fickian transport mechanism. Whereas F 08 follows Higuchi model ($R^2 = 0.952$). The value of n for Korsmeyer release is 0.431. This value indicates that the drug was released by Anomalous/non-Fickian transport mechanism.

CONCLUSION

The in-vitro drug release profile of all formulations was evaluated and this *in-vitro* release studies demonstrated that, the release of Metformin HCL from all tablet formulations was generally immediate. The tablets conforming to good quality, displayed various drug release mechanisms. High concentration of super disintegrants used in the formulations caused high percent release of drug, while lower concentration caused low release. Thus, the release characteristics were significantly influenced by the characteristics and concentration of super disintegrants used. The release characteristics were also influenced by changing the type of disintegrants. Most release mechanism could be well depicted by the Higuchi model with the release from tablets being class 1 diffusion. Disintegration time, % of drug release and dissolution time was also observed for all formulations. Again, the various mechanical and physical parameters of granules and tablets such as the flow properties, hardness, friability etc. were seen to comply with the standards set by the different international organizations e.g. pharmacopeias. Thus the granules and tablets were found satisfactory in terms of its physical parameters as well as the drug release profile from the immediate release tablets.

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