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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 ofMetformin HC l 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 Collidon CL and ,Sodium starch glycolate Crosscarmellose Na as super disintegrants.Wet granulationmethod was adapted for the tablet preparation, m aizes tarchused as a diluent, as a binder 30-Povidone k, sodium starch ,glycolatec ollidon CL andcrosscarmellose Na as super disintegrants in different concentration (2-5%). Aerosol -200 to provide proper flow characteristics and m.agnesium stearate as a lubricant Total nine formations were prepared and evaluated for hardness, t ,hicknessd,iameter 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

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 typesand ,Collidon CL ,Sodium starch glycolate) f disintigrating agentso (Crosscarmellose Nawere 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, 30- Povidon k, Starch glycolate-Na, ,Collidon CL na-Crosscarmallose, 200- Aerosil and stearate-Mg from ACI pharmaceuticals limited, Bangladesh. hydrogen orthophosphate-Potassium Di and Sodium hydrogen -Di orthophasphate collected from UAP laboratories.

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Table 1 Amount (g) and % yield of extracts of *Hypericum ericoides*

Formulations:

,In this research work nine (09)probable formulations were designed to take Metformin Hydrochloride as a model drug and c ontaining threesstarch -uper disintegrants such asNa Crosscarmalose ,Collidon CL,glyccolate 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) and¾of superdisintegrants stated amount of 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 povidone30-k in sufficient amount of .waterThis 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 60^0 C. Finally, these granules are mixed with the above declared quantities of a 4/1 ,200-erosil 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/:Mesurement 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 37^0±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, ,min 15 ,min 10 ,min 5etc, 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;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 formolations: [6]

ribe the release characteristics of a drug Several kinetic models have been proposed to desc The dissolution data of all the formulations are treated in these various .from a dosageform pharmacikinetic models to identify the probable mechanism of release of the drug from the s were fitted in the following four models like zero order ,aThe dissolution dat.dosage form .korsmeyer poling etc ,higuchi plotting ,first order kinetics ,kinetics

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,ite that all the above formulations quite readily meet prerequis 0 Formulation F .crieteria for showing good flowability4showed higher angle of 06 and F ,reposeand lower The lowest value of bulk and .compressibility index and Hausner ratio x and Hausner the lowest value of compressibility inde ,06 tapped densities was given by F .07 and the lowest value of angle of repose was given by F 05 ratio was given by F

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

Formulation	Bulk density (^{3}cm/gm)	Tapped density (^{3}cm/gm)	Compresibility (%) Index	Hausner ratio	Angle of Repose (Degrees)
01 F	0.412	0.533	22.70	1.29	29.248
02 F	0.396	0.519	23.70	1.31	32.619
03 F	0.381	0.54	29.63	1.42	30.963
04 F	0.380	0.476	20.17	1.25	34.25
05 F	0.317	0.397	20.15	1.25	33.89
06 F	0.272	0.37	27.03	1.37	34.56
07 F	0.412	0.533	22.70	1.29	27.474
08 F	0.411	0.512	21.88	1.28	29.248
09 F	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	793.
F 02	576	13.04	3.3	0.26	763.
F 03	578	13.27	3.41	0.25	753.
F 04	576	13.05	3.42	0.17	742.
F 05	579	13.22	3.69	0.14	753.
F 06	579	13.2	3.46	0.15	763.
F 07	576	13.06	3.36	0.24	742.
F 08	579	13.2	3.46	0.32	753.
F 09	578	13.18	3.67	0.27	763.

578 Theoritically the average weight of the tablets of the different formulations should be .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 The average thickness of the tablets also ranged .mm(13.27-13.04) between the ranges of however the variations were not alarming ;mm(3.69-3.22) between, resultremained within .the acceptable range Ofriability of the tablets of different formulations varied ,n the contrary % (0.32-0.14) greatly range from but in pharmacopoeial rangeThe friability was found to be . .This indicates maximum loss of tablets upon attrition.09 the greatest for formulations F According to some authentic references the maximum friability range should be in between As the friability values for none of the formulations exceed .%(1-0.5)1it does not pose ,% Hardness of the tablets of the different formulations varied widely .any serious problems) ranging from8-42.8all ,eptablekg is considered acc 5.10 Since hardness greater than.kg(93. .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

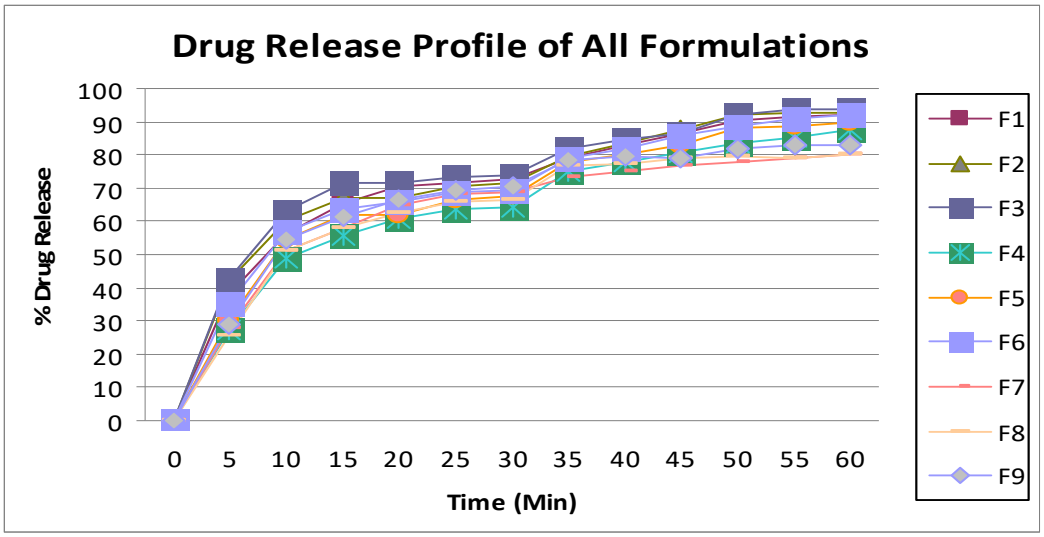
Formulation		Amount (mg)	DT (Sec.)	T 25%	T 50%	T 80%	MDT
Sodium starch glycolate	F01	12	2.2	0.41938	3.7604	16.6412	8.09641
	F 02	16	2	0.16019	2.35189	14.5405	7.08173
	F 03	20	1.9	0.10426	1.51496	9.30054	4.52848
Collidon CL	F 04	12	2.6	1.18329	6.9035	22.8275	11.3629
	F 05	16	2.4	0.64628	4.96364	19.7767	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,was found when (1.90) it was seen that the lowest disintegration time (2.60) sodium starch glycolate was used as a disintegrant and the highest disintegration time .was used as a disintegrant was found when Crosscarmellose sodium All disintegrating agents enhanced disintegration time. the following trend is ,With respect to disintegration time observed amongst the disintegrants, < Collidon CL < Sodium starch Glycolate .Crosscarmellose sodium

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

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.



) of drug release % it was seen that the highest ,5 and table 1 From the figure93.81was (of drug % found when sodium starch glycolate was used as a disintegrant and the lowest 79.) release91With .was found when Crosscarmellose sodium was used as a disintegrant (,of drug release % respect tosametrend like disintegrationis observed amongst thedisintegrants, .Crosscarmellose sodium < Collidon CL < Sodium starch Glycolate

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

Table 5: Summery 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 F0 1, 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 F01 , F02, F03, F04, F05, F06 and F09 was followed Fickian transport mechanism, which appears to indicate a diffusion 01 Class mechanism (Higuchi).

F07 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 F07 was followed Fickian-non/Anomalous 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 byFickian-non/Anomalous transport mechanism.

CONCLUSION

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

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