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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF METFORMIN HYDROCHLORIDE ON LABORATORY SCALE

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ABSTRACT
The purpose of this research is to prepare metformin hydrochloride immediate release tablets by wet granulation technique. In order to obtain the best, optimized product ten different formulations were developed. Different binder, disintegrants and lubricants taken as variables. Weight variation, thickness, hardness, friability, disintegration time, *in-vitro* release and pharmaceutical assay were studied as response variables. Capping was observed in formulation containing PVP K-30. However, in the remaining formulation containing PVP K-90, no capping was observed. The formulation A7 was selected as optimized formulation. The different physical properties and *in-vitro* release profile showed best comparable with the reference product. Optimization has proven an effective tool in product development.
***Keywords*:** Metformin hydrochloride, optimization, anti-diabetic drug.

1. Introduction

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs. Various dosage forms administered orally, the tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids, and because it is more tamperproof than capsules[1-2]. The bioavailability of drug is dependent on in vivo disintegration, dissolution, and various physiological factors. In recent years, scientists have focused their attention on the formulation of quickly disintegrating tablets. The task of developing rapidly disintegrating tablets is accomplished by using a suitable diluent and super disintegrants. The gastrointestinal tract provides sufficient fluid to facilitate disintegration of the dosage form and dissolution of the drug. The large surface area of gastric mucosa favors the drug absorption. Therefore, the oral route has continued to be the most appealing route for drug delivery despite the advancements made in the new drug delivery systems. Banker and Anderson stated that at least 90% of all drugs used to produce systemic effect are administered orally[3].

Metformin is an oral anti-diabetic drug from the biguanide class. It is the first-line drug for the treatment of type-II diabetes, particularly in overweight and obese people and those with normal kidney function, and evidence suggests it may be the best choice for people with heart failure[3-4].

The main use for metformin is in the treatment of diabetes mellitus Type-II, especially when this accompanies obesity and insulin resistance. metformin is the only anti-diabetic drug that has been proven to protect against the cardiovascular complications of diabetes. This was first shown in the United Kingdom Prospective Diabetes Study, a large study of overweight patients with diabetes. Unlike the other most-commonly prescribed class of oral diabetes drugs, the sulfonylurea, metformin (taken alone) does not induce hypoglycemia. Hypoglycemia during intense exercise has been documented, but is extremely rare. It also does not cause weight gain, and may indeed produce minor weight loss. metformin also modestly reduces LDL and triglyceride levels.

Despite decades of clinical use, the molecular mechanisms by which metformin acts still have not been definitively determined and many more mechanisms will be elucidated. Unlike secretagogues, metformin has no effect on plasma insulin concentration increases, and due to reduction in glucotoxicity it has an indirect effect on beta cell secretory function[5].

The objective of the present study was to develop Telmisartan (IR) immediate release tablets using super disintegrants like

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croscarmellose sodium and sodium starch glycolate, which is best comparable with the innovator product by varying different excipients.

2. Materials and Methods

2.1 Materials: Metformin hydrochloride, sodium starch glycolate, croscarmellose sodium, povidone k-30, povidone k-90, hypromellose2910 (6cps), magnesium stearate, sodium stearyl fumarate, microcrystalline cellulose and PEG-400 were obtained from Torrent Research Centre, Gandhinagar. All reagents and solvents used were of analytical grade satisfying pharmacopoeial standards.

2.2 Methods.

2.2.1 Preparation of Metformin HCl Immediate Release Tablets: Wet granulation technique will ensure uniform distribution of drug as well as improve flow property. Therefore, this approach was carry forward for formulation development of metformin Tablets.

2.2.2 Granulation: Granules were prepared by using the rapid mixture granulator. Binder solution was added to the dry mix of the drug and excipients for 2-3 mins with impeller fast and chopper off. Kneading was given for 1-2 minutes with impeller fast and chopper fast.

2.2.3 Drying: Wet mass was dried at inlet air temperature 45 º ± 7 ºC till to get LOD NMT 1.5% w/w.

Sizing: Granules were passed through Oscillating granulated fitted with 0.8 mm SS Screen of oscillating granulator. The granules were collected into poly bag. Yield of sized granules was recorded and particle size distribution test was performed.

2.2.4 Final mixing and Tablet compression: Screened granules were finally blended with lubricants using a suitable mixer with a revolution of 10 rpm for about 15 min thus producing the final mixture. Using a suitable rotary tablet press the final mixture for tablet compression is compressed into tablets. The target weight is 720 mg containing metformin HCl (500 mg).

Dissolution profiles of different formulation are summarized in Figure. 1 and 2. Formulation A1 and A2 showed slow disintegration and also delayed in dissolution. Formulation A3, A4 and A5 were prepared with different disintegrants with different concentration. Trial batch A5 showed good disintegration and dissolution i.e. 83.4 % in 0.1 N

Parameters	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**
Disintegration (min)	8	8	5-6	5 -6	4	4	3	3-4	4-5	4-5
Hardness (N)	128.9	131.5	138.5	136.4	136.4	138.9	141.5	142.9	141.5	141.8
Friability (%)	0.07	0.09	0.07	0.09	0.09	0.09	0.08	0.09	0.08	0.10
Assay (%)	94.5	97.3	95.2	97.6	98.5	98.1	97.6	95.1	94.2	96.1
Weight of the tablet (mg)*	721.4	720.6	720.2	721.6	720.8	720.6	720.2	721.2	720.8	720.14

*Average of 10 tablets

Ingredients (mg)	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**
Metformin HCl	500	500	500	500	500	500	500	500	500	500
Microcrystalline cellulose	150	--	150	150	140	140	130	130	122	122
Dibasic calcium phosphate	--	150	--	--	--	--	--	--	--	--
Croscarmellose sodium	32	32	12	32	42	42	42	42	42	42
Sodium starch glycolate	--	--	20	--	--	--	--	--	--	--
Povidone k-30	30	30	30	30	30	--	--			
Povidone k-90	--	--	--	--	--	30	40	40	40	40
Water	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Magnesium stearate	8	8	8	8	8	8	8	--	16	--
Sodium stearyl fumarate	--	--	--	--	--	--	--	8	--	16
Total	**720**	**720**	**720**	**720**	**720**	**720**	**720**	**720**	**720**	**720**

2.3 Stability Study

The selected batch (A7) was kept at 40°C with 75% RH and the samples were withdrawn at 30 and 60 days for physical and *in vitro* evaluation of drug release [6] .

3. Result and Discussion

All the tablet formulations showed acceptable pharmacotechnical properties and complied with the range specified by US Pharmacopoeia for Disintegration, weight variation, friability, hardness, LOD and Water Content. (Shown in Table 3)

HCl Trial batch A6 and A7 were taken with sized API through 0.3 mm and 0.5 mm screen. Batch A7 gives better dissolution and disintegration. Trial batch A8, A9 and A10 were taken with different concentration of lubricant extragranularly. Here we found one important observation that increased quantity of lubricant produce poor release at last point of time

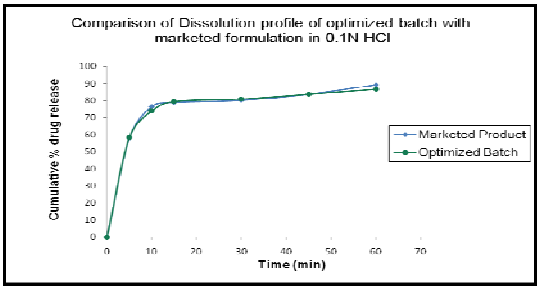

Figure 3 Comparison of dissolution profile of optimized batch with marketed formulation.

Dissolution profile of optimized batch A7 compared with dissolution profile of marketed formulation, indicated in Figure 9.7 and 9.8.

The formulations had a residual drug content of more than 100% after 1 month when stored at 40° C / 75 % RH. These results indicated that the selected formulation is stable. Also, the aged samples showed no change in the physical appearance, hardness or drug content.

Conclusion

The drug release profile for batch A7 (almost similar to the innovator) as indicated by very high F2 value (similarity factor), very low F1 value (dissimilarity factor) and other physical attributes of the dosage form.

This tablet can be commercial by making various optimizations in the present formulation. The *in-vivo* drug release can be checked and

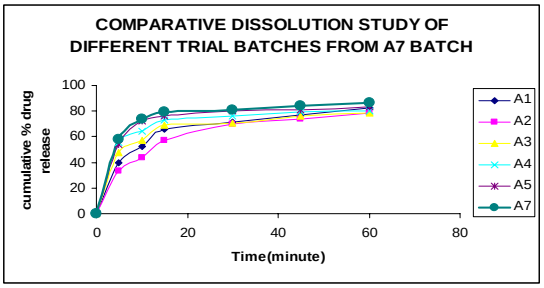

Figure 1 Comparative Dissolution Study of A1 to A5

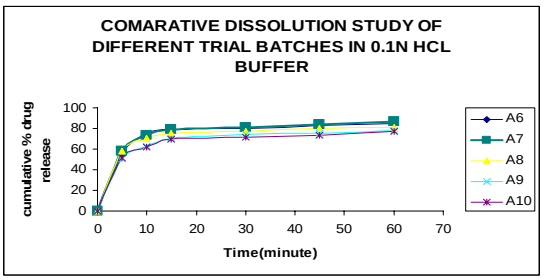

Figure 2 Comparative Dissolution Study of A6 to A10

toxicity study maybe also carried out. By making the combination with some new drug the novel formulation can be developed**.**

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