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Preparation and *In-vitro* Evaluation of Metformin HCl Tablets Containing Sustained Release Beads for Increasing Therapeutic Window

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Abstract

The purpose of present investigation was to develop the dosage form containing metformin for both immediate and sustained release. The SR release tablets of metformin were not useful to control the fasting glucose levels whereas conventional metformin tablets cannot acts for prolonged time, But the tablets prepared by present method useful for control both fasting glucose levels and maintenance dose. Even though many combination therapies available in market as metformin for sustain release and other sulfonylureas for immediate release, The primary concern for considering metformin hydrochloride as monotherapy was its efficient activity, less cost and negligible cardiac risk factors. The immediate release dose was developed by direct compression method and sustained release beads were prepared by inotropic gelation method using sodium alginate and sodium CMC, $CaCl_2$.

The various batches of directly compressed tablets with different percentages of sustained release beads were prepared and evaluated for various physical properties and dissolution profile. Hardness (kg/cm^2) of tablets was decreased and percentage loss in friability is increased as concentration of beads in tablet increased. All the parameters are within range for tablets containing micro beads up to 35% thereafter loss in friability and Hardness (kg/cm^2) are not within range.

Keywords: Metformin HCl; Immediate release; Sustained release beads; Sodium alginate; Sodium CMC; $CaCl_2$; Direct compression

Introduction

The successful optimization and development of drug entity, design of dosage form plays important role. The design of effective drug delivery systems has recently become an integral part of the development of new medicines. Hence, research continuously keeps on ways to develop suitable drug delivery for particular disease. Diseases like diabetes need much attention than others since the glucose levels tends to increase after meal and these glucose levels should maintain for whole the day for proper body activity [1], so an effective dosage form needed which can sub stand for both fasting glucose levels and maintaining glycemic levels all the day. The present dosage form is effectively useful in this case since it contains both immediate release dose for maintaining fasting glucose level and an SR dose for better glycemic control in diabetic starter patients and pre diabetic patients.

The main problem faced in the treatment of type II diabetes mellitus includes cardio vascular risk factors and hypoglycemia. In this aspect metformin is old and extensively preferable first line agent having not only anti hyperglycemic properties but also negligible cardio vascular risks compared with sulfonylurea's [2,3]. The recent studies on metformin show the drug having improvements in endothelial dysfunctioning, hemostasis and oxidative stress, insulin resistance, lipid profiles and fat redistribution. These properties gives decreased adverse cardiovascular out comes of metformin. Apart from these metformin shows anti proliferative role in cancer [3,4] and neuro-protective effect, also plays a potential role in a variety of insulin resistant diabetes mellitus, pre diabetic state [4], and other metabolic abnormalities associated with HIV disease and gestational diabetes [5-7]. Metformin's negligible risk of hypoglycemia in monotherapy and few drug interactions of clinical relevance give this drug a high safety profile.

Metformin hydrochloride is an oral anti hyperglycemic agent used to treat patients with type II diabetes mellitus and it is a first drug of choice in majority of type II diabetic patients. Metformin is chemically (N-N – dimethyl imido dicarbon imidic diamide hydrochloride) [8] belongs to class of biguanides. Metformin is highly hydrophilic drug its oral bioavailability is 50 to 60% [9] and it is having a plasma elimination half-life of 6.2 hours [10-15] with a peak plasma concentration of 4.8 hours.

Materials and Methods

Materials

Metformin HCl and sodium CMC were obtained from Yarrow Chem. Products, Mumbai. Sodium Alginate, Calcium Chloride were purchased from Himedia lab. Avicel pH101, Aerosil, cross povidone and calcium chloride were procured from Reachem Laboratory Chemicals Pvt. Ltd., Chennai, India. All the chemicals were of analytical grade.

Machinery used

UV Spectroscopy (Elite UV- 150 double beam spectrophotometer), SEM Analysis(JEOL Model JSM - 6390LV), Tablet compression machine (Elite Scientific & Equipments), Monsanto Hardness (kg/cm^2) tester (Elite), Vernier calliper (Elite), Roche friabilty tester (M/s. Elite Scientific & Equipments), Dissolution test apparatus(M/s Lab India: Model – DS 8000).

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Methods

Calibration curve of metformin HCl

Calibration curve of metformin HCl was prepared in 0.1N HCl and phosphate buffer of pH 6.8 at using spectrophotometric method at absorbance 232 nm of UV region.

Preparation of sustained release beads of metformin: The micro beads were prepared by ionic gelation method and tablets were prepared by direct compression. The prepared tablets were studied for various physical parameters like Hardness (kg/cm^2), weight variation, friability and in-vitro dissolution profile.

Various batches of drug loaded micro beads were prepared by ionotropic gelation method as shown in Table 1.

Initially sodium alginate and sodium CMC (1:1) were taken in a beaker containing deionized water. Contents are allowed to stir for 10 minutes with gentle heat using magnetic stirrer. Then accurately weighed quantity of metformin hydrochloride was added to solution and allowed stir for 15 minutes. This dispersion was added drop wise via a 20 gauge needle fitted with syringe into a 100 ml of 5% $CaCl_2$ solution. The formed alginate beads were allowed to harden for 20 minutes. Then beads were filtered and washed with deionized water and dried in a hot air oven 60°c for 2 hours [16-20].

Preparation of tablets containing SR micro beads: All the ingredients (Metformin Hcl, Avicel pH 101, Cross povidone, Aerosil in required quantities) as shown in Table 2 were mixed, and then various percentages of sustained release beads and 2% magnesium stearate, talc were added and compressed into tablets [21-27]. All the dosage forms were compressed at similar conditions but the final dosage form was selected based on drug release profiles.

Evaluation of microspheres

SEM analysis: The particle size, shape and surface morphology of microspheres were examined by scanning electron microscopy. Microspheres were fixed on aluminium studs and coated with gold using a sputter coater SC 502, under vacuum (0.1 mmHg). The microspheres were then analyzed by SEM (Figure 1).

Water uptake determination: A known weight (60 mg) of microspheres were placed in distilled water or phosphate buffer (pH 6.8) and shaken occasionally at room temperature (37°C). Due to shaking the separation of Microspheres will takes place, The microspheres were removed, blotted with filter paper and their changes in weight were measured. The water uptake can be calculated from following equation

Water uptake (%) = [Wf-Wo / Wo]*100

Where, Wo=initial weight of the beads

Wf=final weight

Entrapment studies: Drug entrapment efficiency of Metformin HCl micro beads was performed by accurately weighing 50 mg of micro beads and suspended in 100 ml of PBS of pH 6.8 and it was kept aside for 24 hours. Then, it was stirred for 15 min and filtered. After suitable dilution, Metformin content in the filtrate was analyzed spectrophotometrically at 232 nm using U.V. spectrophotometer.

Encapsulation Efficiency = (Estimated drug content /Theoretical Drug content) x 100

Evaluation of tablets containing sr micro beads

Determination of physical parameters of tablet: All the physical parameters like Hardness (kg/cm^2), friability and weight variation were studied. The weight variation test is done by weighing 20 tablets individually; calculating the weight and comparing the individual tablet weight to the average**,** Hardness (kg/cm^2) and friability were measured with Monsanto Hardness (kg/cm^2) tester, Roche friabilator respectively [28-31].

Drug content determination: Five tablets were powdered and the blend equivalent to 100mg of Metformin HCl was weight and dissolved in suitable quantity of 0.1N HCl solution. Solution was filtered and diluted and drug content analyzed spectrophotometrically at 232 nm.

Wetting time: A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of 0.1N HCl solution (simulated saliva fluid). A tablet was put on the paper and the time for complete wetting was measured. Three trials for each were performed.

Disintegration time: The disintegration time of tablet was measured in 0.1N HCl (37°C) according to USP disintegration test apparatus. Three trials for each were performed.

***In-vitro* drug release studies:** The *in-vitro* release of SR micro beads containing tablets were performed using USP type II dissolution test apparatus in 900 ml of medium (0.1M hydrochloric acid) for the first 2 h and then in phosphate buffer (pH 6.8) at 37 ± 0.5°C and stirring rate of 50 rpm for the rest 8hours. Samples (5 ml) were collected periodically and replaced with equal volume of fresh dissolution medium on each occasion. The concentration of SR micro beads loaded tablets was determined spectrophotometrically at 232 nm on UV-Visible spectrophotometer [32-49].

Results and Discussion

Tablets of Metformin HCl containing SR micro beads were

S.no	Ingredients	Quantity
1.	Metformin hydrochloride	2 gm
2.	Sodium alginate	1 gm
3.	Sodium CMC	1 gm
4.	calcium chloride	5%

Table 1: Formulation table for SR micro beads.

S.no	Ingredients	F1	F2	F3	F4	F5
1.	SR micro beads	1gm	2gm	3 gm	4 gm	5 gm
2.	Metformin HCl	4.5 gm	4 gm	3.5 gm	3 gm	2.5 gm
2.	Avicel pH 101	4 gm	3.5 gm	3 gm	2.5 gm	2 gm
3.	Cross povidone	0.5 gm	0.5 gm	0.5 gm	0.5 gm	0.5 gm
4.	Aerosil	0.22 gm	0.22 gm	0.22 gm	0.22 gm	0.22 gm
5.	Magnesium stearate	1%	1%	1%	1%	1%
6.	Talc	1%	1%	1%	1%	1%

Table 2: Formulation table for tablets containing SR micro beads.

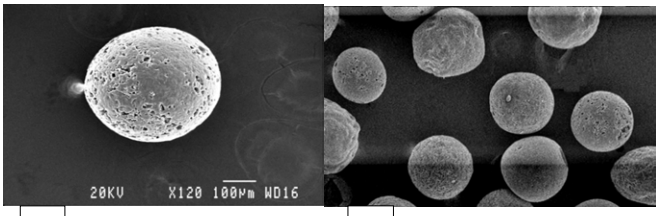

Figure 1: SEM (Scanning Electron Microscopy) Photographs of alginate beads (A) Single (B) Group.

prepared, and evaluated for various properties, primly independent of tablet the micro beads were evaluated for size and shape (SEM), entrapment efficiency, Mechanical strength and swelling index. After the compression into tablet again all these parameters were studied and mentioned in Table 3.

It was evident from the values there is not much variation observed. The tablets of all batches were studied for weight variation (%deviation <7.7%) and percentage loss in friability all the batches except F4 and F5 are within range (<1%), Drug content in all batches is within limit (100 ± 10) this difference is due to less entrapment efficiency of SR micro beads, All other physical parameters like Hardness (kg/cm^2), wetting time are studied and shown in Table 4.

Disintegration time

The disintegration time of various batches were studied (Table 4), and it is in order of F1>F2>F3>F4>F5, from the results it is shown that as the concentration of beads in tablet increased the disintegration time is decreased.

In-vitro drug release studies

The *In-vitro* drug release profiles of metformin HCL (Figure 2). The *In-vitro* dissolution studies showed that all the formulations showed an extended release up to 10 hours , even though all the formulations showed good release formulations F4 and F5 are ignored because of less Hardness (kg/cm^2) and more percentage loss in friability, the percentage drug release of F1,F2,F3,F4,F5 are shown in Figure 2.

The micro beads prepared by ionotropic technique were evaluated for their dissolution profile before they were compressed into tablets and the micro beads separated from the compressed metformin SR tablets were sieved and are also evaluated for their release profile. Both the micro beads from the compressed tablets and uncompressed beads doesn't showed much variation in their dissolution profile and are shown in Table 5, this shows that the prepared micro beads remain un disturbed during compression into tablet.

The drug release kinetics was studied and compared with immediate release dosage form i.e. without micro beads and marketed formulation (Glucophage GF FRANCO). The results were showed in Figure 3.

Conclusion

Formulations F1,F2,F3,F4,F5 showed good release rate but to maintain the drug release with in therapeutic range F1,F2 were not suitable so formulations F3,F4,F5 were considered as best formulations to maintain drug release with in therapeutic window for more time. From the physical characteristics evaluation the formulation F4 and F5 were ignored because of less Hardness (kg/cm^2) and more loss on friability. Therefore the formulation F3 is selected as best one. This formulation is selected as novel formulation for maintaining drug release within therapeutic range and for better bio availability when compared to immediate release formulation and glycophage GF.

S.no	Physical property	Uncompressed beads	Compressed beads
1.	Swelling index	2 ± 0.3	2 ± 0.2
2.	Drug entrapment	84.6	83.2

Table 3: Evaluation of SR micro beads.

S.no	Physical property	F1	F2	F3	F4	F5
1.	Tablet Hardness (kg/cm^2)	4.2 ± 0.432	4.2 ± 0.216	4.1 ± 0.238	3.8 ± 0.315	3.5 ± 0.412
2.	Weight variation test	pass	pass	pass	pass	pass
3.	Friability	0.28	0.36	0.52	1.2	1.96
4.	Content uniformity	97.126	98.12	96.421	94.19	93.549
5.	Disintegration time	30 sec	28 sec	26 sec	21 sec	17 sec
6.	Wetting time	46 sec	50 sec	48 sec	52 sec	56 sec

Table 4: Evaluation of tablets containing SR micro beads.

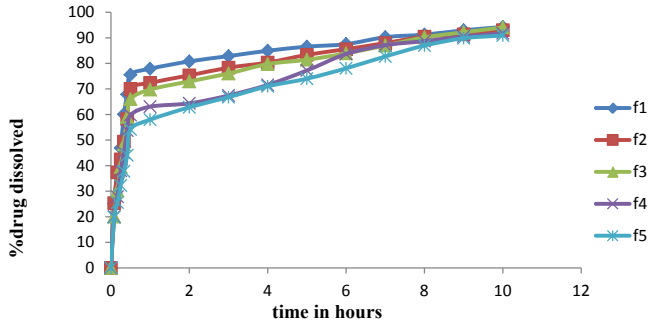

Figure 2: Drug release profiles of tablets containing SR microbeads.

S.no.	Time in hrs.	% Drug release of Uncompressed beads	% Drug release of Compressed beads
1.	1	7.6	10.6
2.	2	19.5	18.5
3.	3	27.5	28.1
4.	4	39.4	42.1
5.	5	44.5	47.5
6.	6	53.4	54.6
7.	7	62.1	61.5
8.	8	68	67.8
9.	9	76	77.2
10.	10	83.4	82.5

Table 5: *In-vitro* dissolution profile SR micro beads (uncompressed).

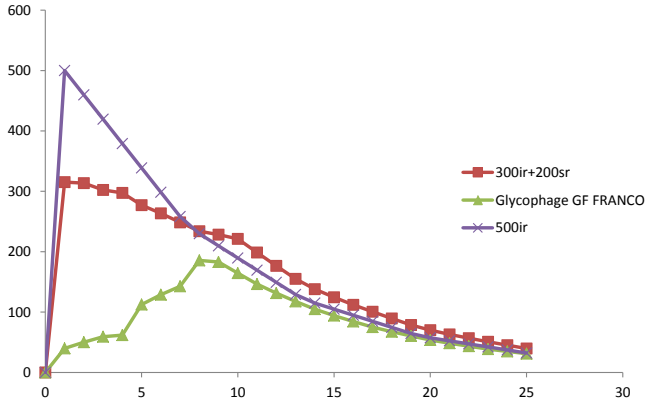

Figure 3: Comparision of plasma concentration for IR relase tablet, SR release tablet (glycophage GF) and tablet containing microbeads.

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