

Formulation, development and evaluation of patient friendly dosage forms of metformin, Part-I: Orally disintegrating tablets

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Metformin hydrochloride is an orally administered antihyperglycemic agent, used in the management of non-insulin-dependent (type-2) diabetes mellitus. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and pediatrics. Unfortunately, a high percentage of patients suffering from type-2 diabetes are elderly people showing dysphagia. In this study, orally disintegrating tablets were prepared using direct compression and wet granulation method. First, the tablets of metformin were prepared using starch RX1500 and microcrystalline cellulose by direct compression. The tablets showed erosion behavior rather than disintegration. Then lactose was incorporated which created pores to cause burst release of drug. But these tablets did not give good mouth feel. Thus, Pearlitol SD 200 (spray dried mannitol) was used to prepare tablets by wet granulation (10% polyvinylpyrrolidone in Isopropyl alcohol as binder). The optimized batches of tablets (LMCT3 and MP13) not only exhibited desired mouth feel but also disintegration time, *in vitro* dispersion time, water absorption ratio, and *in vitro* drug release. All the batches contained 15% starch 1500 and 4% of croscarmellose sodium. The optimized batches prepared by direct compression and wet granulation showed 85% drug release at 4 min and 8 min, respectively. The strong saline and slight bitter taste of the drug was masked using nonnutritive sweetener and flavor.

Key words: Direct compression and wet granulation, metformin hydrochloride, mouth feel, orally disintegrating tablets

INTRODUCTION

Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. Recently more stress is laid down on the development of organoleptically elegant and patient friendly drug delivery system for pediatric and geriatric patients.^[1,2]

Many patients, elderly people and person with dysphagia find it difficult to swallow the tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of noncompliance and ineffective therapy.

Unfortunately, a high percentage of patients suffering from type-2 diabetes are elderly people showing dysphagia. The above problem becomes even more severe due to big tablets (high dose 500-1000 mg) and need for daily intake of the drug. A tablet comprising 1000 mg of metformin hydrochloride would need to

have a size of 19 mm × 10.5 mm (Glucophage® 1000 mg tablets) or more as functional excipients are needed to modify release of drug from the dosage form and would be very difficult to swallow.^[3,4] The only available alternative for such patients is the above mentioned oral solution RIOMET® (500 mg/5 ml). This composition is only available in the United States, and it has well known disadvantages of all kind of syrup compositions.^[3]

Orally disintegrating tablets disintegrate or dissolve in saliva and are swallowed without water. The main purpose of this work is only to improve patient compliance without compromising the therapeutic efficacy.

EXPERIMENTAL MATERIALS AND METHODS

Metformin hydrochloride, croscarmellose, microcrystalline cellulose (MCC) (Intas Pharma, Ahmedabad, India), starch RX 1500 (Colorcon Asia, Goa, India), spray dried lactose (Zydus Cadila Health Care Ltd., Ahmedabad, India), Pearlitol SD 200 (Degussa Pvt. Ltd., France). All other chemicals purchased were of analytical grade.

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Table 1: Formulation of batches of orally disintegrating tablets using starch RX 1500, lactose and MCC

Ingredients % w/w	Batch code			
	LMCT1 (%)	LMCT2 (%)	LMCT3 (%)	LMCT4 (%)
Metformin	50	50	50	50
Lactose (SD)	10	18	20	23
MCC	20	12	10	7
Starch RX 1500	14.5	14.5	14.5	14.5
CCS	4	4	4	4
Mg.stearate	0.5	0.5	0.5	0.5
Sucralose	0.5	0.5	0.5	0.5
Mango flavor	0.5	0.5	0.5	0.5

MCC: Microcrystalline cellulose

Preparation of mixed blend of drug and excipients*Blend of drug and starch 1500, lactose and MCC*

All the ingredients were passed through mesh no. 60. Required quantity for each formulation [Table 1] and all the ingredients were coground in a mortar and pestle. The powder blend was evaluated for flow properties and compressibility behavior.

Granules of drug, starch 1500 and pearlitol

All the ingredients were passed through mesh no. 60. Required quantity for each formulation [Table 2] and all the ingredients were coground in a mortar and pestle. 10% w/v PVP K30 in IPA was used as binder to prepare the granules. The wet mass was screened through sieve no. 60 and dried. The dried granules were sieved through sieve no. 85 and subjected for evaluation of granules. Table 3 shows the formulation design of granules.

The granules and directly compressible blends were evaluated as follows:

Angle of repose^[5]

Angle of repose (α) was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated.

$$\alpha = \tan^{-1} (h/r)$$

Bulk density^[5]

Apparent bulk density (ρ_b) was determined by placing presieved drug excipients blend into a graduated cylinder and measuring the volume (V_b) and weight (M) "as it is".

$$\rho_b = M/V_b$$

Tapped density^[5]

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend

Table 2: Evaluation of directly compressible blend

Property	Batch codes			
	LMCT1	LMCT2	LMCT3	LMCT4
Angle of repose (°)	37	35	33	32
Bulk density (gm/cm ³)	0.50	0.52	0.50	0.50
Tapped density (gm/cm ³)	0.64	0.68	0.66	0.67
% compressibility	21.87	23.52	24.24	25.37
Flowability	Good	Fair	Fair	Poor

Table 3: Evaluation of tablets

Test parameters	Results			
	Hardness	62 N	60 N	52 N
Friability	0.31%	0.62%	0.66%	Capping seen
DT	73s	61s	55s	51s
Wetting time	215s	187s	157s	140s
In vitro dispersion time	135s	127s	87s	78s

DT: Disintegration time, s: Sec

was measured. The tapped density (ρ_t) was calculated using following formula.

$$\rho_t = M/V_t$$

Compressibility index^[5]

The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by % compressibility which is calculated as follows:

$$C = (\rho_t - \rho_b) / \rho_t * 100$$

ρ_t - Tapped density

ρ_b - Untapped bulk density

Hausner's ratio^[5]

Hausner's ratio is an index of ease of powder flow, it is calculated by following formula. Hausner's ratio = ρ_t / ρ_b

ρ_t - Tapped density

ρ_b - Untapped bulk density

Compression of tablets**Compression of powder blend**

The ingredients depicted in Table 1 (except talc and magnesium stearate) were mixed homogeneously and coground in a mortar and pestle. Finally, talc and magnesium stearate were added and mixed for 5 min. The mixed blend of drug and excipients were compressed using a single punch tablet punching machine to produce convex faced tablets weighing 500 mg each with a diameter of 12.8 mm, a minimum of 50 tablets were prepared for each batch.

Table 4: Formulation of batches containing pearlitol using 10% w/v PVP in IPA as binder

Ingredients	Batch code	
	MP13 (%)	MP14 (%)
Metformin	50	60
Pearlitol SD	30	20
Starch 1500	14.5	14.5
CCS	4	4
Mg. stearate	0.5	0.5
Sweetener	0.5	0.5
Flavor lemon	0.5	0.5

Compression of granules

The ingredients depicted in Table 4 (except talc and magnesium stearate) were granulated using 10% PVP in IPA as binder. The dried granules were mixed with talc, magnesium stearate and flavor mixed for 5 min. The mixed blend of granules compressed using a single punch tablet punching machine to produce convex faced tablets weighing 500 mg each with a diameter of 12.8 mm, a minimum of 50 tablets were prepared for each batch.

Evaluation of tablets**Friability test^[5]**

Friability of tablets was determined using Roche friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of six inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability is given by the formula:

$$F = (1 - W_0/W) \times 100$$

where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

Hardness^[5]

Hardness or tablet crushing strength (F_c) (the force required to break a tablet in a diametric compression) was measured using Dr. Schleuniger hardness tester.

Tensile strength^[5]

Tensile strength of tablets were calculated using the following formula:

$$T = 2F_c / \pi d t, \text{ where } F_c, d \text{ and } t \text{ denotes crushing strength, diameter, and thickness of tablet respectively.}$$

Drug content^[6]

Five tablets were powdered and the blend equivalent to 250 mg of metformin was weighed and dissolved in suitable quantity of phosphate buffer of pH 6.8. The solution was filtered, suitably diluted and the drug content was analyzed spectrophotometrically at 233 nm. Each sample was analyzed in

triplicate.

Measurement of liquid uptake^[7]

A glass petridish was partially filled with water and a tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of water occurred from the lower surface of the tablet. The time required for water to reach the center of the upper surface of the tablet was noted as wetting time.

Water absorption ratio^[7]

A piece of tissue paper was folded twice was placed in a small petridish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio R , was determined using the following equation:

$$R = 100 \times W_a - W_b / W_b \text{ where } W_b \text{ is weight of tablet before water absorption and } W_a \text{ is weight of tablet after water absorption.}$$

In vitro dispersion time^[7]

Tablet was added to 10 ml of phosphate buffer solution (pH 6.8) at $37 \pm 0.5^\circ\text{C}$. Time required for complete dispersion of a tablet was measured.

Disintegration Time^[6]**In vitro disintegration time**

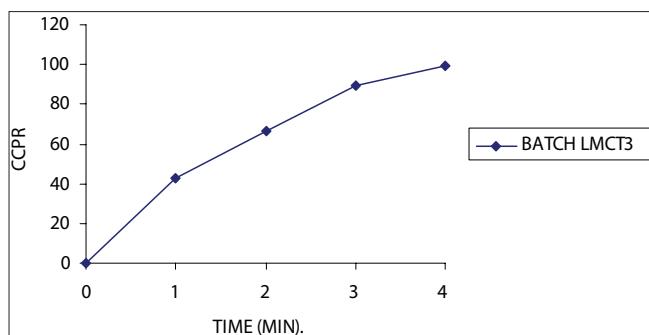
The time required for disintegration of six tablets, placed in each tube of disintegration test apparatus, was measured at $37 \pm 2^\circ\text{C}$ using 900 ml distilled water.

In vivo disintegration time

The time required for tablets to disintegrate in the mouth cavity was determined by holding the tablets in the mouth. The subjects were instructed to gently move the tablet against the upper part of the mouth with the tongue. It is emphasized to the subject that this is a gentle motion with no biting of the tablet. Immediately after the last noticeable granule was disintegrated, the time was again recorded. Test was conducted in duplicate and average time is reported. The test was performed in five healthy human volunteers in the age group of 23 to 28 years.

Dissolution testing^[6]

In vitro dissolution study of Metformin tablets was performed using Electrolab USP Dissolution testing apparatus fitted with paddles. The speed of rotation of paddle was set at 50 rpm. Dissolution study was carried out using phosphate buffer (pH 6.8) maintained at a temp of 37°C . At a predetermined time interval (5 min); 5 ml samples were withdrawn, filtered through Whatman filter paper, 1 ml of the filtered solution was diluted up to 50 ml with phosphate buffer of pH 6.8. Absorption of suitably diluted solution was checked by UV spectrophotometer at 233 nm and drug content was

**Figure 1:** Dissolution profile of batch LMCT3

determined from standard curve. The dissolution experiments were conducted in triplicate.

Taste masking^[8]

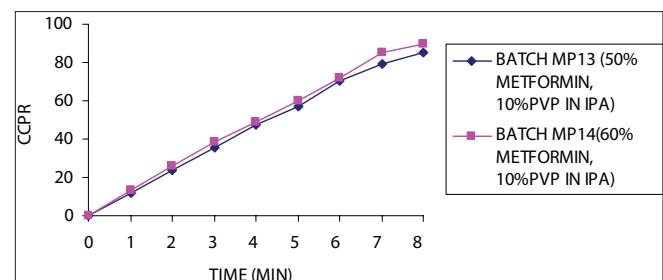
The strong saline and slight bitter taste of the drug was masked using suitable concentration of sweetener and flavor. The taste masked tablets were given to human volunteers to evaluate their mouth feel.

RESULTS AND DISCUSSION

Few trial batches of tablets of metformin were prepared using starch RX 1500 and microcrystalline cellulose by direct compression. The tablets showed erosion behavior rather than disintegration.^[9] Then lactose was incorporated which created pores to cause burst release of drug. But these tablets did not give good mouth feel. Thus, pearlitol SD 200 (spray dried mannitol) was used to prepare tablets by wet granulation (10% PVP in IPA as binder).^[10]

Table 2 shows batch containing higher amount of MCC showed better flow and compressibility. But, we want higher amount of lactose so, batch LMCT3 was chosen. Though the batch LMCT4 contains highest amount of lactose it showed poor compressibility.

Table 3 shows, batches LMCT1 to LMCT4 showed decrease in disintegration time with increase in amount of lactose but it had a negative effect on hardness and friability. Though LMCT4 has lowest disintegration time, it showed capping. The cause of capping was due to poorly compressible metformin (angle of repose 46°C and Carr's index 37, Hausner's ratio >1.25) and high concentration of spray dried lactose (23%). Also

**Figure 2:** Comparative dissolution profile of batch MP13 and MP14

there exists a density and moisture content difference among the drug and diluents. Comparison of batches LMCT2 and LMCT3 revealed LMCT3 showed lower disintegration time (55 s) and acceptable hardness (60 N), friability (0.66%), wetting time and *in vitro* dispersion time which are acceptable. The reason might be due to optimum concentration of lactose and MCC. Thus, LMCT3 was chosen as the optimized batch and was subjected to dissolution study. Figure 1 shows 85% of drug was released within 3 min.

Table 5 shows batch containing low amount of drug which gave better flow and compressibility. Thus, MP13 was chosen for study.

Table 6 shows that both MP13 and MP14 possessed desired hardness, friability and disintegration time meeting in house specifications. The reason might be as the drug is poorly compressible so it required strong binder. The disintegration time of batch MP13 is higher than that of MP14 as it contained higher amount of pearlitol and low amount of drug. Thus, both the batches were subjected to dissolution study.

Figure 2 shows the dissolution profile of batch MP14 was almost similar to that of MP13 but the mouth feel of batch MP13 was better than that of MP14 due to comparatively higher concentration of mannitol in batch MP13 and low concentration of drug. Thus batch MP13 was the best batch.

Finally, dissolution profile of taste masked optimized batches of orodispersible tablets (LMCT3, MP13) were compared with that of market product. Figure 3 shows dissolution profiles of prepared batches were better than that of market product.

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Table 5: Evaluation of granules

Property	Batch codes	
	MP13	MP14
Angle of repose (°)	25.13	26.08
Bulk density (gm/cm ³)	0.56	0.54
Tapped density (gm/cm ³)	0.64	0.63
% compressibility	12.5	14.28
Flowability	Good	Good

Table 6: Evaluation of tablets

Evaluation	Results	
	MP13	MP14
Test parameters		
Hardness	75 N	68 N
Friability	0.43%	0.38%
DT Time	105s	83s

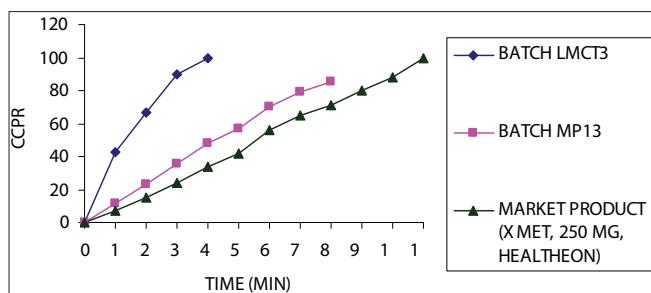


Figure 3: Comparative dissolution profile of market product with optimized batches

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