

# Formulation, development and evaluation of patient friendly dosage forms of metformin, Part-III: Soluble effervescent tablets

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## ABSTRACT

**M**etformin hydrochloride is an orally administered antihyperglycemic agent, used in the management of non-insulin-dependant (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. The above problem becomes even more severe due to high dose (500–1000 mg) and need for daily intake of metformin. Thus, the above titled work was undertaken to provide patient friendly dosage form. Not only metformin is poorly compressible (Carr's index 37), but effervescent ingredients are also poorly compressible so, method of wet granulation was used for preparation of tablets using absolute alcohol as binder. Metformin effervescent tablets were prepared using citric acid (CA), tartaric acid (TA), and treated sodium bicarbonate (heating at 120°C for 30 min), glycine, talc, sucralose, and mango flavor. Controlled heating of sodium bicarbonate formed a sheath or desiccant skin of sodium carbonate on bicarbonate nucleus leading to surface passivation which prevents onset effervescent reaction in presence of moisture leading to stability. Of all combinations, CA and TA in the molar ratio 1:2 was found to be most stable as higher amount of least hygroscopic TA protects hygroscopic CA from the attack of moisture. Also, it was found that using treated sodium bicarbonate in stoichiometric ratio gave substantially stable effervescent tablets on short term stability study (room temperature and humidity and 75% relative humidity (RH) and room temperature) as sodium carbonate preferentially absorbs moisture. All the ingredients selected were water soluble.

**Key words:** *Metformin hydrochloride, soluble effervescent tablets, surface passivation, wet granulation*

## 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.<sup>[1,2]</sup>

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.<sup>[3,4]</sup> 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.<sup>[3]</sup>

Soluble effervescent tablets get quickly dissolved when put in water to give a sparkling solution with good taste which can be easily consumed by patients with dysphagia. Citric acid (CA) is very hygroscopic and it poses challenge to formulators hence, it was selected. Also market preparations like ENO and DISPIRIN contain

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CA and hence they were selected so that comparison of humidity resistance of our formulation can be made. Tartaric acid (TA) is comparatively less hygroscopic so it was used in the present work.

## EXPERIMENTAL MATERIALS AND METHODS

Metformin hydrochloride (Intas Pharma, Ahmedabad, India), sodium saccharin (Parsh Pharm.Chem, Vapi) mango flavor (Dewang Corporation, Baroda). Rest of the chemicals purchased were of analytical grade.

**Controlled heating of base to effect surface passivation.**<sup>[5]</sup> Sodium bicarbonate was chosen as the standard base for the whole work. The base was heated in controlled manner at 120°C for 30 min. Estimation of % of conversion was done by using following titrimetric method. This partially converted base was used for the preparation of tablets.

### Preparation of granules

All the ingredients were passed through mesh no. 40. Required quantity for each formulation [Table 1] and all the ingredients were coground in a mortar and pestle. Absolute alcohol 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. 40 and subjected for evaluation of granules. The granules evaluated as follows:

### Angle of repose

Angle of repose<sup>[6]</sup> ( $\alpha$ ) 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

Apparent bulk density<sup>[6]</sup> ( $\rho_b$ ) 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

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 was measured. The tapped density<sup>[6]</sup> ( $\rho_t$ ) was calculated using following formula.

$$\rho_t = M/V_t$$

### Compressibility index

The simplest way of measurement of free flow property of powder is compressibility,<sup>[6]</sup> an indication of the ease

**Table 1: Formulation and evaluation of batches of effervescent tablet using absolute alcohol as binder**

Ingredients % w/w	Batch code							
	EF1	EF2	EF3	EF4	EF5	EF6	EF7	EF8
Metformin (%)	27	29	28	38	49	38	28	28
Citric acid (%)	30	-	20	15	10	10	10	10
Tartaric acid (%)	-	30	10	10	10	15	20	20
NaHCO <sub>3</sub> (%)	36	34	35	30	24	30	35	-
Heat treated NaHCO <sub>3</sub> (%)	-	-	-	-	-	-	-	35
Saccharin sodium (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mango flavor (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Glycine powder (%)	1	1	1	1	1	1	1	1
Talc (%)	5	5	5	5	5	5	5	5
Test parameters	Evaluation							
	Results							
Granule property	Sticky	Friable	Sticky	Less sticky	Slightly sticky	Non sticky	Non sticky	Non sticky
Angle of repose	Not measured	Not measured	Not measured	58	52	43	37	35
Hardness	-	-	78 N	80 N	75 N	82 N	87 N	85 N
Friability (%)	-	-	0.25	0.30	0.34	0.28	0.22	0.25
Disintegration time (s)	-	-	55	75	105	78	88	95
CO <sub>2</sub> content for a single dose (250 mg metformin)	-	-	155	98	59	96	158	158
% loss of CO <sub>2</sub>	-	-	47	43	40	32	25	08
Appearance of tablet	-	-	(-)	(-)	+	+	++	++
Water, %, up to	100	100	100	100	100	100	100	100

with which a material can be induced to flow is given by % compressibility which is calculated as follows:

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

$\rho_t$  - tapped density

$\rho_b$  - untapped bulk density

#### Hausner's ratio

Hausner's ratio<sup>[6]</sup> is an index of ease of powder flow. It is calculated by following formula. Hausner's ratio =  $\rho_t / \rho_b$

$\rho_t$  - tapped density

$\rho_b$  - untapped bulk density

#### Compression of tablets

The dried granules were mixed with talc, magnesium stearate and flavor for five minutes. The mixed blend of granules 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.

#### Evaluation of tablets

##### Friability test

Friability of tablets was determined using Roche friabilator (Electrolab, Mumbai).<sup>[6]</sup> 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 6 in 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:

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

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

##### Hardness

Hardness<sup>[6]</sup> or tablet crushing strength ( $F_c$ ) (the force required to break a tablet in a diametric compression) was measured using Dr. Schleuniger hardness tester.

##### Drug content

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<sup>[7]</sup> was analyzed spectroscopically at 233 nm. Each sample was analyzed in triplicate.

##### Tablet disintegration

The disintegration test was carried out at 30°C in 250 ml (IP) distilled water. The tablet was put into the beaker containing

the distilled water maintained as at 30°C. The tablet should preferably get dissolved or disintegrate before 5 min or before the effervescence reaction subsides.<sup>[7-9]</sup>

##### Taste masking

The strong saline and slight bitter taste of the drug was masked using suitable concentration of sweetener and flavor. The taste masked<sup>[10]</sup> tablets were given to human volunteers to evaluate their mouth feel.

##### CO<sub>2</sub> gas content

Carbon dioxide gas forms the main basis of effervescent preparation and hence it has to be measured and constantly monitored to study the effectiveness of the formulation and also to study, the changes in various parameters affecting the gas liberation.

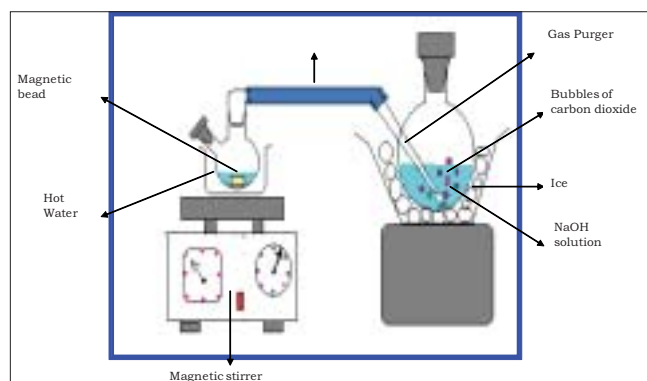
A method and an Instrument as shown in Figure 1 was developed during the present study was used to determine CO<sub>2</sub> content.<sup>[11,12]</sup> The method was based on acid-base back titrimetric method.

##### Resistance to Humidity

Effervescent tablets and granules are formulated and packaged to be protected from moisture; to prevent premature effervescence and loss of CO<sub>2</sub> gas. Presence of water is required for the liberation of CO<sub>2</sub> gas. One may think that measurement of % moisture absorption after exposure to higher relative humidity (RH) may serve the purpose but actually it will not because weight gain due to moisture absorption will then lead to weight loss due to liberation of CO<sub>2</sub>, hence correct prediction cannot be done. Thus, the best way adapted to measure humidity resistance of effervescent tablets or granules was to measure % loss of CO<sub>2</sub> gas after suitable humidity exposure. The conditions chosen were 75% RH, room temperature for a week. The tablets or granules were packed in aluminum foils and at the time of test they were opened and resealed.

##### pH

The pH of the solution when the tablet dissolves is an



**Figure 1:** Instrument for determination of carbon dioxide content of effervescent tablets

**Table 2: Results of short term stability study of batch EF7 and EF8**

Test parameters	Results					
	Initial		Room temperature (after 30 days)		Room temperature/ 75% relative humidity (after 30 days)	
	EF7	EF8	EF7	EF8	EF7	EF8
Hardness	87 N	85 N	65 N	83 N	47 N	80 N
Friability	0.22%	0.25%	0.87%	0.24%	1.23%	0.27%
CO <sub>2</sub> content	158	158	137	155	115	146
Disintegration time (s)	88	95	67	92	43	88
Drug content (%)	99.98	99.98	99.97	99.97	99.98	99.98
Appearance	++	++	-	++	-	++

interesting chemical property. pH monitoring can give the idea of homogenous mixing of raw materials. The pH of the solution is important for taste aspects in a product meant for ingestion. Solutions having acidic pH have better palatability. pH can be measured at a specific time after the tablet has been placed in the water since it is not unusual for effervescent solutions to change its pH on standing.

*Appearance*

The ingredients used in effervescent tablets have very poor tableting properties and hence they do not give tablets with very good appearance. Appearance was judged visually.

Very good (+ + +), good (+ +), fair (+) poor (-), very poor (- -)

*Short term stability study*

The optimized batch EF7 was kept for short term stability study. The condition for stability study were:

- (1) Room temperature around 40°C (RT)
- (2) RT/75% RH.

All the tablets of optimized batch EF7 were suitably packed in groups of 10 No. of tablets each in aluminum foil. The tablets to be tested at room temperature were kept outside at room condition. At the end of one month, the sealed tablets were opened and evaluated for different parameters. 75% RH chamber was prepared using saturated solution of sodium chloride in desiccator.

**RESULTS AND DISCUSSION**

Few trial batches (E1, E2, E3) containing different nonstoichiometric ratio of acid and base were prepared but on evaluation it was found that these tablets have low hardness also low CO<sub>2</sub> content, also sticking to punches and die was observed. Thus, it was decided to use stoichiometric ratio of acid and base.

It is well known that presence of both citric acid (CA) and tartaric acid (TA) in suitable proportion give good

effervescence, thus few batches were prepared with constant amount of CA and with gradually increasing concentration of TA. The reason for choosing more amount of TA compared to CA was comparatively less hygroscopic nature of TA, but we cannot use TA alone as it needs one antioxidant for stability, thus combination with CA was used.

Basing on the ratio of CA and TA in the formulation, amount of base required can be calculated stoichiometrically using the following equation:

$$210 \text{ gm of CA} = 252 \text{ gm of NaHCO}_3$$

$$150 \text{ mg of TA} = 168 \text{ gm NaHCO}_3$$

Table 1 shows the batch EF1 gave sticky mass difficult to sieve as CA is very hygroscopic. But batch EF2 gave sievable mass, but friable granules. Thus, it was decided to use CA and TA blend in suitable ratio. The batches EF3, EF4, and EF5 caused problem in granulation and tableting due to high concentration of hygroscopic CA. Hence it was decided to use higher concentration of comparatively less hygroscopic TA. The batches EF6 and EF7 gave satisfactory granules with reduced problems of sticking to die and punch during tableting. Table 1 shows that batch EF7 was the optimized batch in terms of all evaluation parameters, it also showed comparatively improved stability because two fold amount of TA compared to CA which prevented exposure of CA to moisture as TA was able to form a coat on it. The batch EF7 was subjected to short term stability study.

Table 2 shows the CO<sub>2</sub> content of batch EF7 was significantly

**Table 3: Comparative % moisture absorption by treated and untreated sodium bicarbonate**

Test parameter	Results	
	Untreated NaHCO <sub>3</sub>	Modified NaHCO <sub>3</sub>
		NaHCO <sub>3</sub> : Na <sub>2</sub> CO <sub>3</sub> (1:1) (physical mixture)
		NaHCO <sub>3</sub> partially converted to Na <sub>2</sub> CO <sub>3</sub>
% Moisture absorption	0.45	0.37
		0.25

reduced on storage at room temperature and also at 75% RH for 30 days due to premature effervescence. pH of solution prepared putting tablets into water was affected by storage condition due to liberation of CO<sub>2</sub>. Appearance of tablets were altered also hardness and friability were affected substantially. The cause of decrease in hardness and increase in friability of tablets was due to liberation of CO<sub>2</sub> which had rendered tablets porous.

Hence, it was concluded that the optimized batch EF7 is totally unstable in the short term stability study. The reason was the moisture sensitivity of the effervescent ingredients. The focus was to decrease the moisture sensitivity of either acid or base part to get stable effervescent tablets.

Table 3 showed the heat treated base is substantially stable. The reason was obvious as controlled heat treatment ensured formation of a layer of sodium carbonate on the sodium bicarbonate due to partial conversion. The partial conversion ensures surface passivation of the sodium bicarbonate due to formation of a desiccant skin of sodium carbonate which enhanced the moisture proofness of sodium bicarbonate.<sup>[5]</sup> The surface passivated sodium bicarbonate may also prevent premature effervescence on coming in contact with the moisture. Thus, it was decided to use heat treated base in place of normal sodium bicarbonate to get stable effervescent tablet.

Table 1 shows batch EF8 showed substantial improvement in the stability of the tablet after using heat treated sodium bicarbonate. Also there was non-significant change in hardness, friability, CO<sub>2</sub> content so, it was concluded that

use of treated sodium bicarbonate has definitely contributed to the stability of the tablet. Thus, batch EF8 (containing heat treated sodium bicarbonate) was the optimized stable effervescent tablet batch.

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