A STUDY ON EVALUATE PRE-COMPRESSION AND POST-COMPRESSION PARAMETERS OF THE FORMULATED TABLETS USING FOLIC ACID

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Abstract:
Compressing a small quantity of powder to shape a tablet has been finished trillions of times through myriad pharmaceutical companies. Technical innovations in tablet compression machinery have progressed manufacturing fees to the factor where more than 500,000 drugs in step with hour are viable. Forte capsules were crafted for sublingual, buccal, rectal, and vaginal healing use. Launch of the energetic drug element may also variety from a few seconds for hastily disintegrating tablets to approximately 24 hours for controlled or sustained launch products as they transit the complete length of the gastrointestinal machine. in addition, compressed drugs can be meant to be used in analytical or diagnostic packages, or dissolved in drinks previous to ingestion. As we attempt to deliver gold standard first-class compressed pill merchandise, attention can be focused on activities achieved previous to the compression step, at some point of the compression operation itself, and additionally on the performance characteristics required of the drugs after their creation.

Keywords: Tablets, Compression, Low bulk density, Disintegration time, Dissolution time

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INTRODUCTION

ORAL SOLID DOSAGE FORMS: An Oral Dosage Form is the physical form of a dose of a chemical compound used as a drug or medication intended for administration or consumption by oral route. Common oral dosage forms are tablets or capsules. Tablets are solid preparations each containing a single dose of one or more active substances with or without excipients usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated. The excipients can include binders, glidants and lubricants to ensure efficient tableting; disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavors to enhance taste; and pigments to make the tablets visually attractive. (1) These are included in the formulations to facilitate easy handling, enhance the physical appearance, and improve stability and aid in the delivery of the drug to the blood stream after administration. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.

IMMEDIATE RELEASE TABLETS

The need for new oral drug delivery system continues, due to poor patient acceptance for invasive methods, need for exploration of new market for drugs and coupled with high cost of disease management. Developing new drug delivery techniques and utilizing them in product development is critical for pharma companies to survive this century. An immediate release dosage form allows a manufacturer to extend market.(2,3) Exclusivity, while offering patients a convenient dosage form or dosage regimen. Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as specia Coatings and other techniques. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities.

METHODOLOGY:

EVALUATION OF TABLETS

1. Pre-Compression Parameters:

Bulk Density (D_b)

The Bulk density denotes the total density of the materials as it exists.

D_b = m/Vo

Where, $D_b = m/Vo$

M=Mass of the blend

Vo=Untapped Volume

PROCEDURE:

Weighed quantity of folic acid were transferred into a 50ml measuring cylinder without tapping during transfer the volume occupied by granules was Measured.

Applications:

- Checking the uniformity of bulk chemicals.
- Selecting the size of container, mixing apparatus for the production.
- Determining the proper size of the packing material.

Tapped Density (D_t)

The tapped density is the density of the powder itself, i.e., material exclusive of voids (inter particle spaces) and intra particle pores. The density depends on the type of atoms in a molecule, arrangement of the atoms in a molecule and the arrangement of molecules in a sample.

D_t=m/V_i

Where, m=Mass of blend

V_i=Tapped volume

PROCEDURE:

Weighed quantity of folic acid was taken into a graduated cylinder, volume occupied by granules was noted down. Then cylinder was subjected to 100taps in tapped Density tester.

Application:

•Tapped density is used in the determination of percent porosity.

POROSITY

Whether the powder is porous or nonporous, the total porosity expression for the calculation remains the same. The percent porosity is expressed as

$$\textbf{Porosity } \varepsilon = \frac{V_o - V_i}{V_o}$$

Application:

- Porosity values provide information about hardness, disintegration and tablet porosity

Angle of repose

It is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane.

The angle of repose is designated by θ and given by equation;

Tan θ= h/r θ= $\tan^{-1}$ (h/r) Where; h = height of the pile.

r = radius of the base of the pile.

Application:

- During tableting, improper flow of granules from the hopper leads to under-fill or over-filling of the die cavity. As a result, tablets will have under-weight or over weight, weight variation further affects the content uniformity and dose precision.

It also creates problems of hardness and friability during compression.

Table 1 : *Angle of repose*

Angle of repose	Powder flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

Carr's index (I)

It helps in measuring the force required to break the friction between the particles and the hopper. It is expressed in % and given by:

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where, D_t = The tapped density

D_b = The bulk density

Application:

- It is indirectly related to powder flow, property and cohesiveness.

Table 2: *Carr's Index*

Percent Compressibility	Type of Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-25	Poor
33-38	Very Poor
>49	Extremely poor

Hausner's Ratio

It is the ratio of tapped density to the bulk density. It is given by

Hausner's ratio = D_t / D_b

Where, D_t = The tapped density

D_b = The bulk density

Table 3: *Hausner's Ratio*

Hausner's Ratio	Flow of Powder
1-1.2	Free Flow
1.2-1.6	Cohesive Flow

2. Post-Compression Parameters:

Thickness

Thickness was measured using calibrated vernier calipers. Six tablets of each formulation were picked randomly and thickness was measured individually and average thickness was reported.

Friability

Previously weighed 10 tablets were taken in a Roche friabilator and the friability was checked at 25 rpm for 4 minutes. Then the tablets were dusted and reweighed and the percentage of powder eroded during 4 minutes was recorded.

Friability was than calculated using the following equation.

$$F = \frac{(W_{initial}) - (W_{Final})}{(W_{initial})} \times 100$$

Where, $W_{initial}$ = Initial Weight of Tablet

W_{Final} = Final Weight of Tablet

Limits: Friability of tablets less than 1% was considered acceptable.

Hardness Test

Barrel containing a compressible spring held between two plungers. The lower Hardness of tablets was tested using Monsanto hardness tester. The tester consists of a plunger is placed in contact with the tablet and a zero reading is taken. The upper plunger is than forced against a spring by turning a threaded bolt until the tablet fractures, and then the force of fracture was recorded. In all the cases average of six determinations were taken.

Weight Variation

The USP weight variation test was run by weighing 20 tablets individually. The average

weight was calculated and compared with the individual tablet weight. The tablet meet the USP test, if not more than 2 tablets are outside the percentage limit And if no tablet differs by more than 2 times the percentage limit.

Table 4: *Weight Variation*

Average weight of a Tablet	Percentage Deviation
130 mg or less	±10
>130 mg or <324 mg	±7.5
324 mg or more	±5

Disintegration Time

The disintegration time was determined using disintegration test apparatus at 37°C +2°C. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time taken for complete disintegration of the tablet with no palpable mass in the apparatus was noted. **Percentage Drug Content [71,72]**

Principle:

This method is based on the reaction of folic acid with formaldehyde to yield a colored product having absorption maxima at 360nm.

Reagents:

Preparation of IN sulphuric acid

- 54 ml of sulphuric acid was added to 1000ml water.

Preparation of 0.01 N sodium hydroxide solution

- 0.4gm of Sodium Hydroxide was dissolved in 1000ml to give 0.01 N Sodium Hydroxide solutions.

Preparation of standard solution

- 100mg of folic acid was dissolved in 100 ml 0.01N Sodium Hydroxide solution. From This 1ml solution was taken and diluted to 10ml with 0.01N Sodium Hydroxide solution to get 100 µg/ml which was taken as standard.

Preparation of sample solution

- Ten tablets were powdered in a mortar and powder equivalent to 5 mg of folic acid was taken and extracted with 25 ml of 0.01N Sodium Hydroxide solution by shaking for 15 min. It was filtered and diluted to 50 ml with water.

Procedure:

To each 10 ml of sample and standard; 13 ml of 1 N Sulphuric Acid and 3 ml of formaldehyde were added which were then heated for 1 hour and cooled. The cooled Solution was diluted to 25 ml with water and absorbance was measure at 360nm against reagent blank.

In Vitro Dissolution Studies [73]

Table 5: *In Vitro Dissolution Studies*

Apparatus	USP Electro labs 23 Paddle type
Rotational speed	50 rpm
Volume	500 ml
Temperature	37±0.5°c
Dissolution medium	Distilled water
Sampling intervals	5,10,15,20,25,30,35,40, and 45 minutes

- Sample were withdrawn every 5 min and replaced with fresh medium.
- Absorbance was measured at 283 nm.

Limit: -Not less than 75% of labeled amount of folic acid was dissolved in 45 min.

BLISTER PACKING OF FOLIC ACID TABLETS

Amber colored PVC-PVDC base foil and Aluminum lidding foil are loaded in the Machine The tablets were loaded in the hopper. The base foil passes through the forming units with Teflon heads and cavities are formed. Tablets in the hopper coming down through inclined feeding channel and singling unit and are introduced into the cavities formed. The heat sealable aluminum lidding foil is introduced and the sealing of the foils was done in the sealing station. The non-filled cavities are detected using non fill detecting system and are rejected. The cutting assembly and the trimming station cuts the blister into appropriate size and shape. Here the thickness of PVC/ PVDC layer is 0.850mm while thickness of aluminum foil is0.400mm.

FORMULATION DESIGN

Table 6: Formulae for Preparation of Immediate Release Folic Acid Tablets with 10% Overages.

S.NO	INGREDIENTS	G_1 (WG)	G_2 (DC)	G_3 (DC)	G_4 (DC)
1.	**Folic Acid (10 %overages)**	5.5mg	5.5mg	5.5mg	5.5mg
2.	**Microcrystalline Cellulose pH- 101**	50mg	-----	91.8mg	-----
3.	**Microcrystalline Cellulose pH-102**	-----	50mg	-----	91.8mg
4.	**Lactose**	20mg	20mg	20mg	20mg
5.	**Di calcium phosphate**	13.7mg	17.7mg	25mg	25mg
6.	**Magnesium stearate**	1mg	1mg	1.5mg	1.5mg
7.	**Colloidal silicon dioxide**	0.8mg	0.8mg	1.2mg	1.2mg
8.	**Croscarmellose sodium**	5mg	5mg	5mg	5mg
9.	**PVP K-30**	4mg	-----	-----	-----
10.	**Iso propyl alcohol**	QS	-----	-----	-----
Total Tablet Weight		100mg	100mg	150mg	150mg

Table 7: Formulae for Preparation of Immediate Release Folic acid Tablets with 40% Overages

S.NO	INGREDIENTS	G_5	G_6	G_7	G_8	G_9
1.	**Folic Acid (40 %overages)**	7mg	7mg	7mg	7mg	7mg
2.	**Microcrystalline Cellulose pH-101**	-------	-------	-------	-------	--------
3.	**Microcrystalline Cellulose pH-102**	91mg	91mg	91mg	91mg	92mg
4.	**Lactose**	20mg	20mg	20mg	20mg	22.3mg
5.	**Di calcium phosphate**	24.3mg	24.3mg	24.3mg	24.3mg	25mg
6.	**Magnesium stearate**	1.5mg	1.5mg	1.5mg	1.5mg	1.7mg
7.	**Colloidal silicon dioxide**	1.2mg	1.2mg	1.2mg	1.2mg	2mg
8.	**Croscarmellose sodium**	5mg	--	--	--	--
9.	**Cross povidone**	--	5mg	--	--	--
10.	**Sodium starch glycolate.**	--	--	5mg	--	--
11.	**Pre gelatinized Starch**	--	--	--	5mg	--
Total Tablet Weight		150mg	150mg	150mg	150mg	150mg

Table 8: Evaluation of Pre Compression Parameters

	Evaluation of pre -compression Parameters					
formulations	density	Tapped density	porosity	carr's in density	hausner's ratio	Angle of repose
G_1	0.571	0.740	0.229	18.84	1.21	29.49
G_2	0.555	0.714	0.222	18.31	1.22	28.86
G_3	0.465	0.540	0.139	13.88	1.16	24.87
G_4	0.454	0.526	0.136	13.68	1.15	26.15
G_5	0.488	0.571	0.146	14.54	1.17	26.38
G_6	0.465	0.540	0.140	13.88	1.16	28.13
G_7	0.512	0.625	0.179	18.08	1.22	27.75
G_8	0.526	0.588	0.105	10.54	1.11	22.45
G_9	0.434	0.526	0.174	17.50	1.22	31.02

Table 9: Evaluation of Post Compression Parameters

Evaluation of post -compression Parameters							
co formulations	Tablet hardness test	Friability test	Variation weight	Drug tablet percentage	Drug content	Tablet thickness	disintegrates
G_1	5.6	1.470	2.97	76.70	3.835	2.95	4.26
G_2	5.3	1.503	2.95	77.14	3.857	2.93	4.30
G_3	4.8	0.644	1.54	80.06	4.003	2.55	3.17
G_4	4.7	0.628	1.43	82.34	4.117	2.54	3.31
G_5	4.3	0.789	1.89	111.92	5.600	2.53	3.53
G_6	4.4	0.854	1.76	109.95	5.490	2.54	3.53
G_7	4.7	0.590	1.10	111.02	5.501	2.56	4.18
G_8	4.5	0.545	1.05	112.85	5.642	2.55	2.53
G_9	4.9	1.276	2.19	107.69	5.385	2.54	6.48

Table 10: In Vitro Drug Release Study of Various Formulations

	% Cumulative drug release								
Formulations	**5 min**	**10min**	**15min**	**20min**	**25min**	**30min**	**35min**	**40min**	**45min**
G_1	40.10	42.40	48.80	52.67	56.32	59.51	63.07	66.19	**68.05**
G_2	42.48	43.69	48.21	55.60	57.05	59.11	64.87	67.88	**69.10**
G_3	52.97	55.30	58.92	61.77	64.23	67.19	69.05	70.44	**72.69**
G_4	50.97	54.36	57.29	61.66	65.08	68.27	70.12	72.21	**73.57**
G_5	55.35	59.96	65.11	71.80	76.00	81.61	86.37	89.03	**91.13**
G_6	56.04	58.41	64.98	72.16	78.80	82.88	87.51	90.81	**92.79**
G_7	58.18	55.99	65.00	74.31	76.19	81.95	87.87	89.01	**90.09**
G_8	55.28	59.03	66.25	73.42	80.17	84.67	88.79	91.77	**93.20**
G_9	10.47	19.18	28.47	35.98	40.65	47.22	50.77	53.66	**55.10**

Figure 1: Dissolution Profiles of Batches G_1 and G_2

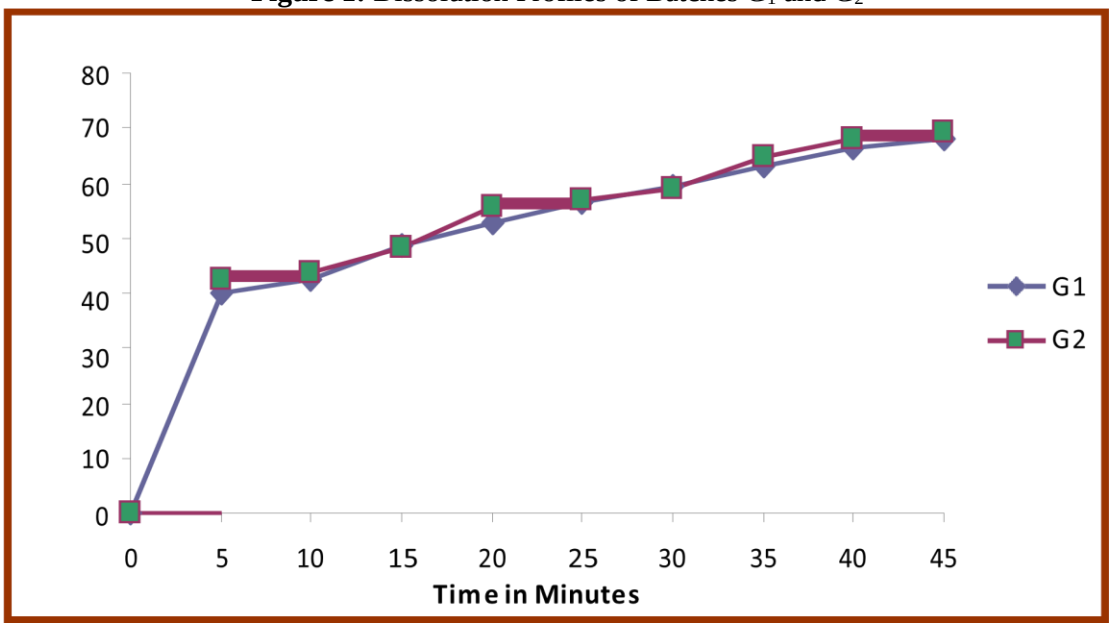
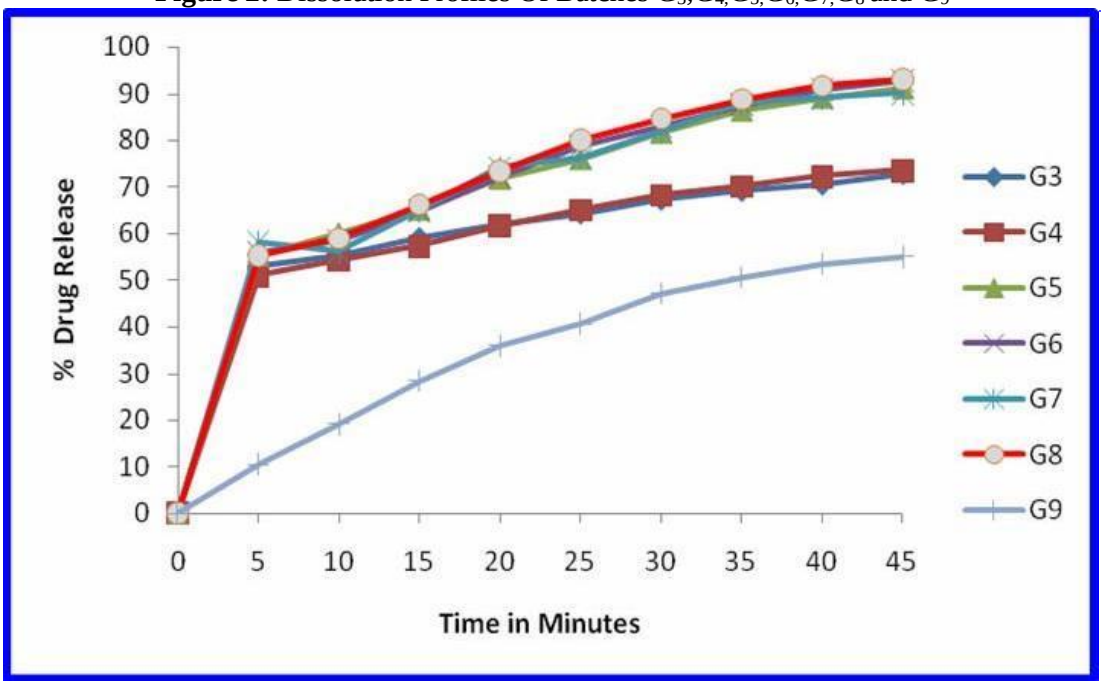


Figure 2: Dissolution Profiles Of Batches G_3,G_4,G_5,G_6,G_7,G_8 and G_9



DISCUSSION

In the present study, various formulations of immediate release folic acid tablets were prepared by wet granulation and direct compression containing 10% and 40% overages.

At first characterization of API was done followed by its compatibility studies with various excipients. Later after the formulation various pre-compression parameters like- bulk density, tapped density, Carr's index, Hausner's ratio, porosity and angle of repose and post compression parameters like hardness, weight variation, friability, disintegration time, content uniformity and in-vitro dissolution were analyzed and results were compared.

The optimized formulation was later scaled up in two batches, out of which one was film coated and both were kept for stability studies. Stability studies were performed for 2 months as per ICH guidelines at 40+20C / 75+5% RH and parameters like, hardness, disintegration time, percentage drug content and in-vitro dissolution studies were evaluated.

Characterization of Folic Acid

It was done on parameters like color, odor, taste and loss on drying and the results were found to be within the limits.

Solubility of Folic Acid

Solubility of Folic Acid in various solvents like water, methanol, hydrochloric acid and 0.01N sodium hydroxide solution were determined. Folic Acid was practically insoluble in water, insoluble in methanol and soluble in hydrochloric acid and 0.0IN sodium hydroxide solution.

UV spectrum analysis

The UV spectrum of Folic Acid was found to have wavelength maxima at 283 nm in 0.01N sodium hydroxide solution, when scanned in a range of UV-spectrum from 200-400 nm.

Standard Calibration Curve of Folic acid at 283 nm.

The absorbance of the standard solution of folic acid at 0-14µg/ml were plotted as absorbance versus concentration which gave a straight line passing from the origin with regression co-efficient 0.9998. So it followed Beer- Lambert's law at the concentration range of 0-14µg/ml.

Compatibility Studies

The drug-excipient interaction study was carried out using FTIR. The spectral data obtained showed that folic acid is compatible with all the excipients used in the formulation. Furthermore, no physical interaction with the active pharmaceutical ingredient was observed.

Evaluation of Pre-Compression Parameters.

- **Bulk Density:** Bulk density of all the formulations from G_1 to G_9 was in the range of 0.434-0.571 g/cc.
- **Tapped Density:** Tapped density of all the formulations varied from 0.526 -0.740 g/cc.
- **Porosity:** It was in the range of 0.105-0.229. All the above results were found to be satisfactory.
- **Carr's Index:** Based on the results obtained we can conclude that G_3 to G_9 showed excellent flow while G_1 and G_2 showed fair flow.
- **Hausner's Ratio:** G_3 to G_8 (except G_9) showed free flow while other formulations showed slightly cohesive flow.
- **Angle of Repose:** Based on angle of repose it was observed that G_3 to G_8 (except G_9) showed excellent flow properties than the rest of formulations.

Evaluation of Post-Compression Parameters.

- **Hardness:** The formulations showed hardness in the range of 4.3-5.6 which were acceptable.
- **Friability:** Friability of all the formulation was less than 1% except in case of G_1, G_2 and G_9 which were little more friable.
- **Weight Variation:** The maximum weight variation from all the formulation was 2.97% and minimum variation was 1.02%. So, that was within the limit of I.P. (not more than 7.5).
- **Percentage drug content and Drug content per tablet:** The percentage drug content and drug content per tablet for G_5 to G_9 were in the range of 107.69112.93% and 4.117-5.385 respectively which were within the limits. This may be due to the addition of 40% overages.
- **Thickness:** Most of the formulations showed an average thickness of 2.63mm
- **Disintegration Time:** All the formulations have different disintegration profile but that confirms within 10 min.

In-Vitro Drug Release:

G_5 to G_8 (except G_9) to which 40% overages was added showed a drug release of more than 89% at the end of 45 min which confirms within the limits given by USP which states that not less than 75% of labeled amount of folic acid was dissolved within 45 min.

G_1, G_2 and G_9 showed an in- vitro drug release of 55 to 70% at the end of 45 min which were not acceptable. G_8 showed maximum drug release of 93.20%.

SUMMARY

The present work involves the formulation development, optimization and in-vitro evaluation of immediate release Folic Acid tablets. To minimize critical process parameters and since folic acid is moisture and heat sensitive, direct compression method was selected for the formulation of immediate release Folic Acid tablets.

Under the pre formulation studies API characterization and drug-excipient compatibility studies were carried out. The API characterization showed compliance with the drug characteristics.

The polymers and other excipients were selected based on the satisfying results Produced during drug- excipient compatibility studies to develop the final formulation.

The final suitable formulation (G_8) was achieved fruitfully by the direct compression technique using pre-gelatinized starch as disintegrant which exhibited acceptable disintegration time (2.53 min), percentage drug content per tablet (112.85%) and in vitro drug release (93.20%).

On considering some important parameters like disintegration time (2.53 min), percentage drug content per tablet (112.85%), in vitro drug release (93.20%) and cost factor G_8 containing pre gelatinized starch as disintegrant was selected as the best formulation.

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