JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

PREPARATION AND EVALUATION OF IMMEDIATE RELEASE FOLIC ACID TABELTS BY USING DIRECT COMPRESSION METHOD

Dr.M.RAMA KOTAIAH[1], BOLLA ANJAL2I, CHENNABOINA MAHESH[2], CHILAKA SMILEY[2], CHITTE NAGAVASAVI[2]

1.Professor, Department of Pharmaceutics, MAM College of Pharmacy, Kasanapllli, Nasaraopet,pin:522601.

2. Department of Pharmaceutics, MAM College of Pharmacy, Kasanapllli, Nasaraopet,pin:522601.

INTRODUCTION [1]

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. 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 [2,3]

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. 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.

METHODLOGY:

PRE-FORMULATION STUDIES:

Characterization of Folic acid *[69,70]*

1. **Visual Examination-** A small quantity of folic acid powder was taken in butter Paper and viewed in well-illuminated place.
2. **Taste and Odor-** Very less quantity of folic acid was used to get taste with the Help of tongue as well as smelled to get the odor.
3. **Solubility-** The approximate solubility's of substances are indicated by the Descriptive terms in the accompanying table. Solvents such as Methanol, Water, hydrochloric acid and 0.01N sodium hydroxide solution were used for the solubility studies.

Table 19: Solubility chart

Descriptive term	Parts of solvent required for 1 part of solute
Very Soluble	Less than 1
Freely Soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very Slightly soluble	From 1000-10,000
Practically Insoluble or Insoluble	Greater than or equal to 10,000

4. **UV spectrum Analysis-** 100 mg of folic acid was accurately weighed and Scanned in the range of 230-380 nm using 0.01N sodium hydroxide solution as

   Practically insoluble or Insoluble Very slightly soluble Slightly soluble Transferred to previously dried 100 ml volumetric flask. Drug was dissolved in

   0.01N sodium hydroxide solution. The solution was suitably diluted and Sparingly soluble Blank.

5. **Loss on Drying –** Determined on 1.000 g by drying in an oven at 100°C to 105°C for 3 hours. The substance to be tested was mixed and accurately weighed. If the Sample was in the form of large crystals, reduce the particle size to about 2 mm by Quickly crushing. Then a glass stoppered weighing bottle was tarred and the sample was placed into it which was again weighed. The sample was then distributed by gentle, sidewise shaking to a depth of about 5 mm. The loaded bottle was then placed in the drying chamber dried at the specified temperature for constant weight. The chamber was opened and the bottle

was allowed to come to room temperature in a desiccator before weighing. The difference between successive weights should not be more than 0.5 mg. The loss on drying is calculated by the formula:

$$\%LOD = \frac{W_2 - W_3}{W_2 - W_1} \times 100$$

Where, W_1=Weight of empty weighing bottle

W_2=Weight of weighing bottle Sample

W_3=Weight of weighing bottle Dried Sample

5.4. PREPARATION OF CALIBARATION CURVE OF FOLIC ACID

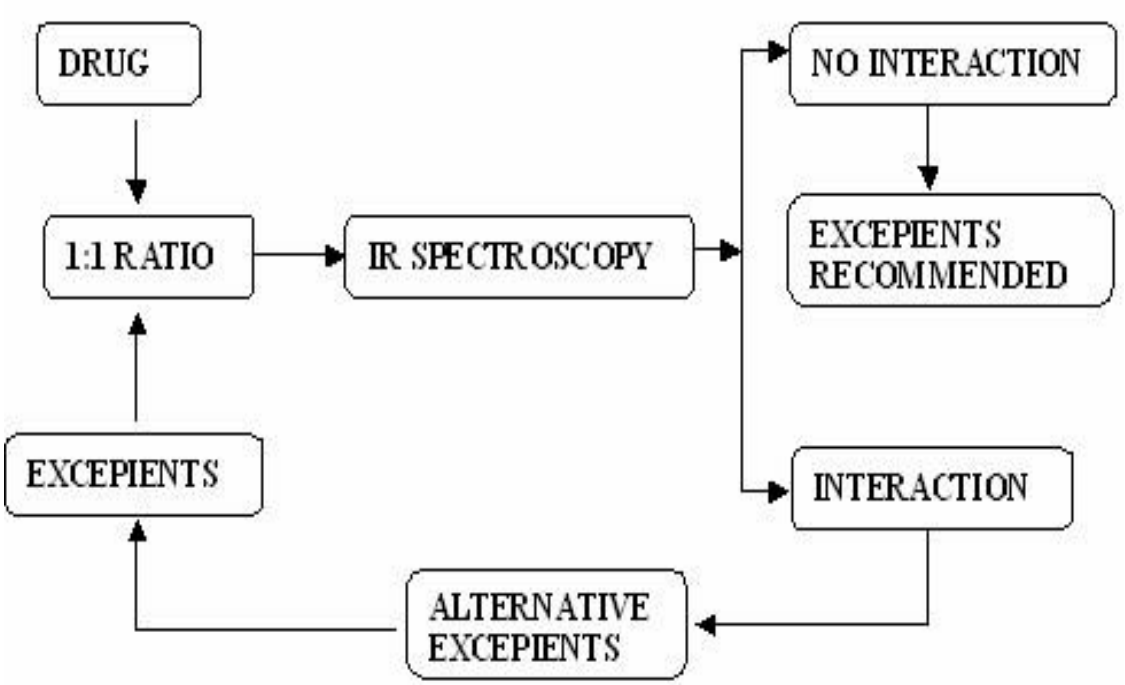
100 mg of folic acid was accurately weighed and transferred to previously dried 100 ml volumetric flask. Drug was dissolved in 0.01N sodium hydroxide solution. The solution was suitably diluted with 0.01N sodium hydroxide solution to get standard concentration of 2, 4,6,8,10,12 and 14 µg/ml. Absorbance was measured at 283 nm using using UVVisible Spectrophotometer.

5.5. COMPATIBILITY STUDIES

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristic of the ingredients used in fabricating the formulation i.e., the drug and all the excipient used in the formulation. The drug and the excipients should be compatible with one another to produce stable, efficacious, attractive and easy to administer and safe dosage form. If the excipient is new and not been used in the formulations containing the active substance, the compatibility studies are of paramount importance. Hence FTIR spectra of pure Folic acid were taken and compared with the different excipients.

Method: -Compatibility study was performed by preparing compatibility blends at different ratios of different excipients with the drug, based on tentative average weight. These blends were stored at accelerated condition of 40°C/75% RH. Control samples were stored at 4°C. The ratio of drug to excipient was 1:1 and samples were kept in double lined poly-bags. The samples were evaluated for any change in the physical characteristics with reference to its controlled sample stored at 4°C for 7, 14 and 30days. Chemical stability was confirmed by FTIR spectrophotometry.

Figure 2: Schematic representation of compatibility studies.



5.6 MANUFACTURING OF IMMEDIATE RELEASE FOLIC ACID TABLET'S

In the present investigation immediate release folic acid tablets were prepared by two Methods

1. Wet Granulation.
2. Direct Compression.

1)Preparation of Folic acid by Wet Granulation:

- All the ingredients were accurately weighed as per formula G_1 and dispensed in clean polythene covers.
- Folic Acid, Di calcium phosphate and Croscarmellose sodium were sifted through Sieve no-30.
- Microcrystalline Cellulose pH-101 and Lactose were passed through sieve no-20.
- Magnesium stearate, PVP K 30 and Colloidal silicon dioxide passed through sieve no-40.
- After sifting all the above ingredients were transferred into a big polythene cover and mixed for 30 min.
- Binder solution was prepared by dissolving weighed amount of PVP K 30 in required amount of Isopropyl alcohol.
- The above blend was taken in a stainless-steel container to which the earlier Prepared binder solution was added slowly until a wet mass like substance was formed.
- The wet mass was passed through sieve no- 16 to get wet granules which were later dried in a tray drier at 50°c for 1 hour.

- The dried granules were again passed through sieve no- 16 and thoroughly mixed with magnesium stearate and colloidal silicon dioxide.

2)Preparation of Folic acid by Direct Compression:

- All the ingredients were accurately weighed as per formula G_2 to G_9 and were Dispensed in clean polythene covers.
- Folic Acid, Di calcium phosphate and Croscarmellose sodium were sifted through Sieve no-30.
- Microcrystalline Cellulose pH-101 and Lactose were passed through sieve no-20.
- Magnesium stearate and Colloidal silicon dioxide passed through sieve no-40.
- Folic Acid and Di calcium phosphate were mixed in a polythene cover marked as DC- I
- Microcrystalline Cellulose pH-101, Lactose and Croscarmellose sodium were Mixed in polythene cover marked as DC-II.
- Magnesium stearate and Colloidal silicon dioxide were mixed in polythene cover marked as DC-III.
- The covers were mixed thoroughly for 30 min.
- Then DC-II and DC-III were added to DC-I and again mixed thoroughly for 30 Min.

3)Procedure for Scale up of Folic acid Tablets:

- Scale up was done by following the same procedure as given for direct Compression.
- Mixing was carried out in a Double cone blender for 15 min.
- This blend is then subjected to direct compression on a Double Rotary Compression Machine (27 station) at 100 rpm to yield folic acid tablets.

4)Tablet Compression:

- G_1 and G_2 - Compressed using 6mm concave punches as per company requirement. G_3 to G_9 – Compressed using 7mm concave punches due to picking and sticking Observed with earlier punches.

RESULTS

Table 27: Characterization of Folic Acid

Test	Specifications Or Limits	Observations
Color	Yellow to Orange Yellow Powder	Yellow to Orange Yellow Powder
Taste	Taste Less	Taste Less
Odor	Odor Less	Odor Less
Loss on drying	Not More Than 0.2%	0.112%

Table 28: Solubility of Folic Acid

Quantity Of Folic Acid	Quantity of Solvents	Inference
100 mg	30 ml of Water	Practically In Soluble
100 mg	100 ml of Methanol	In Soluble
100 mg	100 ml of Hydrochloric acid	Soluble
100 mg	0.01 N Sodium Hydroxide Solution	Soluble

Figure 3: UV spectrum analysis of Folic Acid

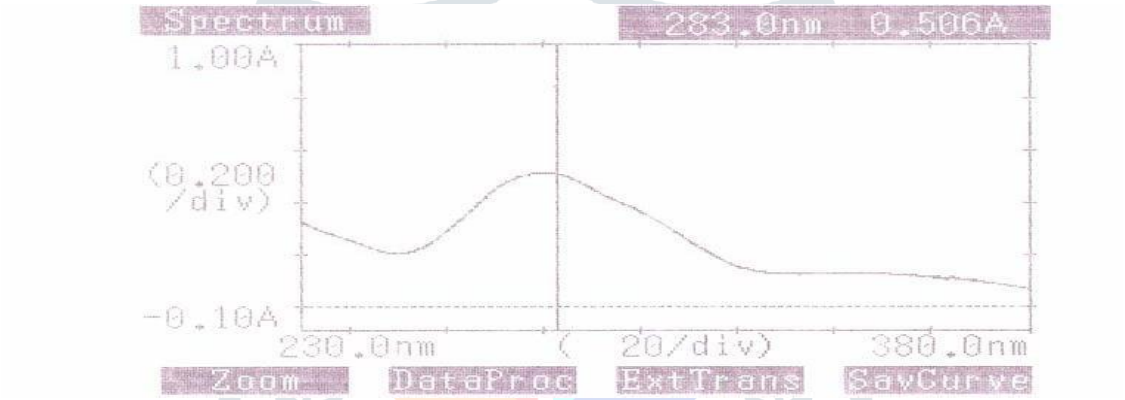


Table 29: Standard Calibration Curve of Folic acid at 283 nm.

Concentration	Absorbance			Average
(µg/ml)	Trial-1	Trial-2	Trial-3	Absorbance
0	0	0	0	0
2	0.127	0.125	0.126	0.126
4	0.237	0.236	0.237	0.236
6	0.346	0.345	0.344	0.345
8	0.451	0.451	0.450	0.450
10	0.553	0.553	0.554	0.553
12	0.662	0.662	0.665	0.663
14	0.765	0.764	0.760	0.763

Figure 4: Standard Calibration Curve of Folic acid at 283 nm.

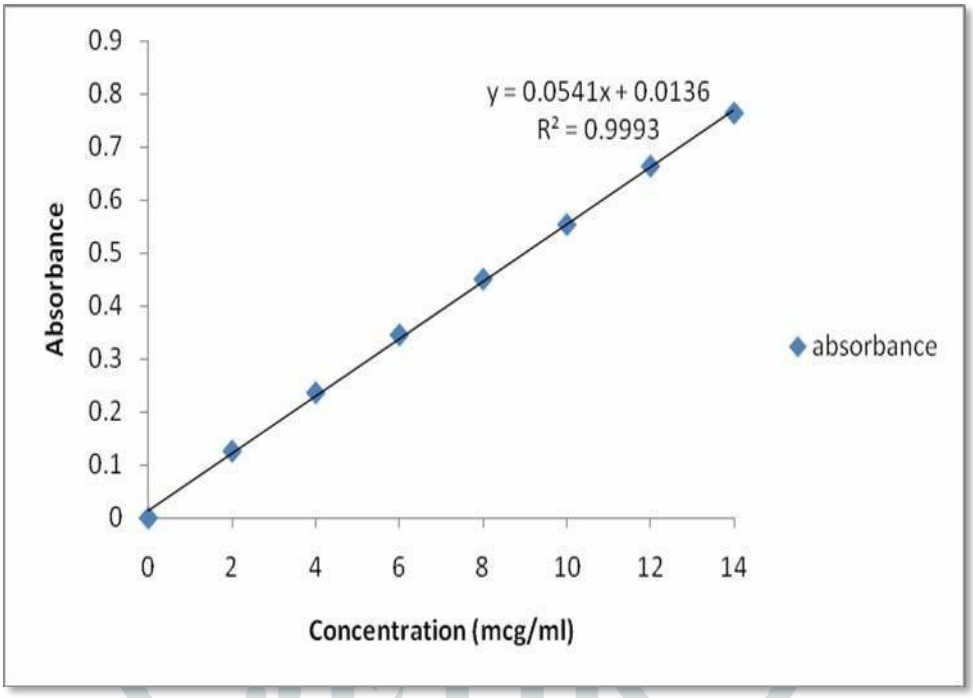


Table 30: Compatibility Studies

S.NO	Drug +Excipients	Ratio	Initial Color	Condition (40^0C/75%RH)			
				7	14	30	Conclusion
1	Folic acid +Microcrystalline cellulose pH 102	1:1	YELLOW Or ORANGE YEL	* *	* *	* *	Compatible
2	Folic acid + Lactose	1:1		* *	* *	* *	Compatible
3	Folic acid + Dicalcium Phosphate	1:1		* *	* *	* *	Compatible
4	Folic acid + Croscarmellose Sodium	1:1		* *	* *	* *	Compatible
5	Folic acid + Magnesium Sterate	1:1		* *	* *	* *	Compatible
6	Folic acid + Colloidal Silicon di oxide	1:1		* *	* *	* *	Compatible
7	Folic acid + Cross povidone	1:1		* *	* *	* *	Compatible

8	Folic acid + pre-gelatinized starch	**1:1**	**LOW POWDER**	* *	* *	* *	Compatible
9	Folic acid + Sodium starch glycolate	**1:1**		* *	* *	* *	Compatible
10	Folic acid Final blend	**…….**		* *	* *	* *	Compatible

Figure 5: IR Spectra of Folic Acid

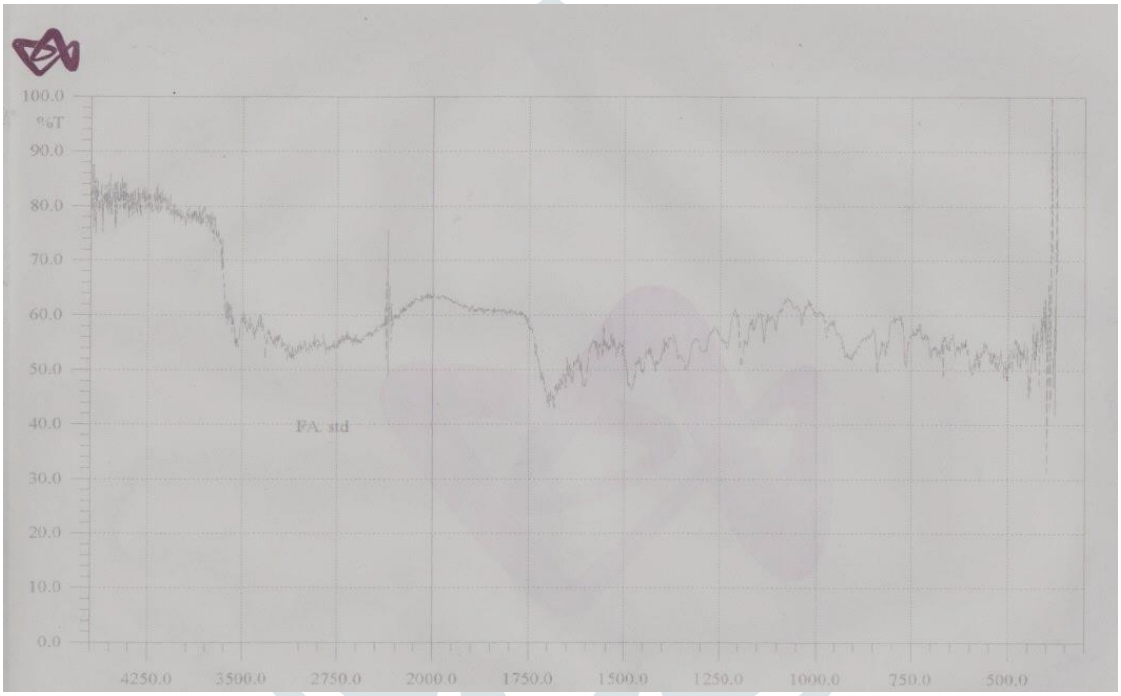
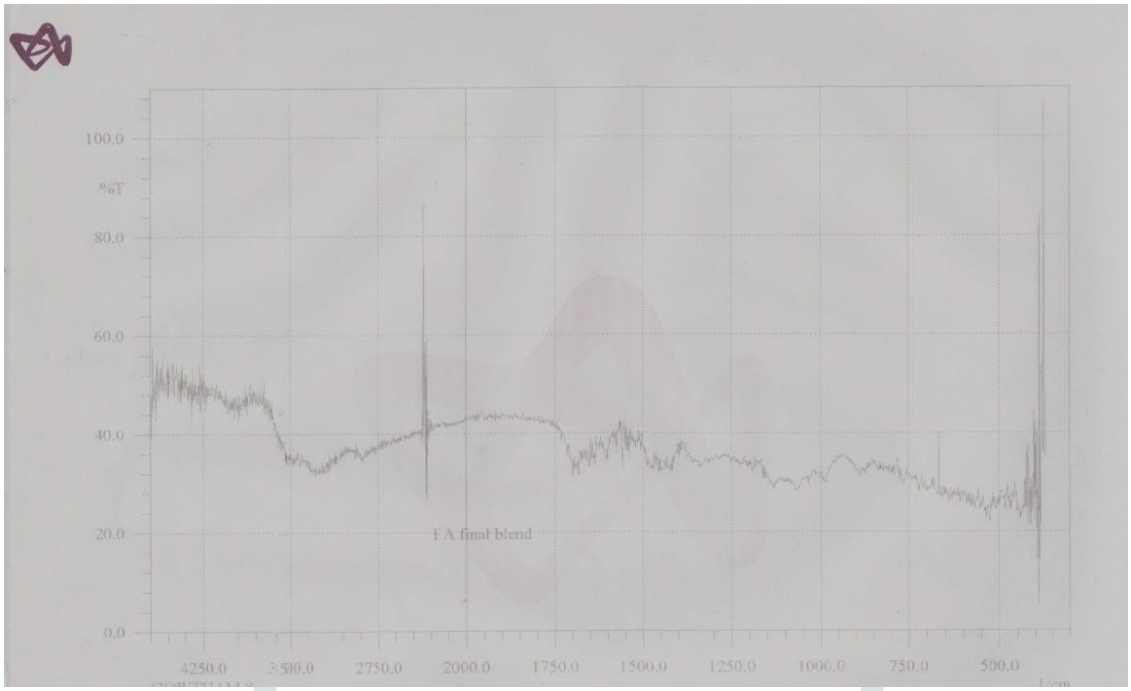


Figure 6: IR Spectra of Folic Acid Final Blend



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.

CONCLUSION

Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatingsand other techniques.

Folic acid (also known as vitamin B, or folacin) were forms of the water-soluble vitamins. Folic acid was itself not biologically active, but its biological importance is due to tetrahydrofolate and other derivatives after its conversion to dihydrofolic acid in the Liver.

Before the preparation of immediate release tablets, the sample of drug provided was characterized for Folic Acid on the following parameters: -Visual Examination, Taste and Odor, Solubility, UV spectrum Analysis and Loss on Drying. The results concluded that the sample was Folic Acid. Then calibration curve of folic acid was taken and the suggested excipients were subjected to compatibility studies with folic acid using FTIR. All the excipients were found to be compatible.

In this present work, immediate release tablets of Folic Acid were prepared by two methods

1.Wet granulation

2.Direct compression

Preparation of Folic acid by wet Granulation

- It was done as per formula G_1 using 10% overages, MCC-101 PH and binder solution prepared by PVPK 30 and Isopropyl alcohol which were then evaluated for pre and post compression parameters. All the pre compression parameters like bulk density, tapped density and porosity and post compression parameters like hardness, thickness and disintegration were found to be satisfactory.

- But some parameters like angle of repose, Carr's index, Hausner's ratio etc were found to be above the desired range which indicated poor flow characteristics.

  Percentage drug content per tablet and in vitro drug release was found to be 76.70% and 68.05% at 45 min respectively, which were not acceptable.

Preparation of Folic acid by Direct Compression

- Direct compression was preferred for the preparation of immediate release tablets of Folic Acid because-
- It is more suitable for moisture and heat sensitive APIs, since it eliminates wetting and drying steps and increases the stability of active ingredients by reducing detrimental effects.
- Here tablets were prepared according to formulae G_2 to G_9 .In case of G_2 where 10% overages and MCC-102 PH were used, percentage drug content per tablet and in vitro dissolution was found to be 77.14% and 69.10 % at 45 min respectively, which were not acceptable.
- Then tablet weight was increased to 150 mg from G_3 to G_9 which were prepared by using various super disintegrants like cross carmellose sodium, cross povidone, sodium starch glycolate, and pre gelatinized Starch. In formulae G_5 to G_9 or 40% overages were added to overcome stability loss. All the pre and post compression parameters were within the limits.
- All the formulations showed in vitro drug release of 89-94% except G_9 which was formulated without disintegrants. G_9 showed poor disintegration time and in vitro drug release of 55.10% which were not satisfactory.
- 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.
- So G_8 containing pre gelatinized starch as disintegrant was selected as the best formulation

BIBLIOGRAPHY

1) Banker GS, Anderson SN. Modern pharmaceutics. 4 ed. New York: Taylor & Francis Group:2005.

2) Allen LV, Nicholas GP, Howard CA. Ansel's pharmaceutical dosage forms & drug delivery systems, 8th ed. New Delhi: Lippincott Williams & Wilkins; 2005.

3) Rudman A. Guidance for industry-Immediate release solid dosage forms. CDER 1995 Nov; 59(83): 48754-59..

4) Herbert AL, Leon L, Joseph BS. Pharmaceutical Dosage forms- Tablets. 2 ed. New York: Vol. I, II and III Marcel Dekker; 1989.

5) Arora V, Gupta VB, Singhal R. Advance in direct compression technologies. Pharma Times 2007; 39(2): 26-27

6) Greaves FC, Beasley MW, Suddith AW, Swarbrick J. Novel approaches to the preparation of low dose solid dosage forms. Pharm Tech 1995; 61-64.

7) Hariharan M, Gupta VK. A novel compression coated tablet dosage form. Pharm Tech 2001; 14-19.

8) Well J. Aulton ME. The science of dosage form design-pre formulation in pharmaceutics. International student edition; 1998.

9) Tousey MD. The granulation process 101. Pharm Tech 2002; 8-13.

10) Herbert AL, Leon L, Joseph BS. Pharmaceutical Dosage forms- Tablets. 2 ed. New York: Marcel Dekker; 1989.

11) Leon L, Herbert AL, Joseph LK. The theory and practice of industrial pharmacy, 3rd ed. Varghese Publishing House; 1991.

12) Geraro AR. Remmington's pharmaceutical sciences. 18th ed. Mack Publishing Co.; 1999.

Colorcon modified release technologies. Innovation In Pharmaceutical Technologies [Online] 2003 Mar [cited 2003 Mar]; 1(3). Available from: URL:http://colorcon.com