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Formulation and In vitro evaluation of Fosinopril fast dissolving tablets

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ABSTRACT

The concept of formulating fast dissolving tablets using super disintegrants offers a suitable and practical approach of faster disintegration and dissolution characteristics. The formulations F1 to F9 Were prepared. Among the various method of preparation fast dissolving tablets were prepared by using super disintegrants like CCS, CP and SSG by direct compression. The formulations F1 to F3 are prepared with 10% concentration of CCS, CP and SSG. The formulations F4 to F6 are prepared with 15% concentration of CCS, CP and SSG. The formulations F7 to F9 are prepared with 20% concentration of CCS, CP and SSG. The prepared tablets of fosinopril were evaluated for precompression parameters like angle of repose, bulk density, tapped density, Carr's index and postcompression parameters like the hardness, friability and weight variation, drug content, disintegration time, and *IN VITRO* dissolution studies. Among the various fast dissolving tablets of fosinopril F7 formulation shows maximum drug release in 30min.

Keywords: Fosinopril, CCS, CP and SSG.

INTRODUCTION

Oral solid dosage forms

A solid dosage form is drug delivery system that includes tablets, capsules, sachets and pills as well as a bulk or unit-dose powders and granules. Among the various dosage forms oral soliddosage forms have greater importance and occupy a prime role in the pharmaceutical market. Oral route of drug administration is widely acceptable and drugs administered orally as solid dosage form represents the preferred class of products. Over 90% of drugs formulated to produce systemic effects are produced as solid dosage forms. Because of these reason whenever New chemical entity (NCE) has discovered, which shows a sufficient pharmacological action, first the pharmaceutical company asks whether the drug is successfully administered by oral route or not. The oral route of administration still continues to be the most preferred route due to its manifold advantages [5].

Tablets and capsules represent unit dosage forms in which the accurate dose of drug to show sufficient pharmacological action can be administered. In case of liquid oral dosage forms such as Syrups, Suspensions, Emulsions, Solutions and Elixirs the patient is asked to administer the medication of 5-30 ml. Such dosage measurements are typically error by factor ranging from 20-50 %, when the drug is self administered by patient [6]. Solid dosage forms are less expensive to shipping and less prone for the degradation when compared to liquid dosage forms [4].

In 1843, the first patent for a hand operated device used to form a tablet was granted." Tablets are defined as solid preparations each containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of particles. They 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 ingredient "liberated". Tablets are used mainly for systemic drug delivery but also for local drug action. For systemic use drug must be released from tablet that is dissolved in the fluids of mouth, stomach and intestine and then absorbed into systemic circulation by which it reaches its site of action [8]. Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer [e.g. simplicity and economy of preparation, stability and convenience in packing, shipping and dispensing] and the patient [e.g. accuracy of dosage, compactness, portability, blandness of taste and ease of administration [10].

They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration [2]. They may have lines or break-marks and may bear a symbol or other markings. Tablets may be coated.

MATERIALS AND METHODS

Table 1: Formulation of fosinopril fast dissolving tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Fosinopril	10	10	10	10	10	10	10	10	10
SSG	10			15			20		
CCS		10			**15**			**20**	
CP			**10**			15			**20**
Mg.stearate	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**
Talc	5	5	5	5	5	5	5	5	5
PVP K30	10	10	10	10	10	10	10	10	10
Sodium bicarbonate	-	--	-	-	-	-	10	10	10
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	200	200	200	200	200	200	200	200	200

Formulation Planning

The fast dissolving tablets containing 10mg Fosinopril were prepared with a total tablet weight of 200mg.

Manufacturing Procedure

- Micro crystalline cellulose, cross Carmellose sodium/sodium starch glycolate/cross povidone, PVP were weighed and sifted through 40 mesh.
- To the above blend Fosinopril was added and sifted through 18 mesh.
- The sifted material was placed in poly bag and mixed for 5 min.
- To the above blend add mg.stearate and Talc, and this lubricated blend was added and placed in poly bag and mixed for 2-3 min.
- The lubricated blend was compressed using 8 mm round punches.

Evaluation of tablets

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters.

Physical Appearance

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

Size & Shape

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

Weight variation test

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests. These tests are primarily based on the comparison of the weight of the individual tablets of a sample of

tablets with an upper and lower percentage limit of the observed sample average. The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Method

Table 2: limits for tablet weight variation test

Average weight of tablet (mg)	% Difference allowed
130 or less	10%
From 130 to 324	7.5%
> 324	5%

Content Uniformity

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets and all capsules intended for oral administration where the range of size of the dosage form available include 50mg or smaller sizes.

Method

Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Thickness and diameter

The thickness and diameter of 10 tablets were recorded during the process of compression using vernier calipers.

Hardness

Hardness, which is now more appropriately called crushing strength determinations are made during tablet production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations.The force required to break the tablet is measured in kilograms. The small and portable hardness tester measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet.

Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Method

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula

% Friability = $(W_1-W_2) / W_1 \times 100$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

Disintegration test

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms.

Method

The U.S.P. device to test disintegration uses 6 glass tubes that are open at the top and 10 mesh screen at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2^0C such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets.

Disintegration time: Uncoated tablet: 5-30 minutes.

Dissolution

Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. Dissolution is considered one of the most important quality control tests performed on pharmaceutical dosage forms and is now developing into a tool for predicting bioavailability.

Dissolution

Stability studies [11]

The stability study of the formulations were carried out according to ICH guidelines at 40 ± 2o C/75 ± 5 % RH for one month by storing the samples in stability chamber (Lab-care, Mumbai).

The purpose of stability testing is to provide evidence of the quality of the drug substance ordrug product, and how it varies with time under the influence of a variety of environmental conditions (heat, humidity, light, air etc).

The final formulation was packed in suitable packing like blister and strip packs and then they will be kept at different temperature, humidity conditions and the samples will be analyzed for their physical and chemical properties.

Table 3: Stability studies Storage conditions

Study	Storage conditions	Minimum time period covered by data at submission.
Long term	25 ± 2°c / 60 ± 5% RH or 30 ± 2°c / 75 ± 5% RH	12 months
Intermediate	30 ± 2°c / 65 ± 5% RH	6 months
Accelerated	40 ± 2°c / 75 ± 5% RH	6 months

RESULTS AND DISCUSSION

Compatibility studies

Drug polymer compatibility studies

FT-IR spectroscopy was employed to ascertain the compatibility of Fosinopril with polymers. The individual drug and drug with polymers were separately scanned. Both the spectra were compared for confirmation of common peaks. Fosinopril with polymers showed no significant variation in height, intensity and position of peaks, suggesting that drug and excipients were compatible. There is no interaction between drug and polymer. Hence, it can be concluded that the drug is in free state and can release easily from the formulation the spectra are reported in the table

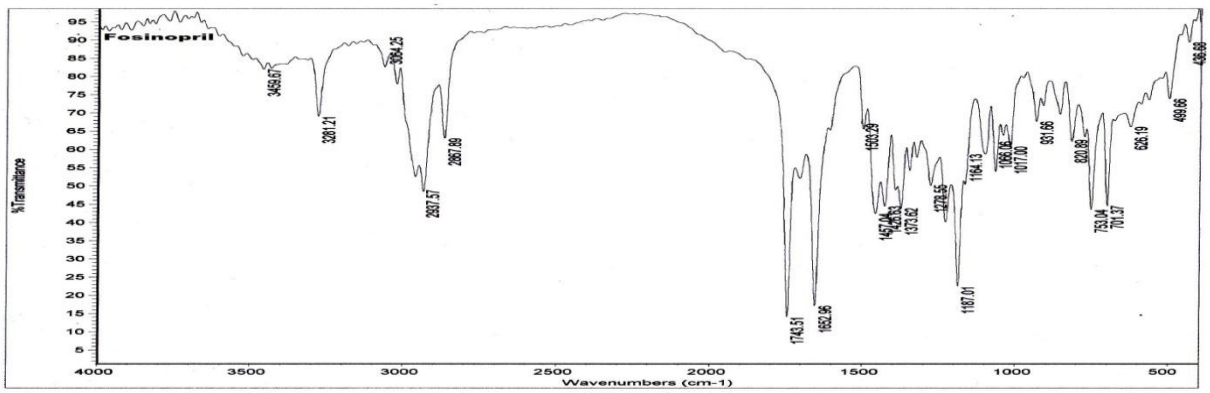

Fig No 1: Ftir Spectra of pure drug

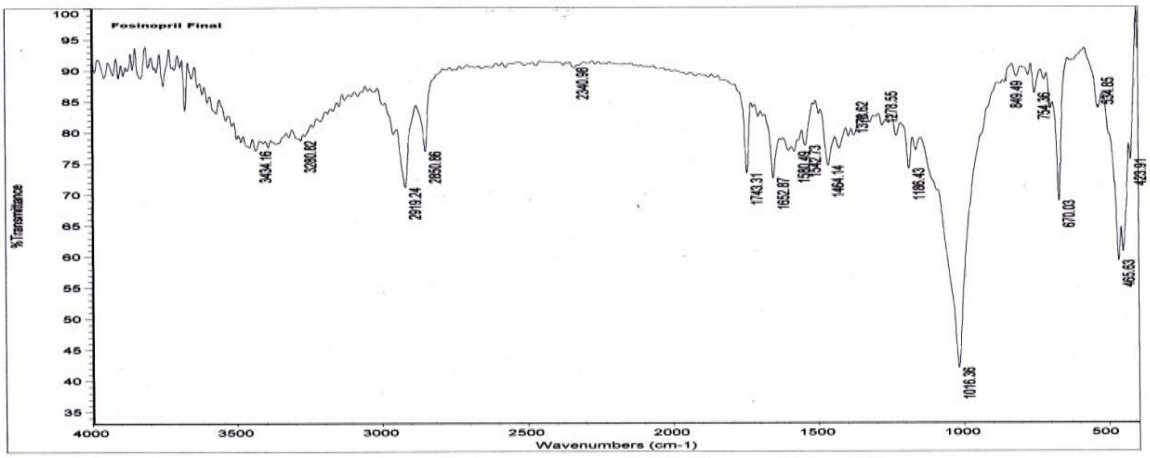

Fig 2: FTIR Spectra of optimized formulation

Table 4: FT-IR Spectra data of FOSINOPRIL fast dissolving tablets

S. No	Functional group	Characteristic peak cm^{-1}	Observed peak for drug cm^{-1}	Peaks for optimized formulation
1	P=O	1300 -1250	1278	1278.55
2	C-N=O	1600 - 1500	1503	1580
3	-CH3	2960 - 2850	2867	2850

Evaluation of Blend

Table 5: Micromeritic properties

Formulation code	Bulk density, gm/ml	Tapped density, gm/ml	Carr's index %	Hausner ratio	Angel of repose
F1	0.453	0.689	34.252	1.520	25
F2	0.489	0.710	31.126	1.451	22
F3	0.710	0.873	19.714	1.251	26
F4	0.721	0.870	17.126	1.206	27
F5	0.718	0.871	18.513	1.223	28
F6	0.410	0.483	15.113	1.178	24
F7	0.420	0.482	15.010	1.131	25
F8	0.541	0.691	21.62	1.276	25
F9	0.484	0.615	21.30	1.270	27

Evaluation of Tablets

Table 6: Post compression studies

Formulation code	Weight variation	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Content uniformity	Disintegration Time (min)
F1	198	6.5	0.65	3.41mm	99.28	4 min 24 sec
F2	198	6.3	0.67	3.43mm	99.16	5 min
F3	199	6.0	0.68	3.45mm	101.1	5 min
F4	200	6.4	0.64	3.42mm	98.68	2min
F5	200	6.1	0.64	3.44mm	99.41	4 min
F6	201	6.0	0.65	3.42mm	102.6	3 min
F7	198	6.2	2.3	3.4mm	99.28	1 min
F8	198	6.5	1.8	3.4mm	99.5	1min 45 sec
F9	200	6.3	0.68	3.43mm	99.6	1min 50 sec

In -vitro drug release study

Paddle method Dissolution data of fast dissolving formulations of Fosinopril by Paddle method (USP II) are reported in Table14.

Table 7: Dissolution Profile

Time in min	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	**15**	**11**	**14**	**17**	**18**	**20**	**21**	**20**	**22**
10	**24**	**20**	**26**	**28**	**29**	**34**	**55**	**49**	**34**
15	**38**	**31**	**34**	**42**	**36**	**48**	**63**	**58**	**45**
20	**46**	**43**	**47**	**54**	**45**	**59**	**88**	**72**	**67**
30	**68**	**60**	**52**	**72**	**66**	**66**	**98.7**	**89**	**80**
45	**75**	**70**	**68**	**97**	**79**	**83**		**90**	**95.6**
60	**87**	**81**	**85**		**86**	**94**			

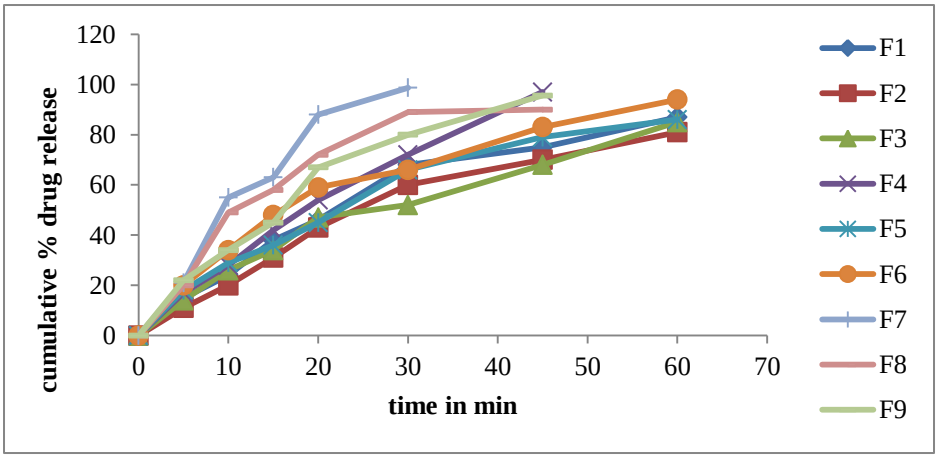

Figure 3: Cumulative % drug release for formulations F1-F9

Stability studies

Fosinopril tablets of F7 formulation were packed in HDPE (High density polyethylene) container with child resistant caps (CRC) and induction sealed. These bottles were charged for stability study at 40^{0}C &75% RH.

After one month

Table 8 Physical evaluation of Tablets for stability studies of Optimized formulation:

Parameter	Initial	40^0C / 75%RH
Colour	white	White
Surface	Smooth	Smooth
Disintegration(min)	1min	1min 20 sec
Assay	99.28	99.0

Observation

The Fosinopril tablets were subjected to stability studies at 40^{o}C and 75% RH for 1 month and from the above results, it was found that there is no significant effect on the tablets

After Three months

Table 9 Physical evaluation of Tablets for stability studies of optimized formulation:

Parameter	Initial	40^0C / 75%RH
Colour	white	White
Surface	Smooth	Smooth
Disintegration (min)	1min	1min 22 sec
Assay	99.28	98.7

Observation

The Fosinopril tablets were subjected to stability studies at 40^{o}C and 75% RH for 3 months and from the above results, it was found that there is no effect on the tablets and was found to be with in the limits according to ICH guidelines.

CONCLUSION

The concept of formulating fast dissolving tablets using super disintegrants offers a suitable and practical approach of faster disintegration and dissolution characteristics. Among the various method of preparation fast dissolving tablets were prepared by using super disintegrants like CCS, CP and SSG by direct compression.The prepared tablets of fosinopril were evaluated for precompression parameters like angle of repose, bulk density, tapped density, Carr's index and postcompression parameters like the hardness, friability and weight variation, drug content, disintegration time, and in vitro dissolution studies. Among the various fast dissolving tablets of fosinopril F7 formulation shows maximum drug release in 30min.

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