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PHYTOCHEMICAL SCREENING AND TLC FINGERPRINTING FORMULATION AND EVALUATION OF FAST DISINTEGRATING TABLETS OF FENOFIBRATE

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Abstract:

Fenofibrate is a drug of the fibrate class. It is a widely used hypolipidemic drug. The poor aqueous solubility of the drug leads to variable dissolution rates. It is slightly soluble in water. Fast disintegrating tablets (FDTs) of Fenofibrate were prepared using different concentrations of superdisintegrants using wet granulation method. The technique is to increase the bioavailability of the tablets and drug release in the patients. The porous granules were then compressed in to tablets. The blend was examined for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The prepared tablets were evaluated for hardness, friability, in vitro disintegration time and in vitro dissolution studies. Fast disintegrating tablets (FDTs) have received ever-increasing demand during the last decade and the field has become a rapidly growing area in the pharmaceutical industry. Fast disintegrating tablets (FDTs) are those solid dosage forms when put on tongue, disintegrate or dissolve instantaneously, releasing the drug, within a few seconds without the need of water. Fast disintegrating tablets (FDTs) aim for designing dosage forms, convenient to be manufactured and administered, free of side effects, offering immediate release and enhanced bioavailability, to achieve better patient compliance. Fast disintegrating tablets have been formulated for pediatric, geriatric, and bedridden patients and for active patients who are busy and traveling and may not have access to water. Such formulations provide an opportunity for product life extension in the many elderly persons which have difficulty in taking conventional oral dosage form (viz., solutions, suspensions, tablets, and capsules) because of hand tremors and dysphasia. The current article is focused on ideal requirements, need for development of FDTs, suitability of drug candidates, super disintegrants employed.

Keywords: *Fast disintegrating tablets (FDTs), Super disintegrants, Enhanced bioavailability, Patient's compliance, Evaluation, dysphasia.*

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INTRODUCTION:

Drug delivery system is an efficient tool for enhancing market, extending product life cycles and creating opportunities. Drug delivery system (DDS) makes a significant contribution to global pharmaceutical sales through market segmentation, and is moving rapidly. Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, non invasive method and ease of administration leading to high level of patient compliance. The most popular dosage forms are being conventional tablets and hard gelatin capsules. One important drawback of such dosage forms is Dysphasia‟ or difficulty in swallowing for many patients; almost 50% of the population is affected by such problem. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. Recently, fast disintegrating drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. To overcome such problems, fast disintegrating tablets or orally disintegrating tablets have emerged as an alternative dosage form. Pharmaceutical technologists have put in their best efforts to develop a fast dissolving/ disintegrating drug delivery system (FDDTs).The Center for Drug Evaluation and Research(CDER), US FDA defined Fast dissolving/disintegrating tablets (FDDTs) are “A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue”. Recently European Pharmacopoeia also adopted the term “Oro Dispersible Tablet” defined as uncovered tablet for buccal cavity, where it disperses before ingestion”. Fast disintegrating tablets (FDT) are also known as fast dissolving, mouth dissolving, rapid-dissolve, quick disintegrating, quick dissolving, and porous tablets, EFVDAS or Effervescent Drug Absorption System. Fast disintegrating tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. When Faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The advantage of mouth dissolving dosage forms are increasingly being recognized in both, industry and academics. The basic approach in development of FDT is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel,explotab), cross linked polyvinylpyrollidone (crospovidone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet. The target populations for these new fast-dissolving/disintegrating dosage forms have generally been pediatric, geriatric, and bedridden or developmentally disabled patients. Patients with persistent nausea, who are traveling, or who have little or no access to water are also good candidates for FDTs. A “Super disintegrants” is an excipient, which is added to tablet or capsule blend to aid in the breakup of the compacted mass, when put into a fluid environment. This is especially important for immediate release product where rapid release of the product is required. These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. The use of superdisintegrants is the basic approach in the development of fast disintegrating tablets (FDTs). Superdisintegrants plays a major role in the dissolution and disintegration of the tablets. It is essential to choose an optimum concentration of superdisintegrants so as to ensure rapid disintegration and high dissolution rates of tablets. Superdisintegrants provide rapid disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. The optimum concentration of the superdisintegrant can be selected according to the critical concentration of the disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrant, where as above this concentration the disintegration time remains almost constant or even increases 34Common superdisintegrants used in formulation are croscarmellose sodium (Vivasol, Ac-Di-Sol), crospovidone (Polyplasdone), carmellose (NS-300), carmellose calcium (ECG-505), sodium starch glycolate (SSG) etc. Recently few ion exchange resins (e.g. Indion 414) are found to have

superdisintegrant property and are widely used in pharmaceutical industry.

MATERIALS AND METHODS:

Fenofibrate was obtained as gift sample from MSN Labs, Hyderabad. Mannitol, Micro crystalline cellulose, Talc, Magnesium stearate used was of Pharmacoepial grade. Crospovidone, Sodium Starch Glycolate (SSG), where obtained from S.D fine chemicals. All chemicals used were of analytical grade.

Preparation of fast disintegrating tablets

Tablets were prepared by wet granulation method. Dissolve the required quantity of MCC in purified water and used as a binder solution. Add binder solution to mixture containing drug, Mannitol, SSG, and Crospovidone was prepared in motor by mixing with pestle. The wet granular mass is obtained and passed through Sieve No.18 to get wet granules which were dried in hot air oven at 60°c for 45 minutes. The dried granules were sifted through Sieve No.20 followed by lubrication with magnesium stearate and Talc. The final blend was mixed thoroughly for 2-3 minutes in the poly bag and tablets were compressed using single punch tablet machine.

Precompression Parameters

Angle of repose (Ɵ)

Angle of repose was determined using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height, h, was obtained. Diameter of heap D was measured. The angle of repose Ɵ was calculated by formula:

$$\text{Tan } Ɵ = h/r \quad Ɵ = \tan^{-1}(h/r)$$

Where Ɵ is the angle of repose, h is the height in cm and r is the radius.

Bulk density (Db)

Apparent bulk density was determined by pouring pre-sieved drug-excipient blend into graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/ml and is given by:

$$Db = M / V0$$

Where M is the mass of powder and V0 is the bulk volume of the powder.

Tapped density (DT)

It was determined by placing a graduated cylinder, containing a known mass of drug excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by:

$$DT = M / VT$$

Where M is the mass of powder and VT is the tapped volume of the powder

Carr's Index

It is expressed in percentage and is expressed by

$$\text{Carr's index} = [\text{d tap-d bulk} / \text{d tap}] \times 100$$

Where, tap= Tapped density or True density, bulk = Bulk density.

Hausner's ratio

Tapped density and bulk density were determined and the Hausner's ratio was calculated by the following formula,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table-1: Specifications for flow properties

Flow Character	Carr's index (%)	Hausner's ratio	Angle of repose [^{0}]
Excellent	≤10	1.00-1.11	25-30
Good	11-15	1.12-1.18	31-35
Fair (aid not needed)	16-20	1.19-1.25	36-40
Passable (may hang up)	21-25	1.26-1.34	41-45
Poor (must agitate/vibrate)	26-31	1.35-1.45	46-55
Very poor	32-37	1.46-1.59	56-65
Very, very poor	≥38	>1.60	.>66

Table-2: Formulation Development of Fenofibrate Fast disintegrating Tablets

Ingredients[mg]	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Fenofibrate	160	160	160	160	160	160	160	160	160	160
Mannitol	35	35	35	35	35	35	35	35	35	35
MCC	60	60	60	60	60	60	60	60	60	60
Sodiumstarch glycolate	10	12	14	16	18	20	11	13	19	15
Cross povidone	20	18	16	14	12	10	19	17	11	15
Talc	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10	10	10
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total	305	305	305	305	305	305	305	305	305	305

EVALUATION OF TABLETS

Hardness

Hardness or crushing strength is the force required to break a tablet in diametric compression. Hardness of the tablets is determined by Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moving along the gauze in the barrel at which the tablet fractures indicates the hardness of the tablet. Six tablets from each batch were taken randomly and their hardness was determined.

Friability

This test is performed to evaluate the ability of a tablet to withstand abrasion in packing, handling and transporting purpose. Twenty sample tablets were rotated at 25rpm for 4 minutes by a USP-type Roche friabilator, then reweighed after removal of fines and the percentage weight loss was calculated according to the following formula. The tablets were found to pass the friability test, if the percentage weight loss was found to be less than 1%.

% Friability= (W0-W)/W0 x100

Where W0=initial weight of twenty tablets, W= weight of 20 tablets after 100 revolutions

Disintegration time

The disintegration test is carried out in an apparatus (Electro lab, Mumbai) containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900 ml which is maintained at 37 ± 2^0C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh (#10) was considered as the disintegration time of the tablet. The disintegration time that patients can experience for fast disintegrating tablets ranges from 30 to 70 sec.

Dissolution Study

The release rate of fenofibrate fast disintegrating tablets was determined using United States pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method) .The dissolution test was performed using 900 ml of Phosphate buffer pH 6.8, at 37 ± 0.5C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus and the samples were replaced with fresh dissolution medium. The samples were filtered through filter paper. Absorbance of these solutions was measured at 249 nm using a UV/Visible Spectrophotometer. The drug release was plotted against time to determine the release profile.

Stability Studies

The optimized formulation was subjected for stability studies at accelerated conditions of a temperature 40 ^{0}C and a relative humidity of 75% and at 0, 10, 20 and 30 days for their physical appearance, hardness, disintegration time, friability and %drug release.

RESULTS AND DISCUSSION:

In present study, an attempt has been made to formulate and evaluate fast disintegrating tablets of fenofibrate by wet granulation method. These tablets were evaluated for pre compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. These are also

evaluated for post compression parameters such as hardness, friability, disintegration time and in vitro dissolution study. Ten formulations were prepared, the powder blend of ten formulations F1 to F10 was evaluated for Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio, which showed the pre-compressed blend, has good flow property. Hardness of tablet was found in the range of 3.2 to 3.9 kg/cm. Friability was found to be below 1% which indicates good mechanical strength of the tablets. The results are shown in Table 3. *In-vitro* drug release studies were performed with all formulations. The results are accordingly tabulated in Table 5. The percentage drug release for the formulation F10 was found 97.07 at the end of 60 minutes. Formulation F10 prepared with sodium starch glycolate, and crospovidone was found to be the optimized formulation than other formulations. The optimized formulation F10 were selected for accelerated stability studies and the tablets possessed the same parameters even after the stressed conditions, indicates good stability properties of formulation in Table 6.

Table-3: Evaluation of fast disintegrating tablets of fenofibrate

Formulations	Bulk density[g/cc]	Tapped density[g/cc]	Angle of repose[^{0}]	Carr's index	Hausner's ratio
F1	1.71	1.96	32.46	12.75	1.14
F2	1.74	1.98	31.63	12.12	1.13
F3	1.69	1.97	34.31	14.21	1.16
F4	1.66	1.92	33.42	13.54	1.15
F5	1.68	1.91	34.24	12.04	1.13
F6	1.76	2.04	32.13	13.72	1.15
F7	1.74	2.02	31.42	13.86	1.16
F8	1.72	2.01	33.46	14.42	1.17
F9	1.77	2.03	34.23	12.80	1.14
F10	1.85	2.09	33.16	11.48	1.13

Table-4: Evaluation of fast disintegrating tablets of fenofibrate

Formulations	Average weight(mg)	Hardness[kg/cm]	Friability[%]	Disintegration time[sec]
F1	304.8	3.2	0.29	64.32
F2	303.7	3.4	0.24	67.21
F3	305.1	3.2	0.27	63.61
F4	303.6	3.3	0.23	68.44
F5	304.2	3.2	0.31	65.26
F6	303.5	3.9	0.22	67.71
F7	305.2	3.6	0.21	69.61
F8	304.9	3.7	0.20	68.64
F9	305.1	3.6	0.18	68.62
F10	304.5	3.8	0.17	62.84

Table: 5 Cumulative Percentage Drug Release of fast disintegrating tablets of fenofibrate

Time [min]	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	Marketed product
5	51.72	41.89	51.83	42.11	56.02	55.92	55.36	45.78	44.01	56.19	55.12
10	62.37	56.21	64.25	56.55	67.35	67.24	57.72	57.12	55.98	67.35	66.25
20	68.32	67.83	77.11	68.32	78.33	74.51	68.31	69.97	67.54	78.57	78.41
30	73.76	79.17	82.44	79.11	79.08	79.24	79.12	78.73	79.06	84.50	83.45
45	88.76	88.23	89.79	91.21	89.26	84.63	84.76	89.95	89.94	90.73	88.62
60	90.15	92.56	91.75	92.44	91.89	92.41	93.86	91.26	94.12	97.07	95.48

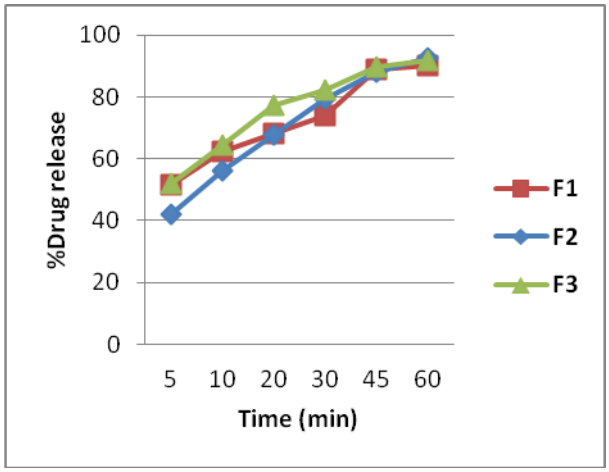

Fig. 1: Dissolution profile of F1, F2, F3

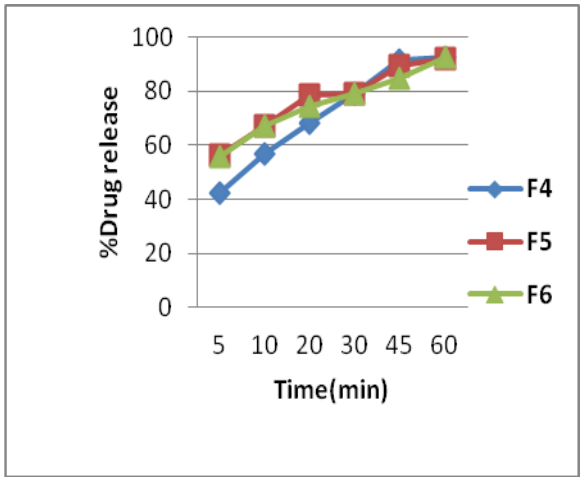

Fig. 2: Dissolution profile of F4, F5, F6

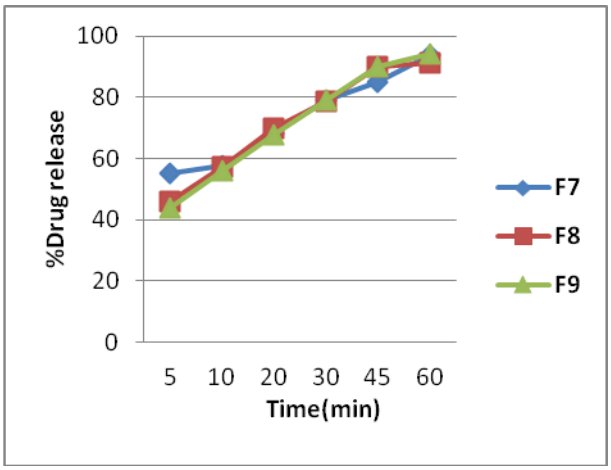

Fig. 3: Dissolution profile of F7, F8, F9

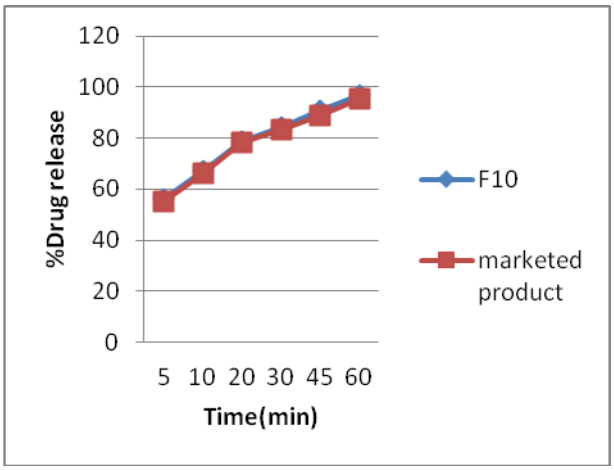

Fig.4:Dissolution profile of F10 & Marketed product

Table 6: Accelerated Stability Studies of the Optimized Batch (F10) at 40^0C/75%RH

S.No	Parameters	Initial	15 days	30 days
1	Average weight of Tablet (mg)	304.5	304.3	304.1
2	Hardness (kg)	3.8	3.6	3.5
3	Friability (%)	0.17	0.19	0.18
4	Disintegration time in seconds	62.84	61.44	61.38
5	%Drug release	97.07	97.15	97.25

CONCLUSION:

The popularity of Fast disintegrating tablets [FDTs] has increased tremendously over the last decade. The key to FDT formulations is fast disintegration, dissolution, or melting in the mouth and this can be achieved by producing the porous structure of the tablet matrix or adding superdisintegrant and/or effervescent excipients. The clinical studies show FDTs can improve patient compliance, provide a rapid onset time of action, and increase bioavailability. However, common people are not much aware of this delivery system. Therefore, pharmacists are responsible to spread the knowledge regarding this system. This dosage form should be handled carefully since they do not have sufficient mechanical strength. The packaging of FDTs is also very important. Patients who suffer from dryness of mouth should not be prescribed with FDTs, because, minimum volume of saliva is necessary for it to disintegrate/dissolution. This dosage form is very much suitable for pediatric patients who having no primary teeth and for geriatric patients who have lost their teeth permanently. Extensive works had been carried out till date in order to evaluate the FDTs and among them many are proved to have significant discriminatory power. Thus, in near future, it is expected that this delivery system will get much importance as that of conventional delivery systems.

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