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Development and Evaluation of fast dissolving tablets of Fenofibrate by enhancing dissolution rate and bioavailability

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A B S T R A C T

In the present work, an attempt has been made to develop fast disintegrating tablets of Fenofibrate**.** In the present work Sodium starch glycolate, Cross povidone and Cross carmellose sodium were employed as super disintegrating agents to enhance the solubility and dissolution rate of selected drug molecule. Camphor was employed as sublimating agent, due to presence of camphor maximum pores will be formed. As the numbers of pores were more the body fluid will penetrates more easily. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F4 formulation showed maximum % drug release i.e., 98.10 % in 25 min hence it is considered as optimized formulation.

Keywords: Fenofibrate**,** Sublimating agent, camphor, sodium starch glycolate, Cross povidone and Cross carmellose sodium.

A R T I C L E I N F O

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1. Introduction

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales

through market segmentation, and are moving rapidly. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance. Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, ease of administration lead to high levels of patient compliance. It is always the aim of a scientist or a dosage form designer to enhance the safety of a drug molecule while maintaining its therapeutic efficacy [1]. Recent advances in NDDS aim for the same by formulating a dosage form, convenient to be administered so as to achieve better patient compliance. Mouth Dissolving Tablet (MDT) is one among such approaches. Improved patient compliance has achieved enormous demand. Consequently demand for their technologies is also increasing many folds. To develop a chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects [2].

The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance. Tablets and capsules are the most popular dosage forms. But one important drawback of such dosage forms is Dysphasia or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. This disorder is also associated with a number of pathological conditions including stroke, Parkinson's disease, neurological disorders, AIDS etc. To solve the above-mentioned problems, pharmaceutical technologists have put in their best efforts to develop a Fast dissolving drug delivery, i.e. Mouth Dissolving Tablet that disintegrates and dissolves rapidly in the saliva, within a few sec without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 10 sec to 3 min. Most of the MDTs include certain super disintegrants and taste masking agents [3]. In the present study Fenofibrate which is a Hyperlipidemic drug is used as a model for the development of fast dissolving tablets. Fenofibrate is used to reduce cholesterol levels in people at risk of cardiovascular disease [4].

2. Material and methods

Fenofibrate (Natco Laboratories, Hyderabad), Crospovidone (ISP pharmaceuticals ISP pharmaceuticals), CCS (S D Fine chemicals limited, Mumbai), SSG (DFE Pharma, Germany), MCC (Nihar traders pvt Ltd), Magnesium Stearate (Himedia Laboratories), Talc (SD fine chemicals Mumbai), camphor (S D Fine chemicals limited, Mumbai).

2.1. Construction of Fenofibrate calibration curve with phosphate buffer pH 6.8: 100mg of Fenofibrate was dissolved in 100ml of phosphate buffer pH 6.8 to give a concentration of 1mg/ml (1000µgm/ml).From the above standard solution (1000µgm/ml) 10 ml was taken and diluted to 100ml with phosphate buffer pH 6.8 to give a concentration of 100µgm/ml. From this stock solution aliquots of 0.2,0.4,0.6,0.8 and 1ml were pipette out in 10ml volumetric flask and the volume was made up to the mark with phosphate buffer PH 6.8 to produce concentration of 2,4,6,8 and 10 µgm/ml respectively. The absorbance (abs) of each conc. was measured at respective (λ_{max}) i.e., 258 nm [5].The results were shown in Table 2.

2.2. Formulation of Oro dispersible tablets of Fenofibrate:

Composition of Fenofibrate oro Dispersible Tablet by direct compression. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 8mm flat punch, B tooling. Each tablet contains 50 mg Fenofibrate and other pharmaceutical ingredients. Total weight of tablet was found to be 120 mg [6]. The composition of tablets was shown in Table 1.

2.3. Pre compression studies of Fenofibrate Oro dispersible tablets [7]

The powder blend was subjected for the following studies

- Angle of repose
- Bulk density
- Tapped density
- Carr's index
- Hausner's ratio

2.3.1. Angle of repose

The angle of repose of powders was determined by the funnel method. Accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powders. The powders were allowed to pass through the funnel freely onto the surface. The diameter and height of the powder cone was measured and angle of repose was calculated by using the given formula. The results were shown in Table 3.

$$\tan\theta = \frac{h}{r}$$

Where,

h = height of the powder cone

r = radius of the powder cone

2.3.2. Bulk density and tapped density

A quantity of 4gms of powder from each formula was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was tapped continuously until no further change in volume was observed. Then bulk density (BD) and tapped density (TD) were calculated by using the given formula. The results were shown in Table 3.

$$BD = \frac{\text{Weight of the powder}}{\text{Initial volume}}$$

$$TD = \frac{\text{Weight of the powder}}{\text{Tapped volume}}$$

2.3.3. Carr's index

The Compressibility of the powder blend was determined by Carr's compressibility index. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is a simple test to evaluate the bulk density and tapped density of a powder and the rate at which it is packed. The formula for carr's Index is given below. The results were shown in Table 3.

$$\text{Carr}'\text{s index (\%)} = \frac{\text{TD} - \text{BD}}{\text{TD}} \times 100$$

2.3.4. Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by using the given formula.The results were shown in Table 3.

$$\text{Hausner}'\text{s ratio} = \frac{\text{TD}}{\text{BD}}$$

2.4. Post compression studies of Fenofibrate Oro dispersible tablets [8]

2.4.1. Thickness

Tablet thickness can be measured using digital vernier calipers. 3 tablets were taken and their thickness was measured and the average thickness for each tablet was calculated. The results were shown in Table 4.

2.4.2. Hardness

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using monsanto hardness tester. The results were shown in Table 4.

2.4.3. Friability test

Friability of the tablets was determined using Roche friability. 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 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. Conventional tablets that lose less than 1% of their weight are acceptable. The results were shown in Table 4.

$$\%\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

2.4.4. Weight variation

The weight variation test is done by weighing 10 tablets individually, calculating average weight and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. The results were shown in Table 4.

$$\%\ \text{Weight variation} = \frac{\text{Average weight} - \text{Initial weight}}{\text{Average weight}} \times 100$$

2.5. Evaluation of Fenofibrate Oro dispersible tablets

2.5.1. Drug Content estimation:

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. Four tablets were weighed and crushed in the mortar. The powder equivalent to 1.25 mg of the drug were weighed and dissolved in 100ml phosphate buffer pH 6.8 to give a concentration of 12.5 µg/ml. 2ml of this solution was taken and diluted to 10ml to give a concentration of 2.5µg/ml. The absorbance of the prepared solution was measured at 258nm using UV Visible spectrophotometer [9].The results were shown in Table 4.

2.5.2. Disintegration test

It is time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes with the bottom containing a 10 mesh sieve. The basket is set a frequency of 28-32 cycles per minute in a medium of 900 ml which is maintained at 37 ± 2^o C. The tablets were placed in the tubes and the time required per complete passage of tablet particles through 10 mesh sieve was considered as disintegration time of tablet [10].The results were shown in Table 4.

2.5.3. *In -vitro* dissolution studies [11]:

In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800). The dissolution fluid was 500ml of phosphate buffer pH 6.8 at a speed of 50rpm at a temperature of 37^{0}c were used in each test. Samples of dissolution medium (5ml) were withdrawn for every 2min and assayed for Fenofibrate by measuring absorbance at 258 nm. For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of phosphate buffer pH 6.8. The results were shown in Table 5 and Fig 1, 2 and 3.

Apparatus used : USP II Lab India DS 800
Dissolution Medium : Phosphate buffer PH 6.8
Dissolution Medium volume : 500ml
Temperature : 37^{0}C
Speed of paddle : 50rpm
Sampling Intervals : 2, 4, 6, 8, 10, 15, 20, 30, 45 & 60 min
Sample withdrawn : 5ml
Absorbance measured : 258 nm
Beer's Range : 2-10µg/ml

3. Results and discussion

It was found that the estimation of Fenofibrate by UV spectrophotometric method at λ_{max} 258nm in pH 6.8 Phosphate buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2- 10µg/ml. The regression equation generated was y = 0.049x + 0.009, R^2 = 0.998. The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 13.06% to 18.18%. The Hausner's ratio fall in range of 1.14 to 1.22. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture. Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 3. The average weight of the tablet is approximately in range of 127 to 118.5mg, so the permissible limit is ±10% (=120mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.Hardness of the three tablets of each batch was checked by using Monsanto hardness tester

and the data's were shown in Table 3. The results showed that the hardness of the tablets is in range of 2.5 to 3.00 kg/cm^2,which was within IP limits. Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table 3 .The result showed that thickness of the tablet is raging from 3.56 to 3.64. Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 3. The average friability of all the formulations lies in the range of 0.30 to 0.51% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Tablets of each batch were evaluated for in vitro disintegration timeand the data's were shown in the Table 3. The results showed that the disintegration time of prepared tablets were in the range of 12.66 to 30.33 seconds. Drug contentwas performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.23 - 99.2%.Invitro dissolution studies were carried out by using 500ml of pH 6.8 Phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 30 min. From the tabular column 7.4 it was evident that the formulations prepared with super disintegrate Cross carmellose sodium showed maximum % drug release in 2 min i.e.110.96% (F9 formulations and the concentration of super disintegrate was 36 mg). So the principle of super disintegrates was found to be useful to produce oro dispersible tablets. F9 formulation was considered as optimized formulation.

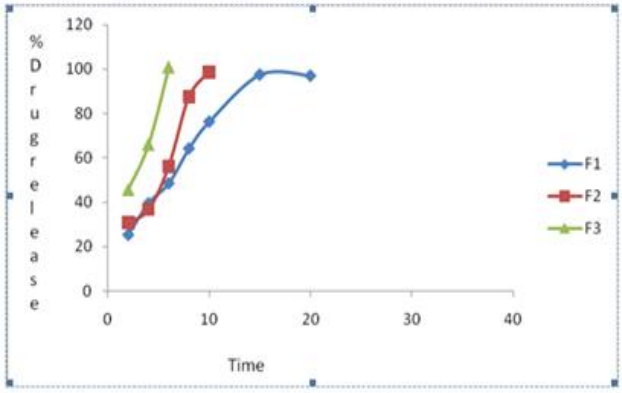

Figure 1: Dissolution profile of formulations prepared with SSG as super disintegrant

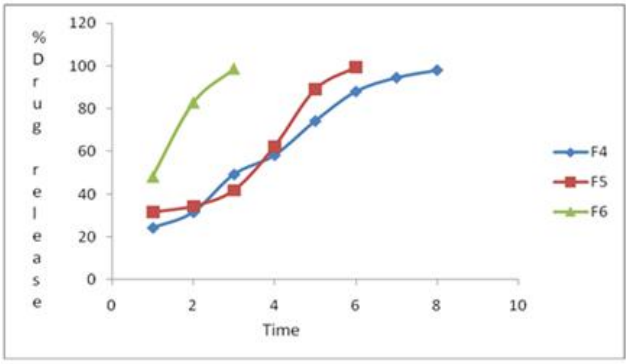

Figure 2: Dissolution profile of formulations prepared with Cross povidone as superdisintegrant.

Table 1: Composition of various tablet formulations

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Fenofibrate	50	50	50	50	50	50	50	50	50
Sodium Starch Glycolate	12	24	36	-	-	-	-	-	-
Cross Povidone (mg)	-	-	-	12	24	36	-	-	-
Cross Carmellose Sodium	-	-	-	-	-	-	12	24	36
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
MCC	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total weight	120	120	120	120	120	120	120	120	120

Table 2: Concentration and absorbance obtained for calibration curve of Fenofibrate In pH 6.8 Phosphate buffer

S. No.	Concentration (µg/ml)	Absorbance* (at 258 nm)
1	2	0.107
2	4	0.215
3	6	0.299
4	8	0.402
5	10	0.507

Table 3: Precompression parameters of powder blend

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner' ratio	Angle of Repose (Θ)
F1	0.45	0.55	18.18	1.22	27.91
F2	0.47	0.55	14.54	1.17	28.23

F3	0.50	0.58	13.79	1.16	29.34
F4	0.46	0.55	16.36	1.19	26.71
F5	0.50	0.58	13.79	1.16	29.34
F6	0.47	0.55	14.54	1.17	28.23
F7	0.50	0.58	13.79	1.16	29.34
F8	0.41	0.50	18	1.21	26.78
F9	0.41	0.50	18	1.21	26.78

Table 4: Post-Compression parameters of tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration Time (sec)	Friability (%)	Assay (%)
F1	120	2.5	3.59	20.33	0.43	97.23
F2	124	2.6	3.64	22.66	0.34	98.55
F3	119	2.5	3.59	30.33	0.49	98.16
F4	121	2.6	3.58	19.00	0.47	99.34
F5	122	2.3	3.59	30.33	0.49	98.16
F6	123	2.7	3.64	22.66	0.34	98.55
F7	122	2.5	3.59	30.33	0.49	98.16
F8	120	2.6	3.56	17.00	0.34	99.25
F9	122	2.5	3.56	17.00	0.34	99.25

Table 5: *In-vitro* dissolution studies of all formulations

Formulation	Appearance	pH	Viscosity	Spreadability	Syringeability
F1	Reddish Brown	6.12 ± 0.98	46552	6.82 ± 0.08	91.23 ± 0.86
F2	Reddish Brown	6.25 ± 1.08	46892	6.86 ± 0.06	95.25 ± 1.08
F3	Reddish Brown	6.56 ± 1.25	47854	7.02 ± 0.12	91.85 ± 0.98
F4	Reddish Brown	6.35 ± 1.12	48235	7.25 ± 0.23	94.89 ± 1.36
F5	Reddish Brown	6.89 ± 0.96	46582	6.96 ± 0.09	92.56 ± 1.39
F6	Reddish Brown	6.68 ± 1.16	41956	6.98 ± 0.20	95.65 ± 0.56
F7	Reddish Brown	6.54 ± 1.25	47145	7.02 ± 0.18	92.56 ± 0.86
F8	Reddish Brown	6.12 ± 1.26	42262	7.25 ± 0.12	94.36 ± 1.02
F9	Reddish Brown	6.25 ± 1.14	48542	7.14 ± 0.09	92.35 ± 0.99
F10	Reddish Brown	6.46 ± 1.18	47558	6.96 ± 0.12	96.58 ± 1.23

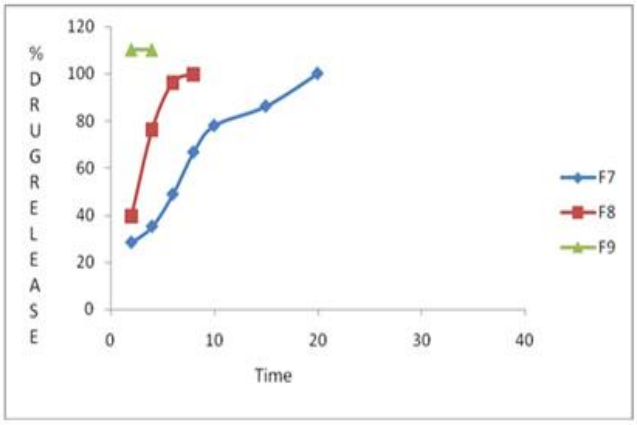

Figure 3: Dissolution profile of formulations prepared with CCS as super disintegrant

4. Conclusion

In the present work, an attempt has been made to develop fast disintegrating tablets of Fenofibrate. In the present work Sodium starch glycolate, Cross povidone and Croscarmellose sodium were employed as super disintegrating agents to enhance the solubility and dissolution rate of selected drug molecule. Camphor was employed as sublimating agent, due to presence of camphor maximum pores will be formed. As the number of pores was more the body fluid will penetrates more easily. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post

compression parameters and they passed all the quality control evaluation parameters as per I.P limits.It was evident that the formulations prepared with super disintegrate Cross carmellose sodium showed maximum % drug release in 2 min i.e.110.96% (F9 formulations and the concentration of super disintegrate was 36 mg). So the principle of super disintegrates was found to be useful to produce oro dispersible tablets. F9 formulation was considered as optimized formulation.

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