

FORMULATION, DEVELOPMENT AND IN VITRO EVALUATION BEZAFIBRATE FAST DISSOLVING TABLETS

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ABSTRACT

The purpose of this study was to use the solid dispersion method to create, test, and assess bezafibrate tablets that dissolve quickly. The goal of the formulation procedure was to improve the bioavailability and rate of dissolution of bezafibrate, a medication that is not very soluble in water. To guarantee the quality and consistency of the tablets, precompression parameters including thickness, diameter, hardness, friability, medication content, and weight fluctuation were adjusted. To ascertain stability under various storage settings, the in vitro assessment comprised measuring dispersion time, wetting time, and dissolution profiles over a three-month period. The results provide important information on the formulation and performance of the bezafibrate fast-dissolving tablets and indicate that they have the potential to enhance drug delivery and patient compliance.

Keywords: solid dispersion, fast-dissolving tablets, bezafibrate, and in vitro testing.

1. INTRODUCTION

Drug delivery systems (DDS) are a tactical instrument for prolonging product life cycles, creating possibilities, and broadening markets and indications. The most common method of achieving systemic effects is oral administration because of its convenience, painlessness, avoidance, adaptability, and—above all—patient compliance. Additionally, solid oral delivery devices are less expensive to produce since they don't need sterile conditions. Tablets are the preferred solid dose form because to its high precision dosing, patient compliance, and production efficiency. The oral route is still the best way to provide therapeutic drugs since it is inexpensive, easy to manufacture, and results in high patient compliance rates. Solid dose forms are used more often than any other type of dosage form. Because oral dosage forms can be self-administered by the patient and are clearly more profitable to manufacture than parenteral dosage forms, which must typically be administered by trained personnel, oral solid formulations in particular hold great promise for being the most convenient drug administration methods.

More than 80 percent of medications designed to have systemic effects are sold in oral dose forms. Today, granules, pellets, tablets, and capsules are the most often used pharmaceutical solid oral dose forms. The company prefers tablets over other solid oral dose forms because to their improved stability and comparatively inexpensive manufacturing, packing, and shipping costs. Powders, granules, pellets, or film-coated multiple units can all be used directly to make the tablets. Nowadays, tablets are the most widely used dosage form, making up around 70% of all pharmaceutical preparations made in an ethical manner. Currently, drug items are made for three different demographics: adults, children, and newborns. It is clear that newborns have different requirements than children between the ages of two and twelve, and that children's needs differ from adults' needs. However, because older people have unique demands that need for dose forms created specifically for them, their needs are being disregarded.

The majority of dose forms given to the elderly are pills or capsules, despite the fact that many senior patients have trouble swallowing them. Although it is straightforward and cost-effective to make uncoated tablets, they are frequently difficult to swallow and can cause discomfort by "hanging" in the throat. Although coated tablets and capsules are a little simpler to swallow, this is a cause for concern as people age and as more medicinal products are given to one person. Although liquid dosage forms are easier to give, they are more expensive, more likely to spill, have inherent stability issues, take up a lot of space per dose unit, and frequently taste bad. It is clear that the demands of the elderly are different from those of other groups and should be given particular consideration when developing new drugs, formulating products, posology, packaging, labeling products, providing patient information, and promoting and selling products. For these patients, a novel and useful dose form might be beneficial.

There are a number of fast-dissolving products available right now. For the administration of high molecular weight proteins and peptides, the development of improved oral protein delivery technology through the use of fast-dissolving tablets that may release these medications in the mouth is extremely promising.

Ideal treatment for a patient with dysphasia is a fast-dissolving pill, which dissolves in the patient's mouth in a matter of seconds without the need for chewing or water. As saliva travels down the stomach, certain medications are absorbed from the mouth, throat, and esophagus. In these situations, the bioavailability is higher than what is seen with traditional dose forms. [1]

Pharmaceutical dose forms intended for oral administration may be challenging for elderly and pediatric patients to chew or swallow. There is growing interest in fast-dissolving dosage forms for oral, sublingual, and buccal administration because tablets that disintegrate quickly when they come into touch with saliva in the buccal cavity may offer a solution to those issues. For these individuals, fast-dissolving or disintegrating tablets are ideal because, when put on the tongue, the active ingredient is released instantly by rapid disintegration or dispersion, followed by drug dissolution.

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In both business and academics, the benefits of oral dissolving dosage forms are becoming more widely acknowledged. Superdisintegrants are the fundamental method utilized in the creation of the fast-dissolving tablet. In the current investigation, croscopolidone, sodium starch glycolate, and croscarmellose sodium were tested; the best one was selected for more research.

Spray drying, molding, mass extrusion, direct compression, freeze-drying, vacuum-drying, and sublimation utilizing sublime agents like menthol and camphor are some of the methods used to prepare mouth-dissolving tablets. However, because low-substituted hydroxyl propyl cellulose (L-HPC) and microcrystalline cellulose (MCC) were utilized as excipients in these tablets, patients can experience a rough mouth because of the insufficient solubilization of this type of tablet in saliva. We tried using Perlitol SD200 as an excipient in place of crystalline cellulose and L-HPC while making this kind of tablet in order to get rid of this kind of oral discomfort. However, because of its low porosity, which makes it difficult for water to enter the tablets, Perlitol SD200, when used as a water-soluble excipient in tablets, does not dissolve quickly in saliva. Researchers have explored the aforementioned methods to optimize the tablet matrix's pore structure [3].

The output of freeze drying is brittle and hygroscopic, and it is laborious. For this reason, the vacuum-drying method was chosen for the current study. After adding a subliming agent to boost the tablets' porosity, vacuum drying was used. A porous hydrophilic matrix is probably going to absorb the disintegrating liquid with ease and shatter rapidly. Using

sublimation materials with Perlitol SD200. As a sublimating agent, we selected ammonium bicarbonate, thymol, camphor, and menthol [4].

2. MATERIALS AND METHODS

Materials

Bezafibrate was acquired from (CHEMICO SCIENTIFIC, ERODE); Avicel pH 102, sodium starch glycolate, magnesium stearate, and talc were acquired from (Cid company, Giza, Egypt); polyethylene glycol (PEG4000), poly vinyl pyrrolidone, and carboxymethyl cellulose (CMC) were acquired from (EL. Nasr pharmaceutical chemicals Co. Egypt); potassium dihydrogen orthophosphate, disodium hydrogen orthophosphate, and absolute ethanol were acquired from (CHEMICO SCIENTIFIC, ERODE); and commercial haloperidol was bought locally. Every reagent and solvent employed was of analytical quality

METHODS

PREFORMULATION STUDIES [14,15]

Both the medicine and the polymer must be chemically and physically defined before being formulated into a dosage form. When creating a dosage form, preformulation studies provide the information required to identify the nature of the drug ingredient and to create a framework for the drug combination with pharmaceutical excipient.

Fourier transform infrared (FTIR) spectroscopy

The compatibility of the drug and its excipients was examined, and the Perkin-Elmer 1600 FTIR spectrophotometer was used to compare the spectra of pure haloperidol powder, Avicel pH 102, polymer, SSG, magnesium stearate, physical combination, and a chosen solid dispersion formula using the potassium bromide disk technique. The resolutions were 1 cm^{-1} , and the wave number scanning range was $4000\text{--}400\text{ cm}^{-1}$.

Differential scanning calorimetry (DSC)

Shimadzu DSC-60 was used to do the analysis. Under a nitrogen purge (30 ml/min), samples containing 5 mg of pure fenofibrate powder, excipients, physical mixture, and a chosen solid dispersion formula were heated in hermetically sealed aluminum pans between 0 and 200 °C at a steady rate of 10 °C/min.

Solubility study:

Distilled water was used to test the solubility of both pure bezafibrate and polymer. In screw-cap bottles, 10 milliliters of water were mixed with an excess of the medication and a weighted amount of physical combination (175.28 mg). For 72 hours, each bottle was shaken in a shaker water bath set at $25^{\circ} \pm 0.5^{\circ} \text{C}$. Once equilibrium was achieved, the solutions were filtered, and a spectrophotometer was used to measure the drug's concentration at λ_{max} 243 nm (Huang and Dai, 2014). [42]

Solubility enhancement ratio was calculated using the following equation.

$$\text{Solubility enhancement ratio (SER)} = \frac{\text{Solubility of drug in presence of polymer}}{\text{Solubility of drug in water}}$$

Preparation of physical mixture:

The precisely weighed amounts of medication and polymer were combined in a glass mortar with a pestle to create a physical combination of bezafibrate with the polymers PEG 4000, PVP, and CMC at various ratios (1:2, 1:4, 1:6, and 1:8). After passing through sieve number 60, this mixture was kept in a desiccator for twenty-four hours.

Preparation of solid dispersion of Bezafibrate

Melting and solvent evaporation techniques were used to create solid dispersions with Bezafibrate and polymer (PEG4000, PVP, and CMC) at the ratios of 1:2, 1:4, 1:6, and 1:8.

Melting method

Bezafibrate alone and the polymer were melted in a porcelain plate to create solid dispersions. A temperature range of 60 to 70 °C was maintained for the fusion process. With vigorous stirring, the molten fluid was promptly cooled and hardened in an ice bath. The solid obtained was crushed, pulverized, scraped, and run through sieve number sixty. Before being employed for additional research, the resulting product was kept in a desiccator (Dhote et al., 2014). [43]

Solvent method

This approach involved dissolving the polymer and bezafibrate in 0.38 milliliters of ethanol. A transparent, solvent-free film was left behind once the solvent was evaporated. To

maintain its weight, the film was further dried. The finished product was kept in a desiccator until it was needed again after the co-precipitate was crushed and the dry powder went through filter number 60 (Adeli, 2016). [44]

Formulation and preparation of tablets

The direct compression method was used to create tablets of solid dispersion, physical mixture, and pure bezafibrate. The solid dispersions and physical mixtures containing 5 mg of bezafibrate were weighed and mixed evenly with diluents (Avicel), lubricant (Magnesium stearate) and super disintegrants (Sodium starch glycolate) according to Table 1. All the ingredients were passed through sieve number 60 prior to mixing and then directly compressed using a compression machine (Single punch tablet machine fitted with 10 mm flat faced punches and dies (Korsh Forgeries; type AO, Berlin, Western Germany) (Yasir and Sara, 2014).

Table 1: Composition of tablets containing bezafibrate solid dispersion.

Code	Formula tion	Type of polymer and Method	Drug (mg)	Polymer (mg)	Ethanol solvent (mg)	Avicel (mg)	Sodium starch glycolate (mg)	Mg. stearate (mg)	Total weight (mg)
FP	Pure drug	-	5	-----	-----	160	8.25	1.73	75.28
FPM	Physical mixture	-	5	40	-----	120	8.25	1.73	75.28
F1	SD1	PEG / solvent evaporat ion	5	40	0.3	120	8.25	1.73	75.28

F2	SD2	PEG / melting	5	40	-----	120	8.25	1.73	74.98
F3	SD3	PVP / solvent evaporation	5	40	0.3	120	8.25	1.73	75.28
F4	SD4	PVP /melting	5	40	-----	120	8.25	1.73	74.98
F5	SD5	CMC / solvent evaporation	5	40	0.3	120	8.25	1.73	75.28
F6	SD6	CMC/ melting	5	40	-----	120	8.25	1.73	74.98

FP:Tablet containingpure drug.

FPM:Tablet containing physical mixture.

F1:Tablet containing PEG solid dispersion prepared by solvent evaporation method. F2:

Tablet containing PEG solid dispersion prepared by melting method.\

F3:Tablet containing PVP solid dispersion prepared by solvent evaporation method. F4:

Tablet containing PVP solid dispersion prepared by melting method.

F5:Tablet containing CMC solid dispersion prepared by solvent evaporation method. F6:

Tablet containing CMC solid dispersion prepared by melting method.

Dissolution studies

The Dissolution Pharma Test type II (pharmatest sp6400, Mph, Germany) was used to assess the in-vitro dissolution study of bezafibrate either alone or from solid dispersions and physical combinations. 900 cc of phosphate buffer (pH=6.8), $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$, and 50 rpm were used for the dissolving test. To the dissolving media, a weight quantity equal to 5 mg of

bezafibrate was added. At 5, 10, 20, 30, 40, 50, and 60 minutes, a sample (5 ml) of the solution was taken out of the dissolving device. The equal amount of new dissolving media was used in lieu of the sample. After being diluted, the extracted materials were filtered through Whatman filter paper and their bezafibrate concentration was measured at $\lambda_{\text{max}} 243 \text{ nm}$. Every run was carried out three times. The standard curve was used to determine the amount of medication dissolved (Yasir and Sara, 2014). [45]

3. RESULTS AND DISCUSSION

There is a significant rate of non-compliance because many patients, particularly the elderly, have trouble swallowing pills, capsules, and fluids. As a result, numerous safer and more advanced drug delivery methods have been developed as a result of non-compliance-oriented research. One example of this is a tablet that dissolves or disintegrates quickly, either because of its fast disintegration or because it dissolves with saliva.

This medication delivery method is significant because it may be administered without water, has a quick start of action, is portable, accurate, and is a good substitute for liquid dose forms. It is also perfect for both pediatric and elderly patients. The terms "rapi-melts," "fast dissolving tablets," "melt in mouth tablets," "rapi-melts," "immediately dissolving tablets," "porous tablets," "Oro-dispersible tablets," and "fast disintegrating tablets" are interchangeable with the term "fast dissolving tablets." These tablets are widely used as the preferred dose form due to their distinctive advantages in terms of patient compliance, quick onset of action, enhanced bioavailability (often bi-pass first pass effect), and high stability.

Since water-insoluble diluents such as microcrystalline cellulose, dicalcium phosphate, and L-HPCA are predicted to produce an intolerable grittiness in the mouth, they were excluded from the research. Mannitol was chosen as a model soluble diluent among the soluble diluents due to its benefits, which include relative moisture insensitivity, economic effectiveness, ease of availability, and negative heat of dissolution. Bezafibrate mouth-dissolving pills were made using the sublimation process and four subliming agents: ammonium bicarbonate, menthol, thymol, and camphor.

Evaluation of precompression properties

A medication and excipient blend was created for each intended formulation, and its pre-compression characteristics were assessed and are displayed in Table 2. For every formulation, the tapped density ranged from 0.67 ± 0.01 to 0.730 ± 0.03 gm/cm³, whereas the bulk density ranged from 0.52 ± 0.04 to 0.58 ± 0.01 gm/cm³. The percentage of compressibility derived from density data ranged from $16.1 \pm 0.03\%$ to $25.8 \pm 0.04\%$. It was discovered that the angle of repose ranged from 25.1 ± 0.03 to 29.7 ± 0.02 . The Hausner ratio was found to range between 0.35 ± 0.05 and 1.22 ± 0.02 . The range of bulkiness was determined to be 1.74 ± 0.02 to 1.89 ± 0.05 . Since all of the formulations exhibit fair to good flow characteristics for direct compression, tablets were made utilizing this method.

Table 2: Results of precompression properties

Formulation	Angle of repose (°)*	Bulk density (gm/cm ³)*	Tapped density (gm/cm ³)*	Carr's index (%) *	Hausner ratio (HR)*	Bulkiness (cc/g)*
F1	28.0 ± 0.01	0.57 ± 0.01	0.69 ± 0.01	17.6 ± 0.05	1.24 ± 0.041	1.74 ± 0.02
F2	29.7 ± 0.02	0.55 ± 0.02	0.73 ± 0.02	24.7 ± 0.04	1.22 ± 0.05	1.80 ± 0.04
F3	25.1 ± 0.03	0.56 ± 0.03	0.71 ± 0.02	21.1 ± 0.04	1.27 ± 0.04	1.76 ± 0.04
F4	26.1 ± 0.01	0.53 ± 0.02	0.72 ± 0.02	25.8 ± 0.04	1.35 ± 0.05	1.85 ± 0.04
F5	27.5 ± 0.02	0.57 ± 0.02	0.67 ± 0.02	20.8 ± 0.03	1.26 ± 0.04	1.89 ± 0.05
F6	25.1 ± 0.03	0.52 ± 0.04	0.68 ± 0.01	16.1 ± 0.03	1.29 ± 0.04	1.75 ± 0.04

*All values are expressed as mean \pm SD, n=3

CRYSTAL PROPERTIES:

The bezafibrate undergoes three rounds of processing, which causes the particle size to fall from 14 μm to 7 μm and increases the surface area. After micronization, bezafibrate's melting point remains unchanged.

Table:3 Particle Size Parameters

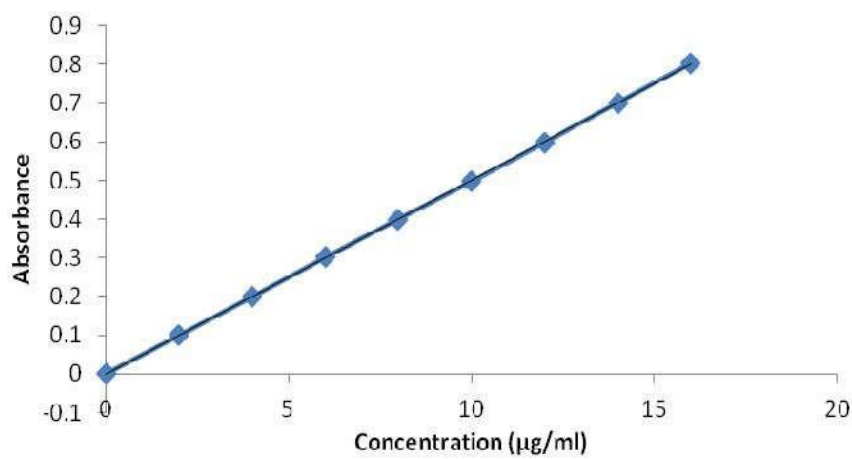
Particle Parameters		Non-micronized	After 1 st cycle	After 2 nd cycle	After 3 rd cycle
Particle size (μm)	D(0.10)	1.323	0.946	0.871	0.800
	D(0.50)	7.004	5.141	4.451	3.925
	D(0.90)	13.713	10.362	9.517	7.832
Surface area (m^2/g)		0.76	1.12	1.48	1.94
Melting point		80	79	81	80

ANALYTICAL PROPERTIES:

The medication complies with Beer Lambert's law in the concentration range of 2–16 mcg/ml, according to the standard calibration curve. The table and standard calibration graph were provided below.

Table:4 Bezafibrate API standard calibration curve data

Concentration ($\mu\text{g}/\text{ml}$)	Absorbance
2	0.099
4	0.199
6	0.301
8	0.400
10	0.497
12	0.598
14	0.701
16	0.803



The linear association between concentration and absorbance was demonstrated by the correlation coefficient values, which were $Y=0.0501X-0.0011$ and $R^2=0.9995$.

Evaluation of post compression properties of fast disintegrating tablet

The direct compression method was used to make the tablets. Due to the free-flowing nature of the powder material, tablets with uniform die fill produced weight variances that were consistent with pharmacopeial requirements. All of the tablets were white, odorless, convex, and flawless, with no flaws on their surfaces. The permitted limit for the drug concentration was between 97.15 and 100.21%, while the tablets' hardness ranged from 3.8 to 4.0 kg/cm². The tablets' good mechanical resistance was shown by their friability, which was determined to be less than 1%. The formulations' diameter ranged from 9.7±0.01 to 10.2±0.01 mm, while their thickness ranged from 2.8±0.02 to 3.2±0.02 mm. Every parameter was discovered to be well within the specified range (table 10).

Table 5: Results of Post Compression Properties of Bezafibrate Tablets

Formulation code	Diameter (mm)*	Thickness (mm)*	Hardness (kg/cm2)*	Friability (%)***	Drug content(%)**	Weight variation (mg)**
F1	10.1±0.02	3.0±0.01	4.0±0.1	0.32±0.01	98.12±0.04	199±0.01

F2	9.8±0.01	3.1±0.02	3.9±0.12	0.45±0.02	98.35±0.05	200±0.01
F3	9.7±0.01	3.2±0.02	4.0±0.05	0.45±0.01	97.15±0.05	198±0.01
F4	10.2±0.01	2.8±0.02	3.9±0.09	0.55±0.04	99.15±0.02	197±0.02
F5	10.1±0.02	2.9±0.02	4.0±0.08	0.61±0.03	100.12±0.03	202±0.02
F6	10.2±0.01	3.0±0.01	3.8±0.01	0.71±0.03	98.45±0.02	201±0.02

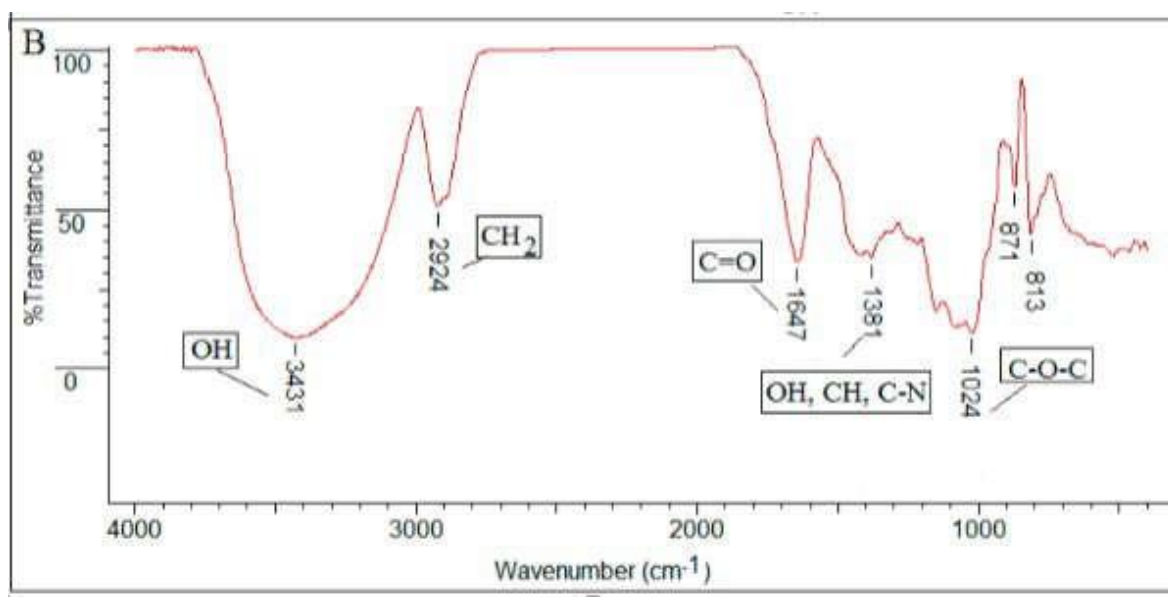
*All values are expressed as mean±SE, n=5; **All values are expressed as mean±SE, n=20;

***All values are expressed as mean±SE, n=10.

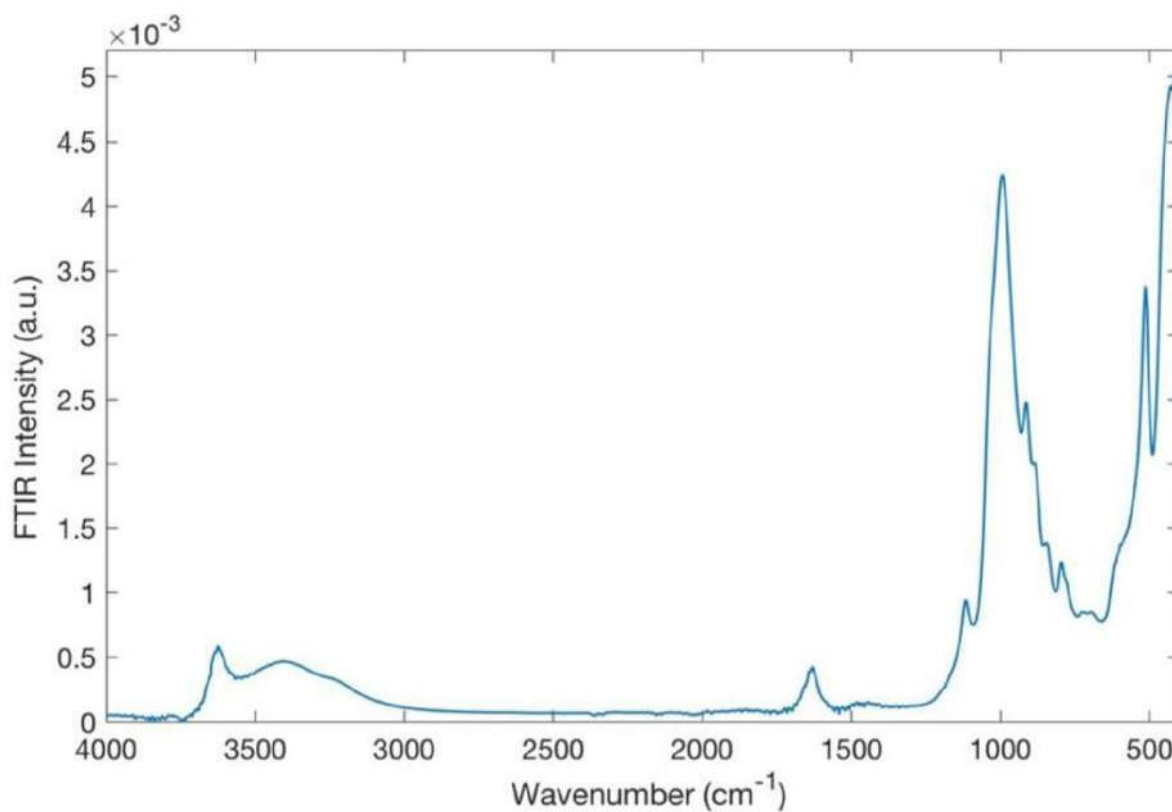
4. Compatibility Studies:

Fourier transform infra-red spectroscopy (FTIR)

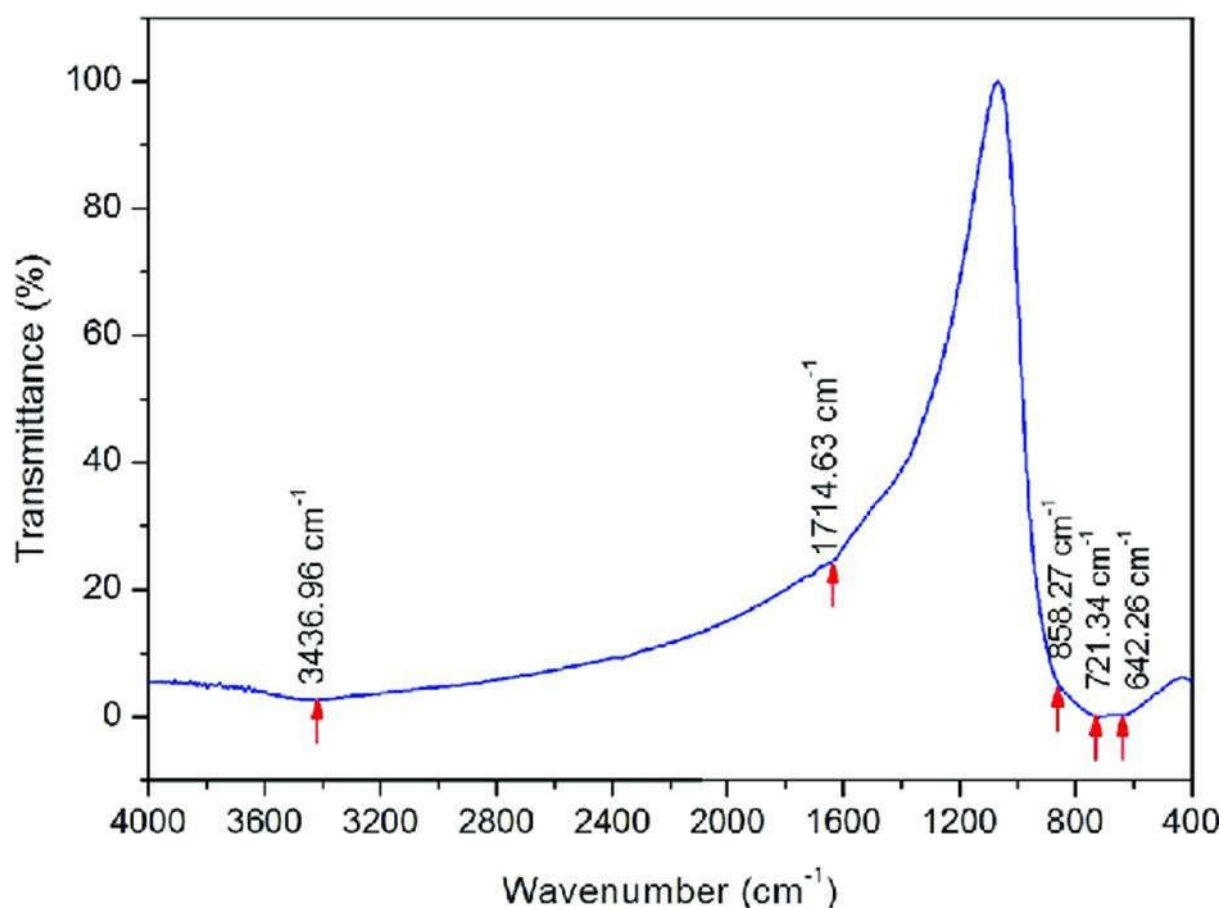
FT-IR was used to determine the infrared spectra of bezafibrate and its physical combination with formulation excipients. and are shown in Figure 2. The spectra of pure bezafibrate revealed distinct peaks at 3431, 2924, 1647, 1381, 1024, 871, and 813 cm⁻¹. The FTIR spectra of bezafibrate and its physical combination with excipients are identical; no peak shift, principal peak disappearance, or principle peak alteration suggests that the drug and excipients are not interacting.



FTIR of Bezaifibrate



FTIR of CarboxyMethylCellulose

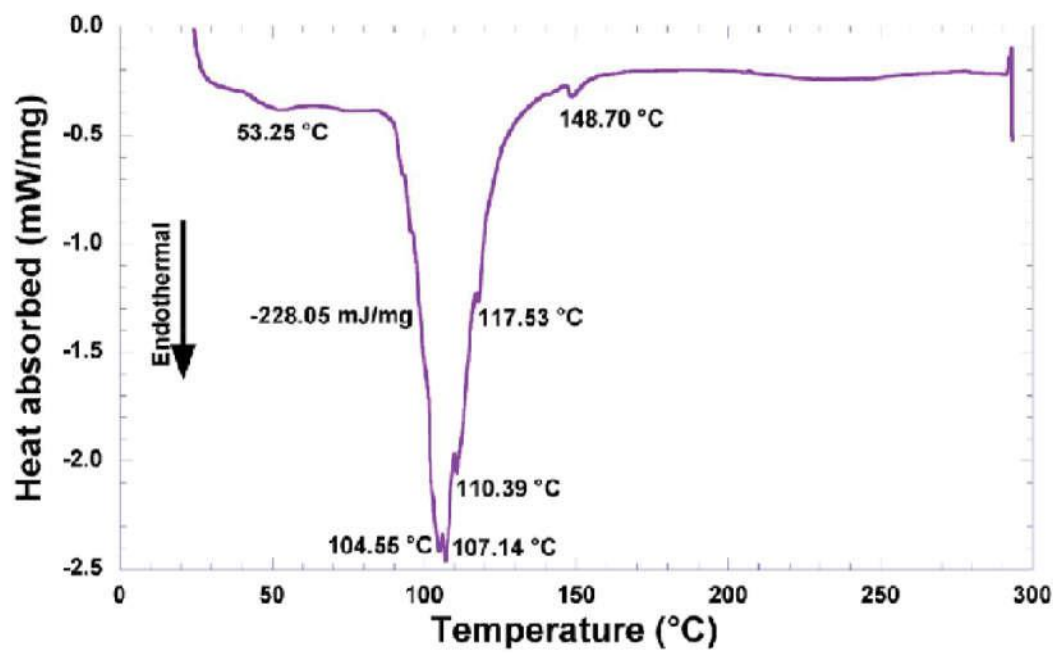


FTIR of Poly Vinyl Pyrrolidone.

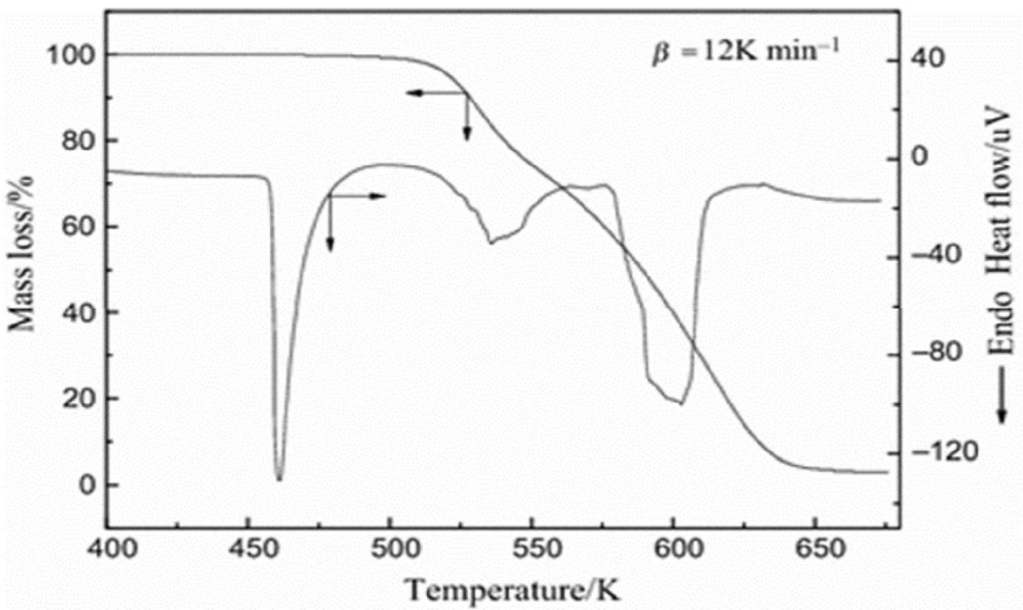
Differential Scanning Calorimetry (DSC)

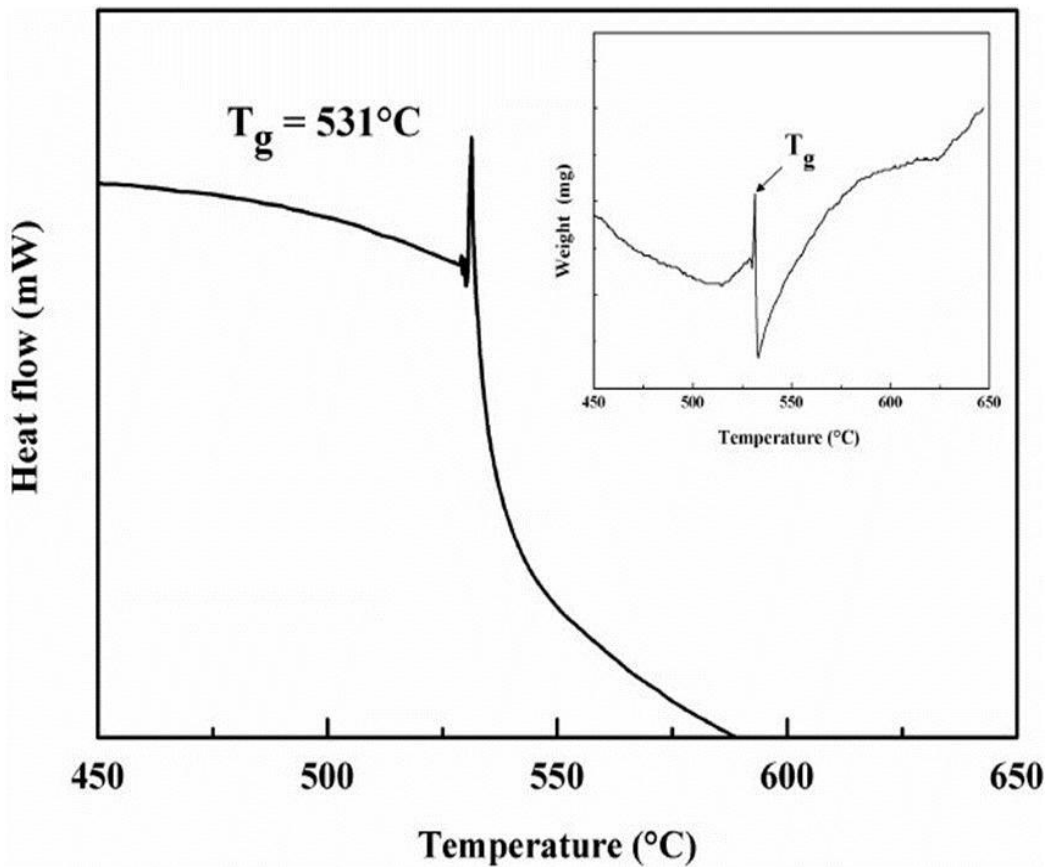
Pure bezafibrate's DSC examination (Figure 3) revealed a distinctive, sharp endotherm peak at 104.55°C, which corresponds to its melting temperature and shows that the medication is crystalline. There was no change or interaction between the drug and excipients, as indicated by the DSC analysis of a physical combination of the drug and excipients, which showed a very slight change in the melting point of bezafibrate in the presence of excipients. The batch that included crospovidone disintegrated the fastest, according to the findings of the early screening investigations. It was chosen for more research as a result. Because polyvinylpyrrolidone is widely utilized in the industry, it was employed as a binder at a concentration of 10% wt/vol. In the initial tablet formulations, subliming chemicals including menthol, camphor, thymol, and ammonium bicarbonate were utilized to improve the pills' porosity. Tablets containing menthol disintegrated more quickly than tablets containing ammonium bicarbonate, camphor, and thymol. In order to examine the impact of varying

amountsofmentholondisintegration time,batches F3through F6were created.Theduration of sublimation (6–12 hours)



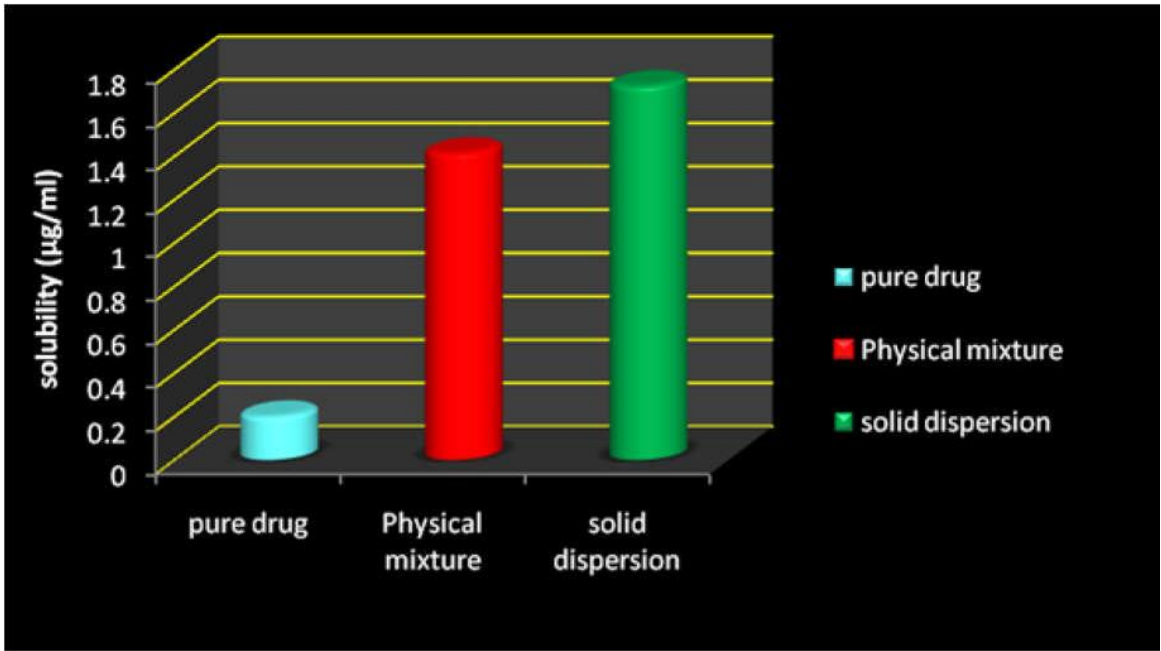
DSCof Bezafibrate





DSC of CarboxyMethyl Cellulose

6.3.3 Stability study



5. Stability Studies of Beza Fibrate, preformulation and formulations.

At one, two, and three months, the optimized formulation F6 was charged on accelerated stability and observed for appearance, hardness, friability, drug content, in-vitro dispersion time, wetting time, and dissolution profile analysis.

Up to three months of stability investigations for F10 formulations at various temperatures show no appreciable differences in appearance, color, odor, taste, hardness, friability, drug content, in-vitro dispersion time, wetting time, and in-vitro dissolution research. Under accelerated temperature and humidity conditions, the formulation remained stable (figure 9).

The different stages of swelling of fast dissolving tablets are shown in

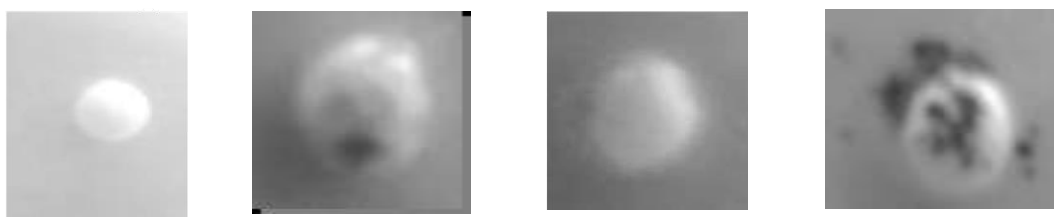


Figure 18: Different stages of Swelling of Fast Dissolving Tablets

6. IN-VITRO RELEASE OF BEZAFIBRATE TABLETS:

Poly Vinyl Pyrrolidone (K-25) was utilized in formulations F1, F2, and F3 at concentrations of 4%, 6%, and 8%, with 4.5 grams of surfactant added in a dry mix. The resulting release was 83.72%, 86.41%, and 84.95%, respectively. Therefore, it was determined to further modify the formulation in order to increase the release rate. When 4.5 grams of surfactant and 6% PVP K-25 were added to the binder solution in the F4 formulation, the release was 89.41%. Only surfactant in varying percentages in dry mix: binder solution as 1:2, 2:1 were utilized in the F5 and F6 formulations, and release was discovered to be 95.44% and 96.34%.

When surfactant was added at 1:2 proportions, the percentage of drug release rose. For even better results, the ideal amount of granulation fluid was applied. Strong swelling properties and a very porous structure of PVPK25 are also responsible for the higher dissolving profile, which is mostly attributable to the inclusion of superdisintegrants such as croscarmellose sodium.

7. SUMMARY AND CONCLUSION

The primary goal of FDT is to accelerate tablet dissolving, which may be achieved by choosing a superdisintegrant with the ideal concentration. Using the sublimation process with menthol, camphor, ammonium bicarbonate, and thymol as sublimating agents, we created mouth-soluble tablets of bezafibrate for the current study.

When creating mouth-dissolving tablets, the sublimation process using a vacuum oven might be a useful substitute for the more costly adjuvant and complex equipment. With batch F6 pills, the wetting time or simulated saliva penetration was found to be extremely quick.

Within the first 10 minutes of the dissolving research, it was discovered that the whole amount of medication from the optimized batch was released. Saliva quickly dissolved these pills (in 10–20 seconds). Popular as a dosage form for the treatment of hyperlipidemia, the produced tablet offers advantages in terms of patient compliance, low dose, quick beginning of action, enhanced bioavailability, minimal side effects, and good durability.

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