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Original Research Article

Evaluation of two different orally disintegrating tablet formulations containing flurbiprofen inclusion complex and its solid dispersion

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Abstract

Purpose: *To prepare orally dispersible tablet formulations (ODTs) by increasing the solubility of flurbiprofen (FB), which has low water solubility.*
Methods: *The ODTs were prepared using direct compression method the inclusion complexes and solid dispersions with the highest solubility were further evaluated. Flurbiprofen, polyvinylpyrrolidone (PVP) solid dispersions were blended together by solvent evaporation method, while the inclusion complexes were co-formulated with beta cyclodextrin (β-CD) by kneading at three different ratios. The ODTs were characterized by differential scanning calorimetry (DSC), Fourier transform infra-red spectroscopy (FTIR) and for their micromeritic properties. In addition, the solubility properties of the inclusion complexes and solid dispersions in distilled water were compared with the solubility of flurbiprofen.*
Results: *The highest solubility value of PVP-FB solid dispersions was found at 1:6 (0.501 mg/mL) and for FB β-CD inclusion complex at 1:2 (0.701 mg/mL). Angle of repose ranged from 28.09 – 32.15 (o); Carr's index from 7.59 to 10.01; and Hausner's ration from 1.05 – 1.15. DSC and spectral studies indicate that FB did not chemically interact with either PVP or β-CD.*
Conclusion: *Orally dispersible tablets containing flurbiprofen β-CD complex exhibit significantly higher bioavailability than the drug alone due to its increased solubility.*

Keywords: *Flurbiprofen, Solubility, Orally disintegration tablets, Inclusion complex, Solid dispersion*

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INTRODUCTION

Solubility enhancement and improved dissolution of poorly water-soluble pharmaceuticals are key challenges for researchers in the pharmaceutical industry. In particular, solid dosage forms' bioavailability is directly related with their water solubility and dissolution of the active substances. Therefore, increased solubility of active substances which are the members of the Biopharmaceutical classification system (BCS) class II is very important in the pharmaceutical industry. Although different methods are used for this purpose, the formation of inclusion complexes and the preparation of solid dispersions are often preferred [1].

Flurbiprofen (FB) is a nonsteroidal anti-inflammatory active substance with poor water solubility and dissolution. Flurbiprofen is commonly preferred for the treatment of rheumatic diseases, and has an inherent solubility of roughly 5.0 x 10^{-5} M. Flurbiprofen tablets and sustained release capsules are thus commercial oral dosage formulations [2].

Cyclodextrins (CDs) are cyclic oligosaccharides of -d-glucopyranose with a hydrophobic inner chamber and a hydrophilic outside surface. CDs have their own unique molecular structure with the different placements of primary and secondary hydroxyl groups. Cyclodextrin and its derivatives have piqued the interest of pharmaceutical researchers over the last two decades due to its ability to form complexes with a wide range of medicinal molecules. CDs are used in the formulation of inclusion complexes, so as to boost the solubility of water-insoluble drugs. The method's performance is determined by the physicochemical characteristics of the medication as well as the cyclodextrin. Spray drying, lyophilization and kneading are the most effective methods for preparing the inclusion complexes of cyclodextrin [3,4].

A solid dispersion is a type of solid complex consisting of a hydrophobic drug dispersed in at least one hydrophilic carrier. Although they are prepared by several methods, solvent evaporation and fusion (melt) methods are two important processes for producing solid dispersions [5,6].

The goal of this study was to compare solid dispersion and inclusion complex formation strategies for enhancing the solubility of poorly water-soluble compounds such as flurbiprofen, which was chosen as a model drug.

EXPERIMENTAL

Materials

Flurbiprofen was a gift by Abdi İbrahim İlaç, Turkey; Beta cyclodextrin (β-CD) and polyvinylprrolidone (PVP) were purchased from Sigma-Aldrich (USA).

Determination the solubility of FB in water at 37 °C

An excess amount of FB was placed in a flask with aqueous solution (5, 10, 15, 20, and 25 % w/v). For 48 h at 37°C, the samples were continuously agitated using a stirrer. After filtering the samples, the drug concentration was determined spectrophotometrically 247 nm [7].

Preparation of beta-cyclodextrin inclusion complex (β-CD)

In the preparation of solid state complexes, the kneading method, which is the most popular method due to its process of manufacturing, was used. With this method, three different combinations of complexes were manufactured by preparing mixtures of 1 : 1 , 1 : 2 , 1 : 3 FB β-CD molar ratios, with mixing duration at 20 min. Ethanol:distilled water (1:1) was used as the solvent [8].

Evaluation of β-cyclodextrin inclusion complex (β-CD)

The optimization was performed according to the results of the dissolution rate and FB assay (%) of prepared inclusion complexes.

Preparation and evaluation of flurbiprofen-polyvinylprrolidone solid dispersion (FB-PVP)

FB and PVP were dissolved in a methanol:distilled water mixture (19 : 1) at three different ratios (1 : 3, 1 : 6, 1: 9; w / w). On a water bath, the solvent was evaporated, and the remaining mass was dried at 50 °C, and sieved to the desired particle size [12 - 14]. Differential scanning calorimetry (DSC), Scanning electron microscopy and Fourier transform infrared spectrometry studies were performed.

Determination of solubilities of pure FB, FB β-CD inclusion complexes and FB-PVP solid dispersions

Excess amounts of pure FB, FB-β-CD inclusion complexes and FB solid dispersions were transferred into distilled water. The contents were sonicated for 1 h at room temperature and shaken for 48 h at room temperature. The amount of FB in the solutions was determined spectrophotometrically at 247 nm [7].

Fourier transforms infrared spectroscopy (FTIR)

FTIR spectroscopy is one of the most common methods used to determine the formation of inclusion complexes and solid dispersions. For this reason, FTIR spectra of prepared solid dispersions and inclusion complexes were recorded using a FTIR spectrophotometer (Perkin Elmer 2000, USA) in 400 and 4000 cm^{-1} range [9].

Differential scanning calorimetry (DSC)

DSC thermograms were examined to confirm the

inclusion complex formation of FB with β-CD and the formation of solid dispersions with PVP. The amount of amorphous and crystalline phases of the prepared complexes and dispersions were evaluated using Shimadzu DSC 60 (Japan) [8,9].

Scanning electron microscopy (SEM)

By determining the morphological features of the inclusion complexes and solid dispersions, imaging with scanning electron microscopy (Tecnai G2 spirit biotwin, USA) was performed to compare with the morphological features of FB, β-CD and PVP. An acceleration voltage of 5 - 20 kV was used for imaging. Images obtained from complexes and solid dispersions are expected to confirm inclusion complex formation from SEM images [9].

Assessment of micromeritic properties of powders

The flow properties of powder mixtures are very crucial for the quality of ODTs. Flow properties were determined by measuring bulk density, stagnation angle, Carr index, Hausner ratio, guided density, and compressibility index. The bulk density of the powder was determined by measuring the volume of a powder of known mass. After beating, the tap density of the powder mixtures was determined. Hausner ratio was calculated based on guided density and bulk density values [10].

Preparation of orally disintegrating tablets (ODTs)

To solve the FB solubility problem, ODTs with a 1:2 molar ratio inclusion complex and a 1:6 solid dispersion were developed using the direct compression method. Parteck ODT® was utilized as a superdisintegrating agent, and magnesium stearate served as an ODT lubricant. Table 1 shows the composition of the ODTs.

Determination of physicochemical properties of ODTs

The physical parameters of the prepared ODTs, including weight variation, hardness, and friability, were investigated. 20 tablets of each formulation were weighed using an electronic balance (Shimadzu Corporation, Tokyo, Japan). Ten tablets were tested for hardness using a hardness tester (Erweka, Germany). In a friabilator, the friability of ten tablets was determined (Erweka, Germany).

Flurbiprofen assay

To determine the amount of FB in ODTs, 10 ODTs were crushed, and the powder equivalent of one tablet was dissolved in pH 7.2 phosphate buffer. The solution was left to stand for 4 h, and shaking was done to complete the solubility process of FB. At the end of the 4 h, after the filtration process, the absorbance values of the samples were read in a UV spectrophotometer (Shimadzu UV - 1800, Japan) at 247 nm. The experiment was performed in triplicate (n = 3) [11-13].

Evaluation of *in vitro* disintegration time

According to the FDA, the disintegration time of an ODT should be 1 min maximum. The disintegration times of the prepared ODTs were identified in distilled water at 37 °C with a USP disintegration device (Erweka, Germany) using six tablets. The test was performed in triplicate [11-13].

***In vitro* dissolution studies**

The release characteristics of FB from ODTs were determined using USP Type II dissolution device (Erweka, Germany) at 50 rpm and 37 ± 0.5 °C. The drug release experiments were carried out in pH 7.2 [11-14].

Stability studies

Stability studies of the two ODT formulations were performed in accordance with ICH guidelines. The appearance, hardness properties and FB amounts of ODTs were determined [8,15].

Table 1: Composition of FB ODTs

	Ingredient (mg)	
Formulation	***FB-β-CD (1 : 2) ODT***	***FB-PVP (1 : 6) ODT***
FB inclusion complex equivalent to 25 mg FB	50	-
FB solid dispersion equivalent to 25 mg FB	-	150
Parteck ODT® (10%)	30	30
Avicel PH 101	147	47
Mannitol	70	70
Magnesium stearate (1%)	3	3
Total tablet weight	300	300

Statistical analysis

The data were analyzed by GraphPad Prism 9.0.0 using ANOVA test at 95 % confidence interval along, and are presented as mean and standard deviation (SD).

RESULTS

Solubility of FB in distilled water

The solubility values of prepared FB - PVP solid dispersions and FB- β- CD inclusion complexes have been shown in Table 2.

FTIR spectra

With pure FB, FTIR analyses of FB -β- CD inclusion complexes and FB - PVP solid dispersions showed major peaks at different wavelengths. The FTIR spectra of prepared solid dispersion at 1:6 molar ratio and inclusion complex prepared by the kneading method FB-β-CD (1:2) molar ratio have been shown in Figure 1.

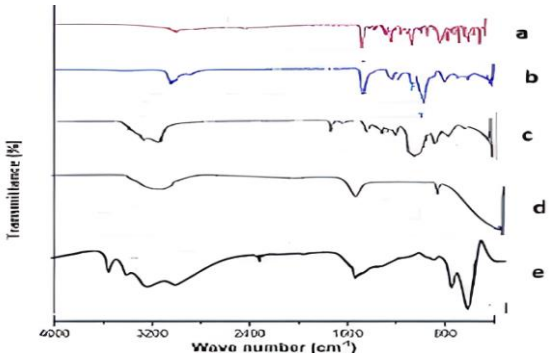

Figure 1: FTIR spectrums of FB (a), β- CD (b), PVP (c), FB- β- CD inclusion complex (d) and FB- PVP solid dispersion (e)

Thermal characteristics

At 116 °C, a sharp endothermic peak corresponding to the melting point of FB was observed. A large endothermic peak was observed around 127 °C. Different peaks were identified at the same place in the improved formulation. A new peak formation was observed at 121 °C in inclusion complexes prepared at a 1:2 molar ratio, and a decrease in the peak of β-CD at approximately 127 °C was also observed. DSC thermograms of FB, β-CD, 1:2 FB β-CD inclusion complex and 1:6 FB-PVP solid dispersion are shown in Figure 2.

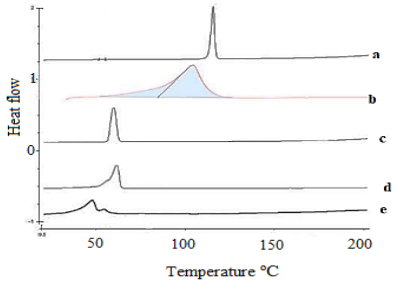

Figure 2: DSC thermograms of FB (a), β- CD (b), PVP (c), FB -β- CD inclusion complex (d) and FB- PVP solid dispersion (e)

Morphology of the formulations

Another evidence of inclusion complex and solid dispersion formation is the evaluation of SEM images. Therefore, SEM images of FB β-CD (1:2) inclusion complex and FB-PVP (1:6) solid dispersion were evaluated in the study. SEM images of FB, β-CD, PVP, inclusion complex and solid dispersion are shown in Figure 3.

Micromeritic properties of powders

Bulk and tapped densities, angle of repose, compressibility index, and Hausner's ratio were computed for prepared powder mixtures. The results, shown in Table 3, indicate that the formulations, including FB solid dispersions and inclusion complexes demonstrated good flow characteristics.

Physicochemical properties of ODTs

Based on solubility tests, 1:2 FB-CD inclusion complex and 1:6 FB-PVP fine solid dispersions were transformed into ODT and assessed for physical properties and in vitro dissolution rate. All of the physical parameters determined for the FB ODTs were shown in Table 4.

Table 2: Solubility of FB-β-CD inclusion complexes and FB-PVP solid dispersions in distilled water at 37 °C

Formulation code	Content	Ratio (molar)	Water solubility (mg/mL)
F1	FB- β- CD	1: 1	0.530 ± 0.02
F2	FB- β- CD	1: 2	0.701 ± 0.08
F3	FB- β- CD	1: 3	0.604 ± 0.15
F4	FB- PVP	1: 3	0.483 ± 0.06
F5	FB- PVP	1: 6	0.501 ± 0.11
F6	FB- PVP	1: 9	0.405 ± 0.14
Pure FB			0.148 ± 0.05

Table 3: Micromeritic parameters of ODT powders

Formulation code	Angle of repose (°)	Carr's index (%)	Hausner's ratio
F1	28.09 ± 1.02	8.89	1.10 ± 1.02
F2	25.14 ± 0.98	8.25	1.08 ± 1.03
F3	32.15 ± 1.10	7.59	1.05 ± 1.01
F4	25.77 ± 0.88	9.95	1.11 ± 1.01
F5	22.03 ± 0.82	8.56	1.15 ± 1.02
F6	27.16 ± 1.15	10.01	1.10 ± 1.03

Table 4: Physicochemical properties of ODTs

Parameter	FB-β-CD ODTs	FB-PVP ODTs
Weight of ODT (mg) Avr±SD	300.84 ± 1.15	300.26 ± 1.09
Diameter of ODT (mm) Avr±SD	7.99 ± 0.02	7.95 ± 0.01
Thickness of ODT (mm) Avr±SD	3.33 ± 0.04	3.28 ± 0.02
Hardness of ODT (N) Avr±SD	31.7 ± 2.28	32.4 ± 1.95
Friability of ODT (%) Avr±SD	0.42 ± 0.02	0.39 ± 0.01
Disintegration time of ODT (sec) Avr±SD	24 ± 2.20	29 ± 1.79
FB Assay of ODT Avr±SD	98.14 ± 1.13	95.55 ± 1.08

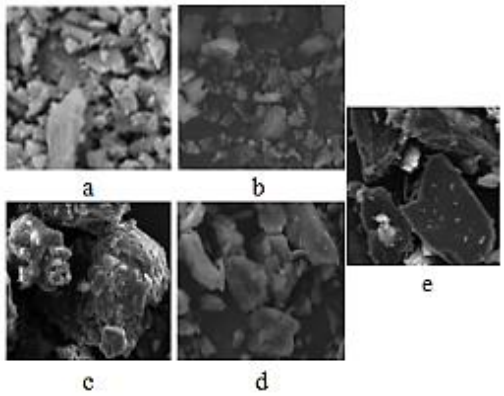

Figure 3: SEM images of FB (a), β-CD (b), PVP (c), FB- β- CD inclusion complex (d) and FB- PVP solid dispersion (e)

Dissolution profile of ODTs

In vitro dissolution tests revealed that tablets containing FB β-CD inclusion complex dissolved faster than PVP solid dispersion of FB. The dissolution profiles are shown in Figure 4.

The dissolution data for FB ODTs were subjected to: (1) difference, and (2) similarity tests. The difference (f_1) factor is proportional to the mean difference between the three profiles, while the similarity (f_2) factor is inversely proportional to the mean squared difference between the three profiles, with emphasis on the largest difference between all time periods. The calculated f_1 and f_2 values have been listed in Table 5.

Stability of the formulations

To prove the formulation's prospective applicability, stability experiments were carried out at 25 ± 2 °C, 60 ± 5 % RH, 40 ± 2 °C, 75 ± 5 % RH for the time, and the formulation was subjected to a drug assay, hardness, and appearance qualities [16-18]. All ODTs retained their white color and rounded shape throughout stability studies. Stability parameters of ODTs are indicated in Table 6.

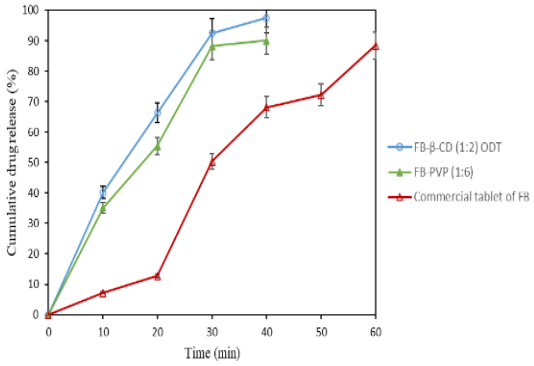

Figure 4: Comparison of FB release from ODTs and commercial tablet

Table 5: f_1 and f_2 factors (commercial FB tablet) versus ODTs

Parameter	FB- β- CD ODTs	FB- PVP ODTs
f_1	17.89	15.93
f_2	27.33	26.15

DISCUSSION

Based on the results obtained, the highest solubility of FB (0.701 ± 0.08 mg/mL) was obtained in the FB-β-CD complex prepared at a molar ratio of 1 : 2. In solid dispersions prepared with PVP, the highest FB solubility (0.501 ± 0.11) was detected with the one prepared at a ratio of 1:6. As a result, it can be said that both CD complexes and solid dispersions of PVP of FB

Table 6: Stability studies of ODTs (mean ± SD)

Parameter	25±2 °C, 60±5%RH				40±2°C, 75±5% RH		
Study period (month)	***0***	***3***	***6***	***9***	***0***	***3***	***6***
FB-β-CD (1:2) ODT							
ODT hardness (N)	32.4 ± 2.11	32.6 ± 1.0	31.8 ± 0.8	31.9 ± 0.6	31.2 ± 1.9	31.2 ± 1.8	32,3 ± 1.0
FB content (%)	91.4 ± 1.4	90.0 ± 0.2	90.1 ± 0.3	91.1 ± 0.2	91.4 ± 1.4	90.9 ± 1.0	90.0 ± 0.4
FB-PVP (1:6) ODT							
ODT hardness (N)	31.6 ± 1.4	33.5 ± 0.9	31.4 ± 0.1	30.5 ± 0.2	32.4 ± 1.2	32.2 ± 1.5	33.2 ± 1.0
FB content (%)	90.1 ± 1.6	92.3 ± 0.2	91.4 ± 1.1	92.1 ± 1.0	92.5 ± 0.6	90.9 ± 0.9	90.8 ± 0.7

increased the solubility of pure FB in water [1,3]. For this reason, it can be said that CD has both hydrophilic and hydrophobic structure, thus increasing the solubility of FB with poor water solubility.

The FTIR spectral analysis of FB alone showed that the main peaks were observed at wave numbers of 1706, 1428, 1208 and 704 /cm. In optimized FTIR spectra formulation, 1815.11, 1526.06, 1306.02 and 512.4 /cm wave were observed [4,5]. The absence of sharp peaks in the FTIR spectra of FB-β-CD inclusion complexes confirms that the two molecules form inclusion complexes. The absence of sharp peaks in the FTIR spectra of FB- PVP inclusion complexes confirms that the two molecules form a solid dispersion [6].

When the DSC thermograms of prepared 1:6 FB-PVP solid dispersions was evaluated, a new peak formation, was observed at approximately 125 °C; No peak was observed at 127 °C. The absence of any melting peak of FB in the DSC thermograms of the inclusion complexes confirmed the formation of inclusion complexes and solid dispersion. [8]. As a result of the examination, it was determined that despite the crystal structure of FB and the void structure of β- CD, the inclusion complexes showed a cubic structure. This can be considered as an indicator of inclusion complex formation. On the other hand, it was determined that the crystal structure obtained from the solid dispersions was quite similar to the inclusion complex [6,8].

When pre-compression tests results were examined, the results of angle of repose, Hausner's Ratio, and Carr's index suggest that the powder mixture has fair to acceptable flow characteristics [16]. According to the results, it has been determined that it is appropriate to prepare ODT without the need to add any glidant to the prepared powder mixtures ($p > 0.05$).

The evaluation results of ODTs according to post-compression test parameters show that all prepared ODTs are acceptable.

The increased dissolution rate could be attributed to a combination of improved wettability, emulsifying impact of carriers, and particle size reduction during inclusion complex formation. When the dissolution profiles of ODTs were compared with the conventional tablet of FB, it was determined that both prepared ODT formulations in this study showed a higher dissolution rate than the commercial tablets [18].

The FDA guideline recommends evaluating these criteria for dissolution profile comparison. According to the guidelines, f_1 values range from 0 to 15, while f_2 values range from 50 to 100. The 1 and 2 factors for the test product versus the reference were determined [18]. When the dissolution properties of ODTs are compared with the market formulation; f_1 factor is less than 15; The f_2 factor being less than 50 indicates that the dissolution properties of ODTs are very different from conventional formulations of FB.

The stability tests of prepared ODTs were performed so as to be in conformity with the ICH recommendations and stable during the period investigated at the prescribed temperature and humidity degrees ($p > 0.05$).

CONCLUSION

The dissolution rate of FB ODTs has been successfully enhanced by formulating them as PVP solid dispersions and β-CD inclusion complex. Formulations containing β-CD inclusion complex demonstrate considerably higher solubility and dissolution rate than conventional FB tablets. Thus, β-CD inclusion complex is a suitable strategy to increase the solubility and bioavailability of FB.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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