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ORIGINAL ARTICLE

Improve Solubility of Acetamidophenol from PEG and Witepsol Suppositories via Formation of Inclusion Complex by β-Cyclodextrin with a Controlled Release Profile

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Abstract

Purpose Acetamidophenol (ACP) is used to treat mild to moderate pain and reduce fever, but low water solubility and poorly dissolution of this compound restricted its bioavailability.

Methods To overcome these problems and enhance the solubility of ACP, inclusion complex between ACP and β-cyclodextrin (β-CD) is formed with various mass ratios of β-CD:ACP (1:1, 1:2, 1:4, 1:8), and the effect of complex formation on solubility and release of ACP from PEG and Witepsol-based suppositories through rectal route of administration is investigated.

Results Inclusion complexes formed with various ratios of β-CD:ACP and loaded in the formulation of suppositories by fusion method utilizing different suppository bases, i.e., Witepsol H15 and polyethylene glycol (4000, 400). FTIR, SEM, and XRD results indicate formation of inclusion complex between β-CD and ACP. Physical characteristics and in vitro drug release of the obtained suppositories are determined by several tests such as weight variation, melting point, hardness, and release rate.

Conclusion Results indicate that PEG-based suppositories containing β-CD:ACP 1:1 mass ratio show the best in vitro drug release characteristic which released 19.3% of ACP after 8 h.

Keywords Suppository · PEG · Witepsol · Acetamidophenol · β-cyclodextrin · Controlled release

Introduction

Suppositories are medicated solid dosage forms which are melted or soften at body temperature shaped for rectal route of administration [1, 2]. Rectal administration of drugs offers many advantages such as elimination of first-pass metabolism, prevention of gastric irritation caused by certain drugs, and avoidance of negative effects of meals on drugs [3]. Suppositories may be useful for long-term treatment of diseases such as arthritis, asthma, diabetes, and AIDS. Despite these advantages, there are some restrictions in daily use of suppositories making them the patient last resort [4].

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Suppositories are prepared by using lipophilic and hydrophilic bases. In order to reduce the frequent use of drugs, many researchers have suggested that using water-soluble bases with some additives can prolong the absorption of the drug from the rectum leading to controlled release of the drug. Polyethylene glycols (PEGs) are one of the most widely used water-soluble polymer suppository bases existing in a variety of molecular weights [1]. PEGs of different molecular weight can be combined to reach the desired drug release rate profile. The drug release from suppository bases can be affected by the nature of the base and the additives and its concentration which may lead to an increase or decrease in the rate of drug release [5]. Problems controlling drug release from polymeric bases are common due to their high surface area to volume ratio, but the incorporation of cyclodextrins may overcome this problem [6]. Acetamidophenol is a synthetic derivative of p-aminophenol that produces analgesic effects. Acetamidophenol is a white, odorless, and crystalline powder with a melting point of 170 °C which has a poor solubility in suppository bases. Among all the approaches implemented to enhance drug solubility, complexation with cyclodextrins is one of the most promising ones [7]. Cyclodextrins are a group of cyclic

oligosaccharides obtained from starch. Among all the natural cyclodextrins, β-cyclodextrins (β-CDs) have the most use in pharmaceutical industry due to its cavity size, availability in pure form, and low cost. Cyclodextrins have a hydrophilic exterior and a hydrophobic cavity in which the drug molecule enters and changes in its physicochemical properties occur [8]. The purpose of this study was to prepare suppositories of Acetamidophenol and inclusion complex of Acetamidophenol using β-CD incorporating different suppository bases and evaluate its effect on the physicochemical characteristics and release parameters of suppositories.

Materials

Polyethylene glycol 4000 (PEG, Merck, > 98%), Polyethylene glycol 400 (PEG, Merck, > 98%), β-cyclodextrin (β-CD) (Aldrich, > 98%), Acetamidophenol (ACP, Acetamidophenol, > 98%), NaOH (Merck, > 98%), and ethanol (EtOH) (Merck, > 98%) were used without further purification and were used as received. Hard fat H15 (H15) and potassium dihydrogen phosphate were from Daru Pakhsh Company, Tehran, Iran, and Ameretat Shimi Pharmaceutical, respectively.

Methods

Complex Formation of β-CD/Acetamidophenol

The inclusion complex of β-CD with ACP is prepared by adding ACP solution in ethanol (5.0 ml of 14.5 wt%) to β-CD solution in ethanol (5.0 ml of 5.0 wt%) at 40 °C. The suspension is stirred at room temperature (25 ± 1 °C) for 2 h, then stays at room temperature (25 ± 1 °C) for 24 h. The obtained solid is collected and then dried at 50 °C in an oven for 24 h. The dried complex is characterized by XRD, SEM, and FTIR [9].

Preparation of Suppositories

Suppositories are made by fusion molding method. For this purpose, the suppository base (PEG or Witepsol) is melted, and then, the ACP or ACP:β-CD with various ratios are dispersed or dissolved in the molten base (Table 1). In formulations P1 and H1, no β-CD is used. In formulations P2, P3, P4, P5, and H2, the ACP:β-CD mass ratio is 1:1, 2:1, 4:1, 8:1, and 8:1, respectively. The mixture is removed from the heat and poured into a suppository mold. When the mixture has congealed, the suppositories are removed from the mold. The fusion method can be used with all types of suppositories and must be used with most of them. Suppositories are generally made from solid ingredients and drugs, which are measured by weight. When they are mixed, melted, and poured into suppository mold cavities, they occupy a volume—the volume of the mold cavity. Since the components are measured by weight but compounded by volume, density calculations and mold calibrations are required to provide accurate doses [4].

Calibration of Molds

The molds should be calibrated before preparing the suppositories because they may vary in their capacity. The base is melted alone and filled in the mold, and the mean weight is calculated after removing from the mold. The mean weight is taken as a true capacity of the molds. The same procedure is repeated for other bases [4].

Evaluation of Suppositories

Visual Characterization

Six randomly selected suppositories are assessed for surface homogeneity and absence of fissuring, fat blooming, and pitting [10].

Weight Variation

The prepared suppositories are evaluated for weight variation according to the method of British Pharmacopoeia [9]. Twenty suppositories are made using each respective base and are individually weighed using balance (Sartorius AG, Gottingen, Germany), and the average weight is calculated. The weight variation is then estimated by subtracting the weight of each suppository from the average weight. No suppository weight should deviate from average weight by more than ± 5% [4, 11].

Table 1 Formulation of obtained suppositories

Formula	H1	H2	P1	P2	P3	P4	P5
PEG 4000/400 (mass ratio = 6:4)	–	–	1.2/0.8	1.2/0.8	1.2/0.8	1.2/0.8	1.2/0.8
H15 (g)	1.4	1.4	–	–	–	–	–
ACP (g)	0.3	–	0.3	–	–	–	–
ACP:β-CD mass ratio	–	8:1	–	1:1	2:1	4:1	8:1

Mechanical Strength (Hardness)

This test is done using Erweka hardness tester (Type SBT, West Germany): The temperature inside the testing chamber is maintained at 25 ± 1 °C by means of circulating water from thermostat connected to the tester. The suppository is placed into the holding device with the tip upwards, and the test chamber is then closed with glass plate. An initial load (600 g) is given by the entire suspended block, and at regular intervals of 1 min, a disk of 200 g is added until the suppository crush. The mass required to crush the suppository is then calculated as the sum of the initial load, and masses add until the suppository collapses. The measurement of hardness is carried on all suppository formulations with ACP and ACP:β-CD [4]. Each test is done for three times and average data is reported [4, 11].

Disintegration Test

Disintegration test is performed on six suppositories of each base using USP tablet disintegration (Model PTW, Germany) test apparatus. The suppositories are immersed in 160 ml of distilled water maintained at 37 °C. The time for complete disintegration of water-soluble bases and complete melting of oily bases is determined [12]. Each test is done for three times and average data is reported [4, 11].

Melting Time

The ascending melting time method is used to determine the melting time of each base type of suppository using Erweka (Model SSP, Germany) test apparatus. Briefly, a pipette of 10 cm in length having a narrow opening on one side and broad opening on another side is used. The pipette is dipped into water bath at 37 °C where both ends remain in the bath. The sample suppository is inserted from the top of the pipette and pushes till it reaches the narrow end. The time at which the suppository reaches the narrow end after melting completely represents the melting time [4, 10]. Each test is done for three times and average data is reported.

Drug Content

The uniformity of drug content for each base (20 suppositories) is determined by dissolving PEG base suppositories in 100-ml phosphate buffer of pH 7.4 by stirring slowly at 37 °C for 1 h. The absorbance is measured by spectrophotometry HACH (Model DR5000) test apparatus at a wavelength of 243.3 nm after dilution. The procedure is repeated to determine the uniformity of drug content of lipophilic base suppositories using repeated extraction with phosphate buffer (pH 7.4). To ensure complete extraction of the drug from the bases, blank suppositories without the drug are prepared and

Table 2 Evaluation of suppositories for various parameters

Formula Tested (from Table 1)								
Attribute	P1	P2	P3	P4	P5	H1	H2	
Average length (±0.5 cm)	3.5	3.7	4.0	3.7	4.1	3.6	3.8	
Average width (±0.05 cm)	1	0.9	0.9	0.9	0.8	1	0.8	
Average label claim (±0.5%) $N = 20$	95.41 (90.50–99.85)	98.83 (93.5–102)	105.4 (100–108)	95.43 (90.50–100.50)	96.00 (92.50–98.50)	89.83 (83.55–92.50)	89.06 (84.50–93.50)	
Weight variation (±0.005%), $N = 20$	0.043 (0.035–0.460)	0.041 (0.030–0.0450)	0.038 (0.036–0.0395)	0.028 (0.027–0.0295)	0.071 (0.060–0.075)	0.021 (0.019–0.023)	0.010 (0.085–0.012)	
Average hardness* (±0.1 kg/cm^2), $N = 3$	1.933 (1.890–1.950)	1.800 (1.750–1.820)	3.466 (3.265–3.560)	2.800 (2.755–2.850)	1.166 (1.050–1.230)	6.35** (6.250–6.420)	6.20** (6.10–6.35)	
Average disintegration time* (±1 min), $N = 6$	20 (19.5–21)	21 (19.5–22)	15 (14.5–16)	15 (14–16.5)	14 (13–15)	41 (40.5–41.5)	42 (41–42.5)	
Average melting time* (±1 min), $N = 3$	40 (39–42)	45 (43–46)	28 (27–29)	35 (33–37)	26 (25–27)	19 (18–21)	22 (20–23)	

*Range of results in brackets

**The most suitable level of hardness is 1.8–2.0 kg

subjected to the same analytical procedure to serve as the blank for spectrophotometric determination [11, 12].

Dissolution Test

In vitro dissolution studies of ACP and ACP:β-CD suppositories are carried out in USP basket test apparatus (Pharma Test, Type PTWS) using a rotating basket at 100 rpm at 37 ± 0.5 in 900-ml phosphate buffer of pH 7.4 as dissolution medium. At determined time intervals, 5-ml sample is withdrawn by a syringe and replaced by 5 ml of fresh buffer. To determine the drug release of withdrawn samples, they are analyzed by measuring the absorbance by a UV-Vis spectrophotometer at 243.3 nm. Then, cumulative percent of ACP and ACP:β-CD released is calculated and plotted against time [4, 11]. Each test is done for three times and average data is reported.

Characterization

Infrared spectra are recorded with a Bruker IFS 48 FTIR spectrometer. X-ray diffraction (XRD) is used to study the complex formation between ACP and β-CD at ambient conditions; a Xpert Philips diffractometer (USA) with nickel-filtered Cu Kα radiation is used in this work. Data is collected at a rate of 2°θ min over the 2θ = 5°60° range. Scanning electron microscopy (SEM), Philips XL30 (Poland), is used to study the distribution and size of particles and the microstructures of complexes [13–17].

Results and Discussion

Suppositories of ACP and ACP:β-CD are prepared by fusion method utilizing different bases such as PEG 4000,400 and hard fat H15. The results of visual and physiochemical characterization are shown in Table 2. The length and width of random suppositories are randomly measured from each formulation. PEG- and H15-based suppositories containing ACP and ACP/β-CD show that obtained suppositories are uniform without any fissuring and fat blooming (Fig. 1).

Weight variation studies for all suppositories show that the deviation in weight of all prepared suppositories is less than 0.5 from the average weight which is in acceptable range based on British Pharmacopoeia standards and which indicates that calibration of mold is perfect. All suppositories have uniformity of drug content, which is within acceptable range of 85–100% indicating that drug is dispersed uniformly in suppositories [18]. Suppositories should have good mechanical strength for packaging and transportation. Weight of a single suppository is 2.4 g. Hardness and mechanical strength of obtained suppositories containing ACP and ACP:β-CD show optimum hardness (1.5–2.5 kg) [9]; results indicate that PEG-based suppositories P1, P2, P3, and P4 are in acceptable range. In P2, P3, and P4 by increasing the ratio of Acetamidophenol to β-CD, hardness increases due to complex formation between Acetamidophenol and β-CD molecules. But in P5, hardness is less than acceptable amount which is related to much higher ratio of Acetamidophenol to beta-cyclodextrin in the inclusion complex. By increasing the amount of Acetamidophenol in comparison with β-CD, the

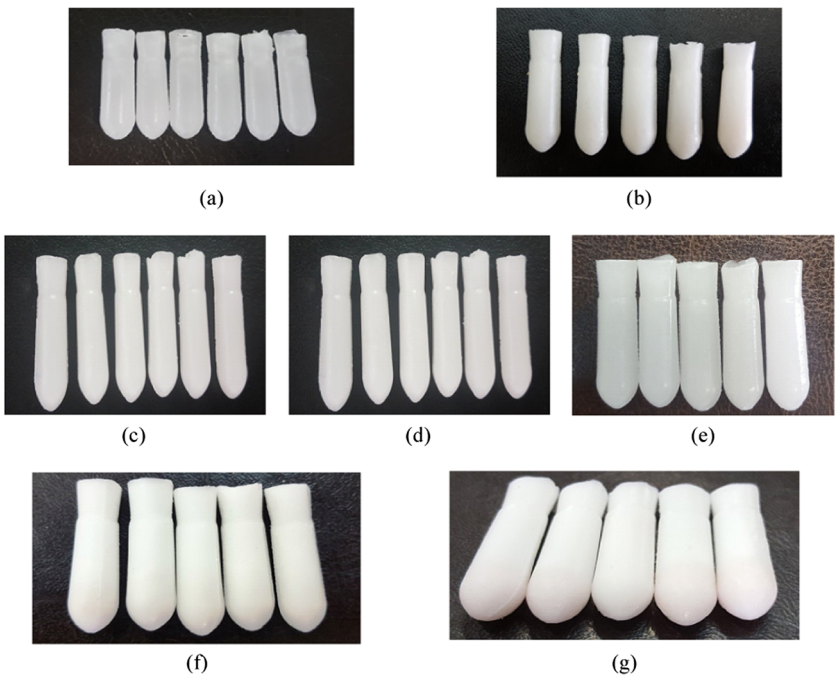

Fig. 1 PEG- and H15-based suppositories **a** P1, **b** P2, **c** P3, **d** P4, **e** P5, **f** H1, and **g** H2

complex became saturated and a large number of ACP molecules do not form complex with β-CD, so they easily separate from the system and do not show good strength. P1 and P2 show the most suitable level of hardness (1.8–2 kg) which contain pure ACP and ACP/β-CD with 1:1 mass ratio. This is due to formation of inclusion complex between ACP and β-CD with 1:1 mass ratio [9].

In the H1 and H2 suppositories, the hardness is more than 6 kg, which is not a good fit for superstructures. Significant increase in the hardness is seen for H15-based suppositories which is preferable for suppository applications. To reduce the hardness, other grades of hard fat such as E75 or combination of 10% polysorbate 80 with hard fat can be used as based component [10]. The melting time of the PEG-based suppositories is longer than H15-based suppositories which is related to higher melting temperature of PEG than H15. In formulation P2 where the ACP:β-CD ratio is 1:1, the highest melting time is observed which shows that the inclusions between ACP and β-CD molecules have formed successfully. In P3, P4, and P5 by increasing the ratio of Acetamidophenol to β-CD melting time decreases. The lowest melting time is related to P5 and H2, which contains ACP:β-CD 8:1 mass ratio. In these compounds, the amount of ACP is more than β-CD and a large number of guest molecules (ACP) cannot form inclusion complex with β-CD, so thermal stability of suppositories is decreased. By determination of optimum ratio of ACP and β-CD, ACP incorporated in β-CD cavity and physical properties of ACP improves, so stability of the suppositories increases. Disintegration time for PEG-based suppositories is within 20 min, which is related to hydrophilicity of PEG and fast dissolution rate in distilled water. Disintegration time for H15-based suppositories is about 42 min and indicated that melting temperature of H15 plays an important role in disintegration time.

In P2, ACP:β-CD ratio is 1:1 and limited number of ACP molecules can form inclusion complex based on reversible hydrogen bonding between β-CD and ACP, which delays the destruction time of suppositories and disintegration time increases very small amount compared to P1. In P3, P4, and P5, an amount of ACP increased compare to β-CD, so susceptible hydroxyl groups for formation of reversible hydrogen bonding are increased, so water solubility of suppositories increases significantly and disintegration time significantly decreases [19].

In vitro Dissolution Studies

The release profile from different suppository formulations is shown in Fig. 2. Percentage cumulative drug release from suppositories of PEG (P1) and Witepsol (H1) is found to be 59.06 and 35.49% respectively after 4 h (Table 2). The higher release is due to hydrophilicity and better dissolution of PEG. On the other hand, in hydrophobicity of fatty bases (hard fat H15) and non-miscibility of the base with dissolution media, the release rate of this base is low [12].

In P2, P3, P4, and P5 by addition of β-CD to drug, drug release rate decreases due to the formation of a complex between ACP and β-CD, which is insoluble in water, and thus, this complex reduces drug diffusion through the base and prolongs the release time. The initial burst is because of free drug molecules in the formulation, which further *follows* the slow release from the complex [20].

Among all the formulations, P2, which is containing ACP/β-CD 1:1 mass ratio, determines the optimum ratio with the slowest release of 19.51% after 8 h. As the amount of ACP increases in comparison with β-D in P3, P4, and P5 formulations, drug release rate increases which indicates that less complex is formed between drug and β-CD, so the number of the free drug molecules increases which leads to faster release rate. In suppositories containing fatty bases, H1 and H2 show percentage cumulative release of 35.49 and 29.83% after 4 h, respectively, which proves the fact that addition of β-CD to the drug and complex formation decreases drug release rate [8].

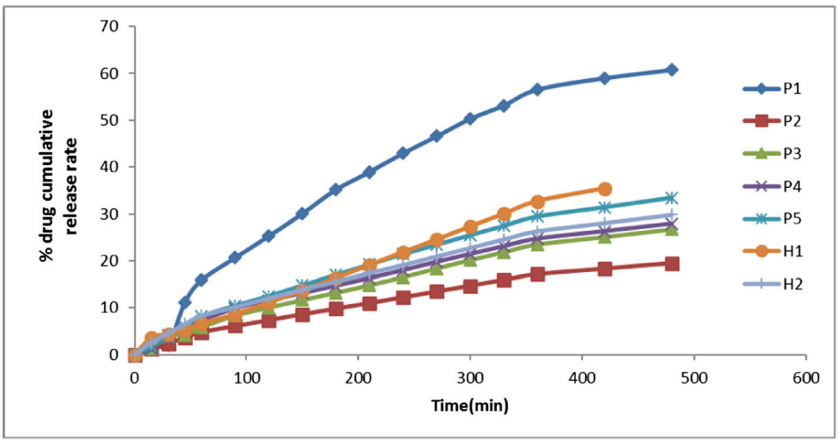

Fig. 2 In vitro release of ACP and ACP:β-CD from PEG- and Witepsol-based suppositories

Drug Characterization Analysis

Complex formation and microstructure of drug complexes (ACP:β-CD) are investigated by SEM, FT-IR, and XRD.

Scanning Electron Microscope

The SEM images in Fig. 3 clearly show the changes in microstructure of ACP:β-CD in comparison with pure ACP and β-CD. It is found that an increase in amount of ACP in P3, P4, and P5 leads to an increase in particle size. As the amount of ACP increases, some ACP units can be placed in β-CD cavity and the rest of ACP units have branch interactions with each other or to the surface of β-CD and that results in bigger particles.

Fourier Transform Infrared Spectroscopy

FT-IR spectrum is a strong mean to show the existence of both host and guest molecules in the formed complex between guest molecule and β-CD. Changes in shape, position, and number of the absorbance bonding show if the complex has formed. FT-IR spectrum of pure ACP, β-CD, and their complexes is shown in Figs. 4 and 5. FTIR spectrum of Acetamidophenol shows absorption bands at 3340 to 3160 cm^{-1} (hydroxyl groups), at 1650 and 1600 cm^{-1} (unsaturation aromatic ring), and at 1560, 1500, and 830 cm^{-1} (aromatic ring). β-CD shows characteristic absorption bands at 3340 cm^{-1} (O-H stretching, vibration), 2920 cm^{-1} (O-H stretching), 1650 cm^{-1} (O-H bending), 1430 cm^{-1} (O-H deformation), 1160 cm^{-1} (C-O-C stretching and O-H bonding), and 1435 cm^{-1} (C-O-C stretching).

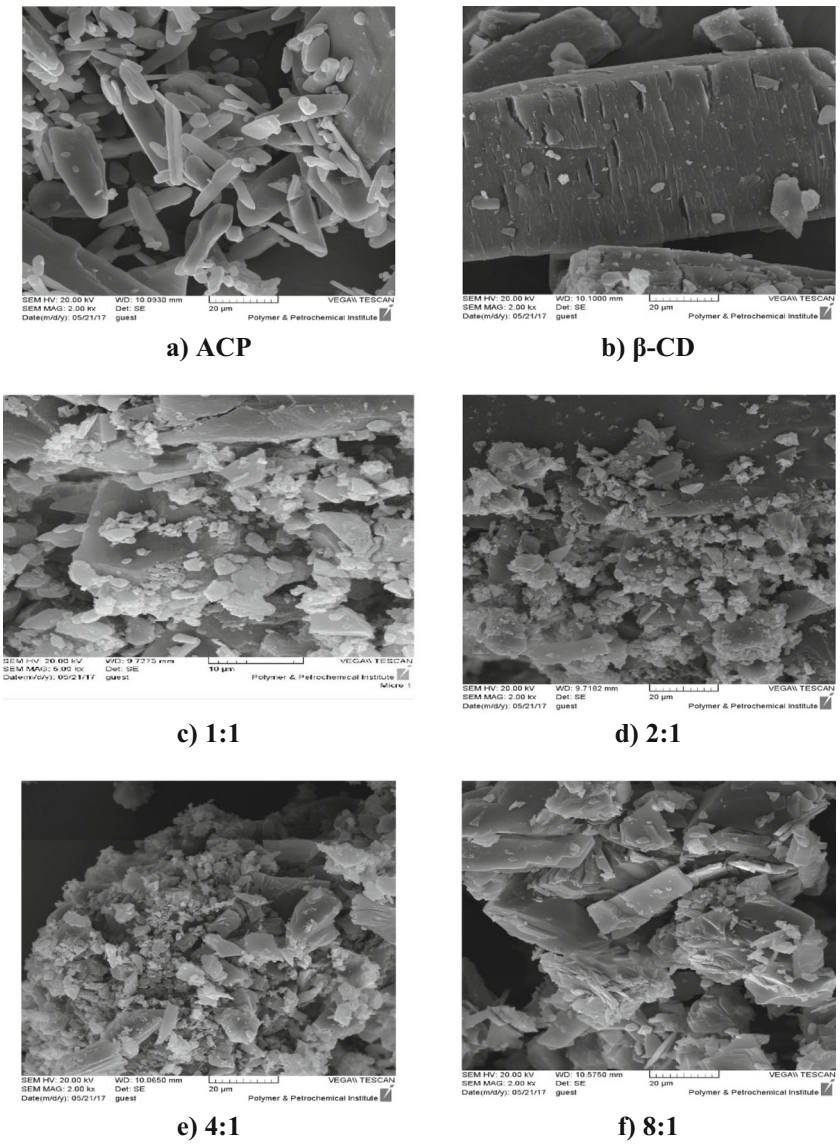

Fig. 3 SEM images of ACP and β-CD and their complexes in different ratios. **a** ACP, **b** β-CD, **c** ACP:β-CD complex (1:1), **d** ACP:β-CD complex (2:1), **e** ACP:β-CD complex (4:1), and **f** ACP:β-CD complex (8:1)

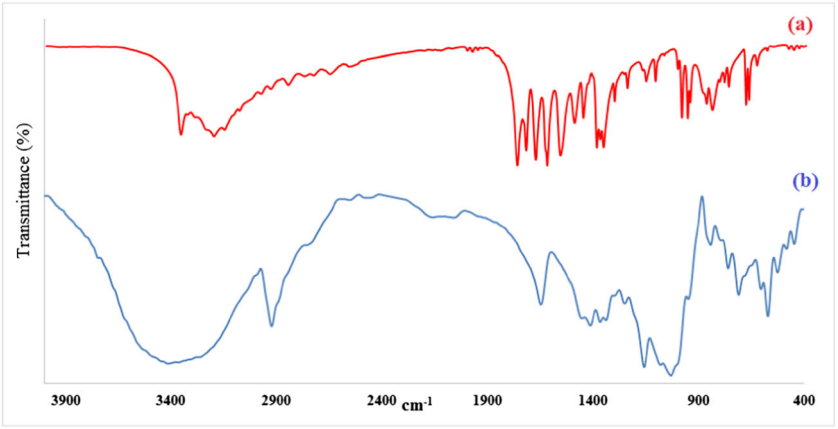

Fig. 4 FTIR spectrum of (**a**) Acetamidophenol and (**b**) β-CD

By formation of inclusion complex between via intermolecular hydrogen bonding of ACP with β-CD ACP, only one broad absorption is seen for hydroxyl group at 3384 cm^{-1} which indicates insertion of ACP in to β-CD cavity (Fig. 6(a–d)).

In P3 containing ACP/β-CD 2:1 mass ratio due to the large number of the formed complexes, the amount of hydroxyl and reversible interactions decreases. As it is shown in β-CD spectrum, CH_2 bonds are visible in β-CD spectrum at 2900–3000 cm^{-1} which is found in P2 and P3, but they are not found in P4 and P5 as the amount of β-CD decreases in comparison with that of ACP. Moreover, despite the C-O and C-C peaks in β-CD and P2 which are glucose bonds at 1025–1100 cm^{-1}, these peaks are not found in P3, P4, and P5.

X-ray Diffraction

X-ray diffraction spectrums of ACP, β-CD, P2, P3, P4, and P5 in different conditions, and their peaks have been shown in Fig. 6 and Table 3, respectively. X-ray diffractions clearly show the complex formation between ACP and β-CD. The most common morphology is when a guest polymer places in the host cavity and the molecules accumulate on each other. Pure β-CD is found to have a cage structure which is attached to β-CD on both sides. Channel structure is verified by resulted peaks at 2θ = 13, 18, 20, 25 and cage structure by peaks at 2θ = 8, 12, 23. The results show that the complex formed between ACP and β-CD is a combination of channel and cage structure.

Conclusion

In the present study, drug release from Acetamidophenol suppositories is investigated in the absence and presence of β-cyclodextrin. It can be concluded that Acetamidophenol suppositories prepared by both hydrophilic and hydrophobic bases, and PEG 4000/400 and hard fat H15, respectively, show official standards of weight variation and drug content but PEG-based suppositories offer better physical properties.

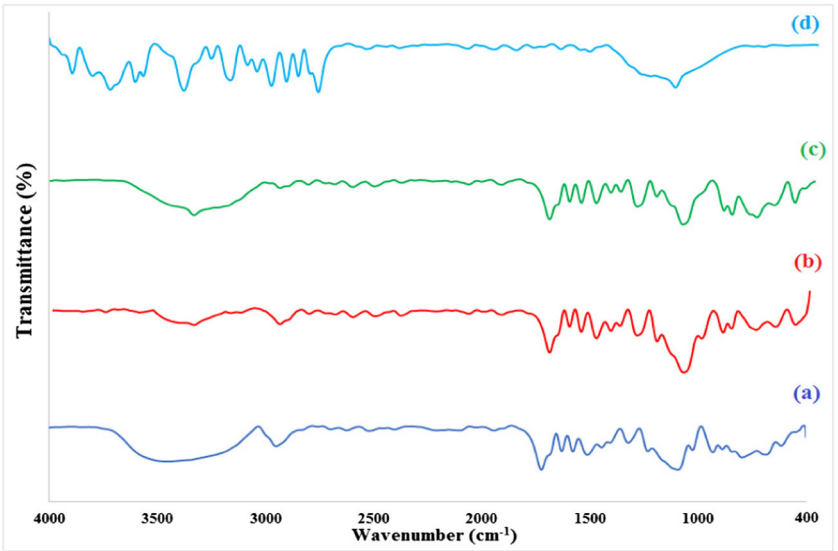

Fig. 5 ACP:β-CD complex FT-IR spectrum. (**a**) P2 (1:1), (**b**) P3 (2:1), (**c**) P4 (4:1), and (**d**) P5 (8:1)

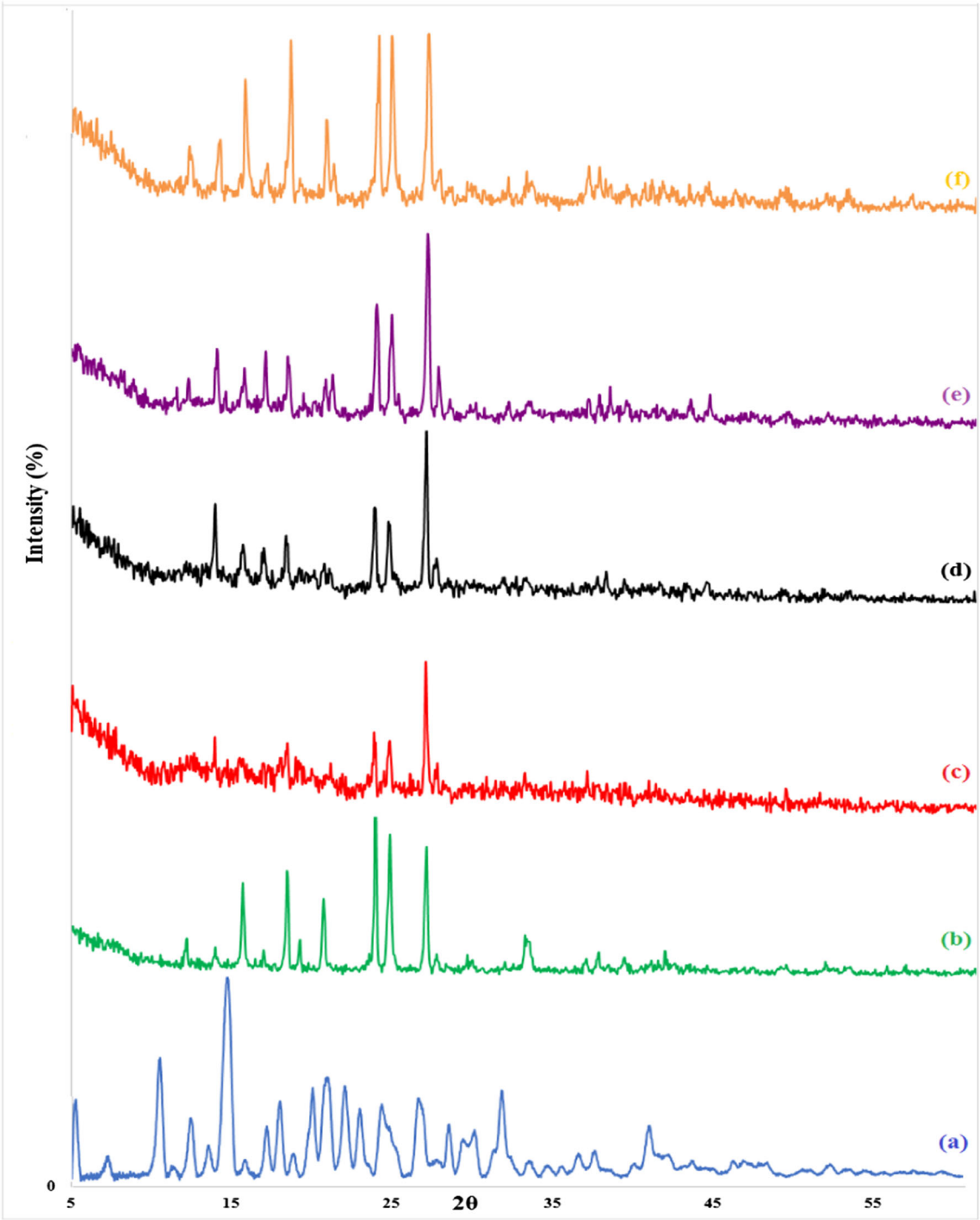

Fig. 6 XRD spectrums. (**a**) β-CD, (**b**) ACP, (**c**) P2 containing ACP/β-CD (1:1), (**d**) P3 containing ACP/β-CD (2:1), (**e**) P4 containing ACP/β-CD (4:1), and (**f**) P5 containing ACP/β-CD (8:1)

Generally, drug release from suppositories depends on drug solubility in the base and chemical structure of the base, and these factors can increase or decrease drug release rate. It is found that release of ACP from PEG suppositories is higher than oily bases. Incorporation of β-CD in drug formulation leads to slower drug release rate as β-CD forms a complex with ACP. It can be concluded that the results of suppositories are controlled by type of the base used. The optimum ratio of ACP/β-CD for inclusion formation is 1:1 mass ratio which shows acceptable hardness and controlled drug release. In other formulations, drug release increases due to increased amount of Acetamidophenol to β-CD which indicates less inclusion formation between ACP and β-CD. Also, the results obtained from by SEM, XRD, and FTIR clearly indicate

Table 3 Peaks found in XRD in ACP/β-CD complex

Peak (2θ)	Compound
ACP	2θ = 12.05,15–16,18,20,23.4,24.3,26,32.45,40.8
β-CD	2θ = 5–7,8,10,12,13.4,16,17,18,19,21,22,24,27,32,34.8
P2	2θ = 5–7,8,12,13,14,15,17,18,23,24,26,32,35
P3	2θ = 5–8,10,12,13,15,16,17,18,20,23–24,26,31
P4	2θ = 5–8,11,13,14,15,16.65,17,20–21,23,24,26,27,32
P5	2θ = 5–8, 12,13,15–16,7,18,20,23,24,26–27,32.7,36

inclusion complex formation between β-CD and ACP at various ratios. SEM images of pure ACP, β-CD, and their complexes are different which confirms the formation of inclusion complex.

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