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ORIGINAL ARTICLE

Development of Orally Disintegrating Tablets from Solid Dispersions Containing Tolvaptan/Cyclodextrin Complexes

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ABSTRACT

Objectives: Tolvaptan is a compound that is practically insoluble in water and poorly soluble at physiological pH, and is used to treat low blood sodium levels in adults with conditions such as heart failure and certain hormonal imbalances. Increasing the water solubility and dissolution rate of tolvaptan could increase its bioavailability and, consequently, its efficacy. This study aimed to increase the efficiency of tolvaptan by enhancing its solubility and dissolution rate, and to develop a fast-acting dosage form that improves convenience for patients with swallowing difficulties.

Materials and Methods: Solid dispersion (SD) formulations were developed by the rotary evaporation method using hydrophilic polymers (polyvinylpyrrolidone and polyethylene oxide), solubility enhancers (Solutol HS-15 and Gelucire 44/14), and complexing agents (β-cyclodextrin and hydroxypropyl-β-cyclodextrin). Various characterization studies were performed on developed formulations, including solubility studies, X-ray diffraction, differential scanning calorimetry, Fourier transform infrared spectroscopy, and scanning electron microscopy analyses, *in vitro* dissolution tests, and release kinetics studies.

Results: The solubility of tolvaptan in the 2-hydroxypropyl-beta-cyclodextrin (HPβCD)-SD2 formulation containing 2-hydroxypropyl-β-cyclodextrin, was the highest at 0.2314 mg/mL, which was approximately 8.7 times that of pure tolvaptan. Based on the results, HPβCD was selected as the complexing agent as the optimal SD formulation. In the dissolution study, at least 90% of the tolvaptan in the HPβCD-SD2 formulation dissolved in all buffer solutions within 25 min. Orally disintegrating tablets (ODTs) were prepared using the HPβCD-SD2 formulation; formulation code 59, which had a friability of ≤1% and a disintegration time of ≤180 s, was selected as the final tablet.

Conclusion: A new SD formulation with increased solubility and dissolution rate compared with pure tolvaptan was developed. The developed ODTs may be an alternative to the current commercial product.

Keywords: Solid dispersion(s), orally disintegrating tablet, tolvaptan, cyclodextrin, solubility and dissolution rate

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INTRODUCTION

Solid dispersion (SD) is an important formulation development strategy defined as the dispersion of one or more active substances in a solid, inert carrier or matrix prepared by solvent evaporation, melting, or solvent-melting.[1–3] In the solvent evaporation method, an SD is obtained after the solvent evaporates from the solution containing the drug and carrier; the resulting solid mass is then pulverized and milled.[4,5] In this method, heat degradation of drugs or carriers can be prevented because organic solvents evaporate at low temperatures.[5,6] Methods such as hot-plate heating, vacuum drying, rotary evaporation, spray drying, freeze drying, spray-freeze drying, and ultra-fast freezing are used to remove the solvent quickly.[7] The rotary evaporation method is a solvent evaporation technique that involves evaporating a dispersion or solution under vacuum in a rotating flask for a specified period, resulting in the formation of a solid film on the inner glass surface of the flask when it is heated. This method is rapid, relatively inexpensive, and readily available.

Cyclodextrins (CDs) can form inclusion complexes with active substances that have low solubility and dissolution rates, thereby improving their properties owing to their hydrophilic outer surfaces.[8,9] In terms of formulation development, CDs offer advantages, such as reducing particle size to the molecular level, increasing wettability and porosity, and converting the drug's crystalline state into an amorphous form.[7,10,11] The aim of a study was to increase the oral bioavailability of sulfamethoxazole, which has low solubility and a low dissolution rate, by enhancing its solubility and dissolution rate. For this purpose, 2-hydroxypropyl-beta-cyclodextrin (HPβCD): sulfamethoxazole (1:1) complexes were prepared, and SDs were prepared using polyethylene glycol 20000 and polysorbate 20. The solubility of sulfamethoxazole was increased by forming complexes with CDs and by preparing SDs of these complexes.[12]

Although tablets are widely used today, many elderly individuals and children may have difficulty swallowing them. Orally disintegrating tablet (ODT) formulations are being developed for these patients. The Food and Drug Administration (FDA) defines an ODT as a solid dosage form that disperses rapidly, usually within a few seconds, when placed on the tongue, and contains a medicinal substance or an active ingredient.[13] According to the European Pharmacopoeia, ODTs disperse *in vitro* in water within 3 min.[14] ODTs have many advantages, such as applicability to patients who have difficulty swallowing or who refuse to swallow, rapid drug effects, no water requirement, improved stability, and increased bioavailability.[15] In general, excipients such as fillers, superdisintegrants, glidant-lubricants, sweeteners, and salivary-stimulating agents are used in ODT formulations.[16] In a study, orally disintegrating risperidone tablets were developed using SD and CD technologies. An SD of risperidone was prepared using methyl-CD; an increased dissolution rate was observed. They found that the disintegration time of SD ODTs containing risperidone prepared with Ac-Di-Sol and mannitol was 22.83 ± 3.66 s.[17]

Hyponatremia can occur frequently in older adults, especially in those who are hospitalized or living in long-term care facilities,[18] as well as diarrhea that occurs in childhood.[19] Tolvaptan, a vasopressin V2 receptor antagonist, is used to treat hyponatremia by increasing low blood sodium levels in adults with conditions such as heart failure and certain hormonal imbalances, and it plays a role in regulating renal fluid excretion.[20,21] Tolvaptan is a BCS 4 drug that is practically insoluble in water, with low solubility at all pH values.[22] It is important to improve its efficacy by enhancing the solubility and dissolution rate in water. In a study, SDs of tolvaptan were prepared by hot-melt extrusion and spray-drying techniques using hydrophilic polymers such as Soluplus, Kollidon VA64, and Kollidon 30. In the solubility study conducted in distilled water, the solubilities of pure tolvaptan, tolvaptan in SD prepared by spray drying, and tolvaptan in SD prepared by hot-melt extrusion were 0.04 ± 0.02, 0.32 ± 0.10, and 0.29 ± 0.05 mg/mL, respectively. In the *in vitro* dissolution test performed in distilled water containing 0.22% sodium lauryl sulfate (SLS), 39.60% of pure tolvaptan, 93.50% of tolvaptan in SDs obtained by hot-melt extrusion method, 91.40% of tolvaptan in SDs obtained by spray drying, and 94.20% of tolvaptan in the commercial product were released within 60 min.[23] In another study, conventional ODTs containing pure tolvaptan and superdisintegrants were prepared by wet granulation. As a result of the study, the disintegration time ranged from 40 ± 0.01 to 105 ± 0.01 s, and friability ranged from 0.64 ± 0.02 to 0.86 ± 0.02%.[24]

It is important to increase the efficacy of tolvaptan in elderly and pediatric patients by enhancing its solubility and dissolution rate, and by improving patient compliance through reduction of side effects. Developing innovative dosage forms, such as ODTs rather than conventional solid dosage forms, increases patient compliance in older adults and pediatric patients. This study aimed to prepare CD-free and CD-containing SD formulations of tolvaptan using hydrophilic polymers and solubility enhancers by rotary evaporation, and to compare the solubility and dissolution rates of these formulations. After comparing the SD formulations for solubility and dissolution rate, the optimum formulation was prepared as an ODT using various excipients and rendered suitable for patient administration. To the best of our knowledge, no studies in the literature have reported formation of CD complexes with tolvaptan, preparation of SDs of these complexes, or development of ODT dosage forms.

MATERIALS AND METHODS

Materials

Tolvaptan was donated by Abdi İbrahim Pharmaceutical Company (Türkiye). Gelucire 44/14 was obtained from Gattefossé (France). HPβCD was provided by Roquette (France). βCD was purchased from Central Drug House (P) Ltd. (India). Polyvinylpyrrolidone (PVP) and Solutol HS-15 were acquired from BASF (Germany). SLS and methanol were purchased from Sigma-Aldrich (Germany).

Methods

Preparation of CD-free, βCD, and HPβCD-containing SD formulations

The phase solubility study was carried out in our previous work.[25] In the phase-solubility study of βCD and HPβCD, both CD molecules exhibited a linear increase in solubility with increasing CD concentration. Consequently, a 1:1 (drug:CD) inclusion complex was formed between the drug and CD, and an AL-type phase-solubility diagram was obtained. To produce CD-free SDs, 0.2 g of tolvaptan (2% *w/v*) was first dissolved in methanol; hydrophilic polymers (5–10% *w/v*) were then added, and the mixture was stirred with a magnetic stirrer for 1 h. Then, 0.5 g of solubility enhancers (5% *w/v*) were added and mixed until homogeneous. To produce SDs with CDs, 0.2 g of tolvaptan (2% *w/v*) was dissolved in methanol, and 0.2 g of CDs (2% *w/v*) were added and mixed using a magnetic stirrer for 24 h; hydrophilic polymers (5–10% *w/v*) were then added. Then, 0.5 g of solubility enhancers (5% *w/v*) were added and mixed until homogeneous (Table 1). The mixing continued for 1 h. A total of 10 mL of solution was obtained. The solvent from the final mixture was removed using a rotary evaporator (Büchi Rotavapor R-100) at 50 °C for 1 h. The resulting solid mass was milled into a powder.

Characterization of tolvaptan-CD complexes

After tolvaptan formed a complex with the CDs, X-ray diffraction (XRD) and differential scanning calorimetry (DSC) analyses were performed to characterize the physical and chemical changes in the substances' structures.

Characterization of the SDs

Solubility studies

The solubilities of five tolvaptan-loaded SD formulations—CD-free (SD), βCD (βCD-SD), and HPβCD (HPβCD-SD)—were determined in distilled water at 37 °C. SD was placed in vials containing an excess of tolvaptan and was stirred in a water bath for 1 h. Tolvaptan solubility was determined spectrophotometrically at 260 nm (n = 3; Table 2).

Table 1. The composition of SD formulations containing CD-free, βCD, and HPβCD.

Formulation code	Tolvaptan (%)	PVP K90 (%)	PEO N80 (%)	Solutol HS-15 (%)	Gelucire 44/14 (%)	βCD (%)	HPβCD (%)
SD1	2	10	-	-	-	-	-
SD2	2	10	-	5	-	-	-
SD3	2	10	-	-	5	-	-
SD4	2	-	10	5	-	-	-
SD5	2	5	10	-	-	-	-
βCD-SD1	2	10	-	-	-	2	-
βCD-SD2	2	10	-	5	-	2	-
βCD-SD3	2	10	-	-	5	2	-
βCD-SD4	2	-	10	5	-	2	-
βCD-SD5	2	5	10	-	-	2	-
HPβCD-SD1	2	10	-	-	-	-	2
HPβCD-SD2	2	10	-	5	-	-	2
HPβCD-SD3	2	10	-	-	5	-	2
HPβCD-SD4	2	-	10	5	-	-	2
HPβCD-SD5	2	5	10	-	-	-	2

CD, cyclodextrins; HPβCD, 2-hydroxypropyl-beta-cyclodextrin; PVP, polyvinylpyrrolidone; SD, solid dispersion.

Table 2. Solubility results in distilled water of five SD formulations containing CD-free (SD), βCD (βCD-SD), and HPβCD (HPβCD-SD).

Solubility (mg/mL)	SD	βCD-SD	HPβCD-SD
Formulation code			
1	0.0293 ± 0.0102	0.0280 ± 0.0096	0.0277 ± 0.0105
2	0.1125 ± 0.0047	0.1114 ± 0.0147	0.2314 ± 0.0080
3	0.0668 ± 0.0019	0.0596 ± 0.0078	0.0313 ± 0.0080
4	0.0568 ± 0.0025	0.0080 ± 0.0017	0.0615 ± 0.0043
5	0.0339 ± 0.0058	0.0183 ± 0.0145	0.0374 ± 0.0058

CD, cyclodextrins; HPβCD, 2-hydroxypropyl-beta-cyclodextrin; PVP, polyvinylpyrrolidone; SD, solid dispersion.

XRD, DSC, and fourier transform infrared spectroscopy (FT-IR) analyses

XRD, DSC, and FT-IR analyses of the SDs were performed to examine changes in the physical and chemical structure of tolvaptan after solvent evaporation. The solid-state structural characteristics of tolvaptan, excipients, and SD were evaluated by XRD. An X-ray diffractometer (Rigaku ULTIMA IV) using Cu Kα radiation, operated at 30 mA and 40 kV, was used for XRD analysis. Scanning was performed at a scan rate of 1° min^{-1} over an angular range of 3–60° (2θ). The changes in the melting point of tolvaptan, active ingredient-polymer incompatibilities, and effects of amorphous-crystalline transformations on solubility were examined. DSC (Shimadzu, DSC-60, Japan) analysis was performed on pure tolvaptan, excipients, and SDs. In a nitrogen environment, the samples were heated from 25 °C to 360 °C at a rate of 10 °C/min. Tolvaptan, excipients, and SD were scanned in the range 650–4000 cm^{-1} using a spectrum 400 FT-IR spectrometer (Perkin Elmer, USA).

Scanning electron microscope (SEM) analyses

The surface morphologies of the SDs were examined using SEM. The SD formulations were coated with gold/palladium before SEM imaging. Images were taken from different parts of the SDs at 500x, 1000x, and 5000x magnification.

In vitro dissolution testing and release kinetics studies

After ODTs disintegrate in the mouth, the active ingredients dissolve in the gastrointestinal tract and are absorbed there, resulting in therapeutic efficacy in the organism. To estimate the dissolution rates of low-solubility active substances in the gastrointestinal system, *in vitro* dissolution tests were performed in buffers with pH 1.2, 4.5, and 6.8. The dissolution rate of tolvaptan in the SD formulation was measured in 900 mL of dissolution medium at 37 °C using the USP paddle method (50 rpm) specified by the FDA for tolvaptan. The dissolution rate studies were performed in distilled water, pH 1.2, 4.5, and 6.8 buffers, and SLS-containing buffers prepared by adding 0.22% SLS to these buffers. After the samples were filtered, their absorbance was measured using a validated ultraviolet (UV) spectrophotometric method, and the concentrations were calculated from the calibration equation.

Using DDSolver Software, the data from the dissolution rate study were fitted to the Weibull, Hixson-Crowell, Korsmeyer-Peppas, zero-order, first-order, and Higuchi models to identify potential mechanisms underlying the dissolution of tolvaptan from SDs. The adjusted coefficients of determination (r^2adj) obtained from the kinetic models were used to select the most suitable model (Table 3).[26]

Determination of drug content

Ten mg of the prepared SDs was precisely weighed and mixed until dissolved in 20 mL of distilled water (n = 3). After the SDs were dissolved, the solution was filtered through a membrane filter and tolvaptan was quantified by UV spectrophotometry at 260 nm.

Production of ODTs containing SD (SD-ODTs)

Various tablet formulations were prepared using the following excipients: Primogel, Ac-Di-Sol, Avicel-PH101, mannitol, xylitol, Ludiflash, Gantrez AN 119, Gantrez AN 139, Aerosil, Mg Stearate, sucrose, HPβCD, Na saccharin, Avicel PH102, Croscarmellose Na, Pharmaburst 500, sodium starch glycolate, Kollidon CL-SF (Tables 4 and 5). An amount of the SD formulation containing 15 mg of tolvaptan (equivalent to a commercial 15 mg tolvaptan tablet; 142.5 mg of SD formulation corresponds to 15 mg of tolvaptan) was weighed and then mixed with excipients. Then, the powder mass was compressed to produce SD-ODT formulations using an Erweka EK0. The optimum SD-ODT formulation was determined after examining the friability and disintegration time of the ODTs. Characterization studies of the tablets were performed.

Tablet characterization studies

Diameter-thickness-hardness in tablets

The diameters and thicknesses of 10 prepared tablets were measured using a digital micrometer (Mitutoyo), and the deviations were determined. The hardness values of 10 different tablets were measured using a tablet hardness tester. Determination of hardness is important in ODT pressing, since excessive tablet hardness may reduce porosity and prolong disintegration time.[27]

Table 3. The adjusted coefficient of determination (r^2adj) for kinetic models was obtained from experimental data in SLS-free and 0.22% SLS buffers of the HPβCD-SD2 formulation via DDsolver.

Kinetic models	Zero order	First order	Higuchi	Korsmeyer-Peppas	Hixson-Crowell	Weibull
Distilled water	0.602	0.998	0.945	0.977	0.995	0.999
pH 1.2	0.543	0.986	0.930	0.982	0.991	0.999
pH 4.5	0.907	0.999	0.995	0.993	0.992	1.000
pH 6.8	0.830	0.988	0.990	0.991	0.968	1.000
0.22% SLS-distilled water	0.496	0.962	0.932	0.998	0.932	0.985
0.22% SLS-pH 1.2	0.519	0.976	0.925	1.000	0.951	0.987
0.22% SLS-pH 4.5	0.511	0.927	0.872	0.998	0.835	0.984
0.22% SLS-pH 6.8	0.576	0.872	0.904	0.999	0.788	0.991

HPβCD, 2-hydroxypropyl-beta-cyclodextrin; SD, solid dispersion; SLS, sodium lauryl sulfate.

Table 4. Tablet formulations of solid dispersions prepared with super dispersing agents such as Primogel, Ac-Di-Sol, Avicel PH 101, Ludiflash.

mg / Number	SD	Primogel	Ac-Di-Sol	Avicel-PH 101	Mannitol	Xylitol	Ludiflash	Gantrez AN 119	Gantrez AN 139	Aerosil	Mg stearate	Total ODT weight
1	142.50	142.50	71.25	-	-	-	-	-	-	1.80	3.60	361.65
2	142.50	213.75	71.25	-	-	-	-	-	-	2.20	4.40	434.10
3	142.50	285	71.25	-	-	-	-	-	-	2.50	5	506.25
4	142.50	-	285	-	-	-	-	-	-	2.10	4.20	433.80
5	142.50	142.50	285	-	-	-	-	-	-	2.50	5	577.50
6	142.50	142.50	213.75	-	-	-	-	-	-	2.50	5	506.25
7	142.50	71.25	142.50	-	-	-	-	-	-	2.50	5	506.25
8	142.50	-	142.50	100	100	-		-	-	5	10	500
9	142.50	100	142.50	50	50	-	-	-	-	5	10	500
10	142.50	100	192.50	50	-	-	-	-	-	5	10	500
11	142.50	-	250	-	-	100	-	-	-	2.50	5	500
12	142.50	-	100	-	-	250	-	-	-	2.50	5	500
13	142.50	-	200	-	-	-	-	150	-	2.50	5	500
14	142.50	-	250	-	-	-	-	100	-	2.50	5	500
15	142.50	100	142.50	-	-	-	-	100	-	5	10	500
16	142.50	112.50	100	-	-	-	-	100	-	5	10	470
17	142.50	112.50	100		-	30	-	100	-	5	10	500
18	142.50	100	142.50	50		50	-	-	-	2.50	5	492.50
19	142.50	100	142.50	-	57.50	50	-	-	-	2.50	5	500
20	142.50	100	170	-	-	30	-	50	-	2.50	5	500
21	142.50	80	200	-	67.50	-	-	-	-	2.50	5	497.50
22	142.50	100	150	50	-	-	-	-	-	2.50	5	450
23	142.50	100	100	-	-	30	70	-	-	2.50	5	450
24	142.50	100	100	-	-	30	60	50	-	2.50	5	490
25	142.50	70	200	-	-	20	-	60	-	2.50	5	500
26	142.50	130	130	-	-	40	-	50	-	2.50	5	500
27	142.50	50	150	-	-	40	-	-	100	2.50	5	490
28	142.50	50	160	-	-	30	-	-	100	2.50	5	490
29	142.50	50	190	-	-	-	-	50	50	5	10	497.50
30	142.50	60	150	-	-	-	-	50	50	20	5	477.50
31	142.50	30	150	-	-	30	-	50	50	20	5	477.50
32	142.50	30	145	-	-	30	-	60	60	25	5	497.50
33	142.50	30	150	-	-	30	-	50	50	30	5	487.50
34	142.50	40	160	-	-	-	-	50	50	40	5	487.50
35	142.50	30	180	-	-	-	-	50	50	30	5	487.50
36	142.50	147.50	20	-	-	-	-	50	50	30	10	450
37	142.50	157.50	20	-	-	-	-	50	50	30	10	460
38	142.50	167.50	30	-	-	-	-	40	40	20	10	450

ODT, orally disintegrating tablets; SD, solid dispersion.

Table 5. Tablet formulations of solid dispersions prepared with super-dispersing agents such as Primogel, Ac-Di-Sol, Avicel PH 102, Croscarmellose Na, Pharmaburst 500, Na starch gluconate.

mg Number	SD	Primogel	Ac-Di-Sol	Mannitol	Ludiflash	Aerosil	Mg stearate	Sucrose	HPβCD	Na Saccharine	Avicel PH102	Croscarmellose Na	Pharmaburst 500	Sodium starch glycolate	Kollidon CL-SF	Total ODT weight
39	142.50	-	-	-	-	22.50	10	285	-	-	-	-	-	-	-	460
40	142.50	142.50	-	-	-	22.50	10	142.50	-	-	-	-	-	-	-	460
41	142.50	-	-	-	-	22.50	10	71.25	213.75	-	-	-	-	-	-	460
42	142.50	40	-	107.50	-	20	10	-	-	10	100	40	-	-	-	460
43	142.50	25	-	120	-	10	5	-	-	7.50	80	-	-	-	10	400
44	142.50	30	-	125	-	15	5	-	-	7.50	97.50	-	-	-	7.50	430
45	142.50	40	-	120	-	20	5	-	-	7.50	87.50	-	-	-	7.50	430
46	142.50	30	-	100	-	15	4	-	-	5	78.50	-	-	-	5	380
47	142.50	30	-	100	-	15	4	-	-	5	78.50	-	-	-	25	400
48	142.50	40	60	107.50	-		10	-	-	-	80	-	-	-	-	450
49	142.50	40	60	107.50	-	20	10	-	-	-	80	-	-	-	-	470
50	142.50	40	60	107.50	-	20	10	-	-	-	80	-	-	-	10	480
51	142.50	-	-	-	357.50	-	-	-	-	-	-	-	-	-	-	500
52	142.50	60	-	287.50	-	30	10	-	-	-	-	60	-	-	10	600
53	142.50	80	-	329.50	-	40	14	-	-	-	-	80	-	-	14	700
54	142.50	100	-	302.50	-	45	14	-	-	-	-	80	-	-	16	700
55	142.50	120	-	282.50	-	45	14	-	-	-	-	80	-	-	16	700
56	142.50	142.50	-	259	-	45	14	-	-	-	-	80	-	-	17	700
57	142.50	-	-	-	-	-	-	-	-	-	-	-	357.50	-	-	500
58	142.50	20	-	-	-	-	-	-	-	-	-	-	337.50	-	-	500
59	142.50	-	-	-	-	-	-	-	-	-	-	-	332.50	25	-	500

HPβCD, 2-hydroxypropyl-beta-cyclodextrin; SD, solid dispersion.

Friability in tablets

Friability was measured to assess the mechanical strength of the tablets. The European Pharmacopoeia Considers the friability of uncoated tablet formulations below 1% to be acceptable. Thus, the integrity of the tablet is maintained, and the mechanical strength is adequate.[28] The friability values of 20 tablets were determined after 100 rotations (4 minutes) using a friability tester (Pharma Test PTF 20E).

Disintegration test on tablets

Disintegration is an essential parameter of ODTs. According to the European Pharmacopoeia 9 monograph "Orodispersible tablets", ODTs must disperse in less than 3 min.[29] The test was performed in 900 mL of distilled water at 37 ± 0.5 °C.

Statistical analysis

All experimental measurements were performed in triplicate, and the data were expressed as the mean and standard deviation. Kinetic models were fitted to data from dissolution rate studies using the DDSolver Software (DDSolver: an add-in program for modeling and comparison of drug dissolution profiles).[30]

RESULTS

Characterization of tolvaptan-CD complexes

In the XRD analysis of pure βCD, sharp peaks corresponding to the crystal structure were observed at 4.53°, 9.09°, 12.57°, 17.91°, and 18.87° (Figure 1A). In the literature, XRD analyses often show a sharp peak characteristic of pure βCD.[31]

In the DSC study, the melting peaks of pure βCD, HPβCD, and tolvaptan at 300–350 °C disappeared as a result of the formation of the inclusion complex (Figure 1C and D). This indicates that tolvaptan and CDs form inclusion complexes.[32]

Characterization of the SDs

Solubility studies

SD formulations were prepared using the ingredients of five formulations coded HPβCD-NF1, HPβCD-NF2, HPβCD-NF3, HPβCD-NF4 and HPβCD-NF5, which were described in our previous study.[25] In the preformulation studies of SDs, polymer solutions containing CD (β-CD or HPβCD) and CD-free solutions were prepared. In these formulations, PVP K90 and PEO N80 were used as the hydrophilic polymers; Solutol HS-15 and Gelucire 44/14 as solubility enhancers; and βCD and HPβCD as complexing agents. A solubility study was performed on three SD formulations: CD-free (SD), βCD (βCD-SD), and HPβCD (HPβCD-SD). An increase in solubility relative to pure tolvaptan was expected owing to the use of a hydrophilic polymer, solubility enhancers, and the formation of an inclusion complex between tolvaptan and CD. In the solubility study, tolvaptan solubility in the HPβCD-SD2 formulation was highest. While the solubility of pure tolvaptan in distilled water was 0.0266 mg/mL, the solubility of tolvaptan in the HPβCD-SD2 formulation containing 2-HPβCD was 0.2314 mg/mL (Figure 2).

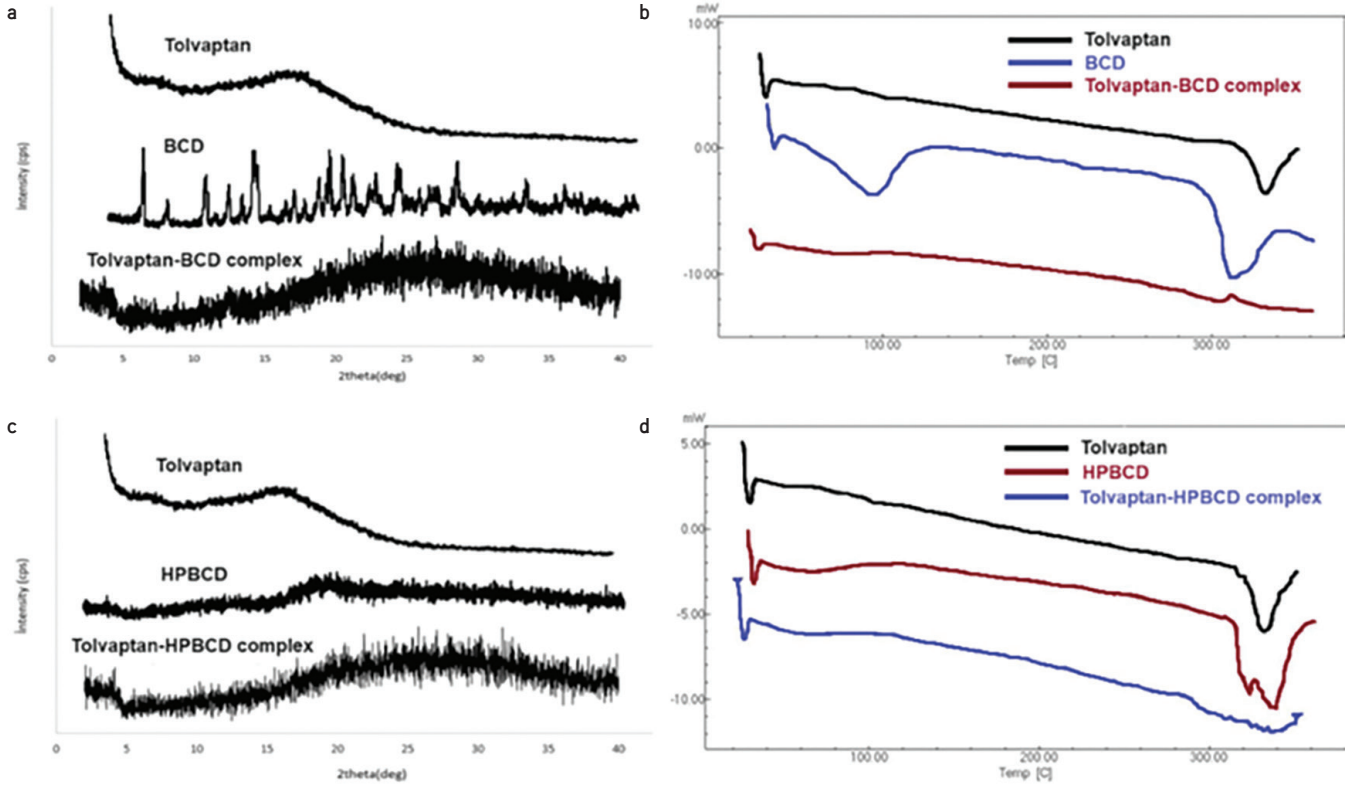

Figure 1. XRD diffractograms; (a) tolvaptan, βCD and tolvaptan-βCD complex, (b) tolvaptan, HPβCD and tolvaptan-HPβCD complex, and DSC thermograms; (c) tolvaptan, βCD and tolvaptan-βCD complex, (d) tolvaptan, HPβCD and tolvaptan-HPβCD complex.

HPβCD, 2-hydroxypropyl-beta-cyclodextrin; XRD, X-ray diffraction.

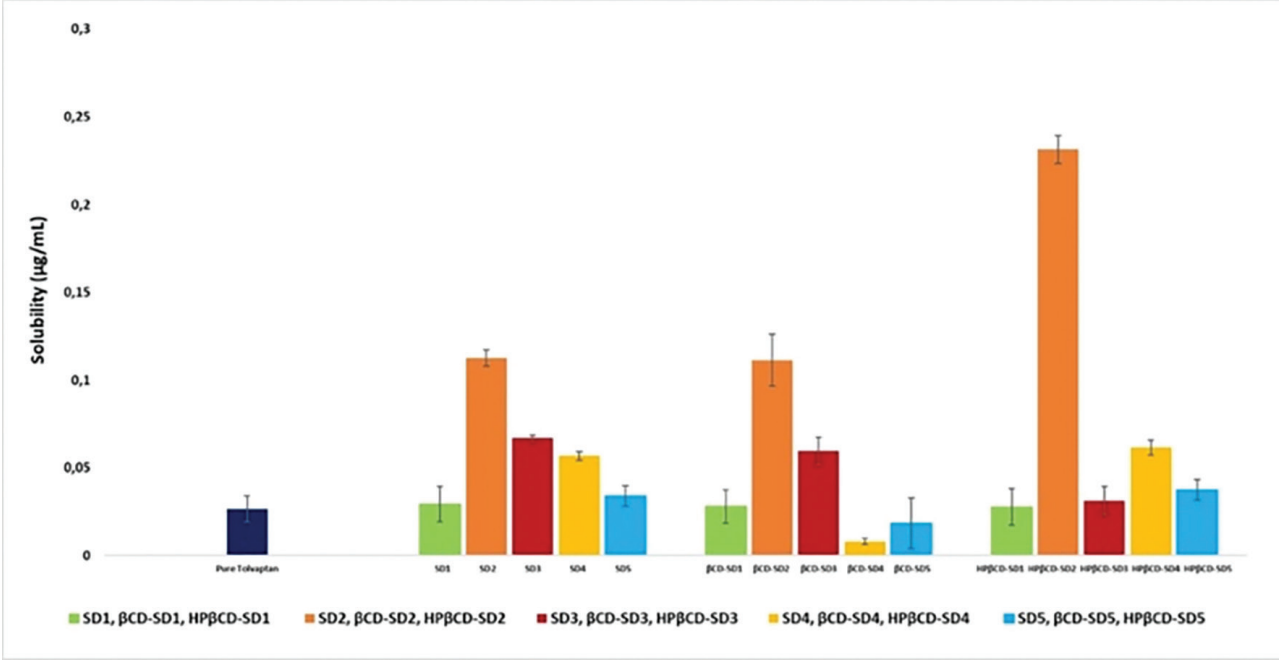

Figure 2. Solubility results in distilled water of pure tolvaptan and five SD formulations containing CD-free (SD), βCD (βCD-SD), and HPβCD (HPβCD-SD). CD, cyclodextrins; HPβCD, 2-hydroxypropyl-beta-cyclodextrin; SD, solid dispersion.

The solubility of tolvaptan in the HPβCD-SD2 formulation was approximately 8.7 times that of pure tolvaptan (Table 2). Therefore, HPβCD was chosen as the complexing agent, and HPβCD-SD2 was selected as the optimal SD formulation. Further studies have been conducted using this formulation.

XRD, DSC, and FT-IR analyses

XRD analyses of the five SD formulations were performed, and their diffractograms were obtained (Figure 3A). Tolvaptan did not produce any peaks due to the formation of an amorphous structure. No peaks were observed for the HPβCD-SD1 and HPβCD-SD2 formulations. The amorphous structure was preserved in these formulations. Characteristic sharp peaks of Gelucire 44/14 (19.219° and 23.360°) were observed in the HPβCD-SD3 formulation; characteristic sharp peaks of PEO N80 (19.140° and 23.340°) were observed in the HPβCD-SD4 formulation; and characteristic sharp peaks of PEO N80 were observed in the HPβCD-SD5 formulation.

DSC measurements were performed on the active ingredient HPβCD-SD2 and on the excipients of the HPβCD-SD2 formulation. The melting peaks of pure tolvaptan and HPβCD were observed between 300 and 350 °C. These peaks disappeared with the formation of the inclusion complexes. No peaks corresponding to tolvaptan or HPβCD were observed in the HPβCD-SD2 formulation (Figure 3B). FTIR analyses of tolvaptan, HPβCD-SD2, and the excipients were performed (Figure 3C). Pure PVP exhibited a broad absorption band between 3700 and 3000 cm^{-1} [33] and a C=O stretching band at 1655 cm^{-1}.[34] The C=O stretching vibration was observed at 1732 cm^{-1} in Solutol.[35] In pure HPβCD, a broad O-H stretching band was observed in the range of 3000–3600 cm^{-1}.[36] In the HPβCD-SD2 formulation, peaks corresponding to PVP were observed, whereas peaks corresponding to tolvaptan could not be distinguished because tolvaptan was present at a low concentration.

SEM analyses

SEM analyses of the SDs were performed. Solid masses without a specific shape were obtained for all the formulations. Studies have reported that SD masses are produced without a defined shape (Figure 4).[37-39]

In vitro dissolution test and release kinetics studies

Because of the low solubility of pure tolvaptan in SLS-free buffers, sink conditions could not be achieved. To provide sink conditions for pure tolvaptan in SLS-free buffers, 5.6–12.3 Liters of dissolution medium are needed. Sink conditions could not be achieved for pure tolvaptan in SLS-containing buffers (0.22% SLS at pH 1.2, 4.5, and 6.8). In the HPβCD-SD2 formulation, the solubilities of tolvaptan in SLS-containing and SLS-free buffers range from 0.2 to 1.6 mg/mL. In this case, studies were conducted under sink conditions in all buffers. The dissolution rate of the HPβCD-SD2 formulation was studied in buffers with and without 0.22% SLS. At least 90% of Tolvaptan in the formulation was dissolved in each buffer within 25 min (Figure 5).

The r^2adj values were compared as criteria for creating kinetic models from the data in the dissolution studies[40] and for determining the accuracy of these results. As r^2adj approaches 1, the kinetic model's similarity to the correct dissolution profile increases. After comparing these mathematical values, the dissolution profiles of the optimal formulation of HPβCD-SD2 in distilled water and in pH 1.2, 4.5, and 6.8 buffers were evaluated based on r^2adj, and the Weibull model was identified as the most

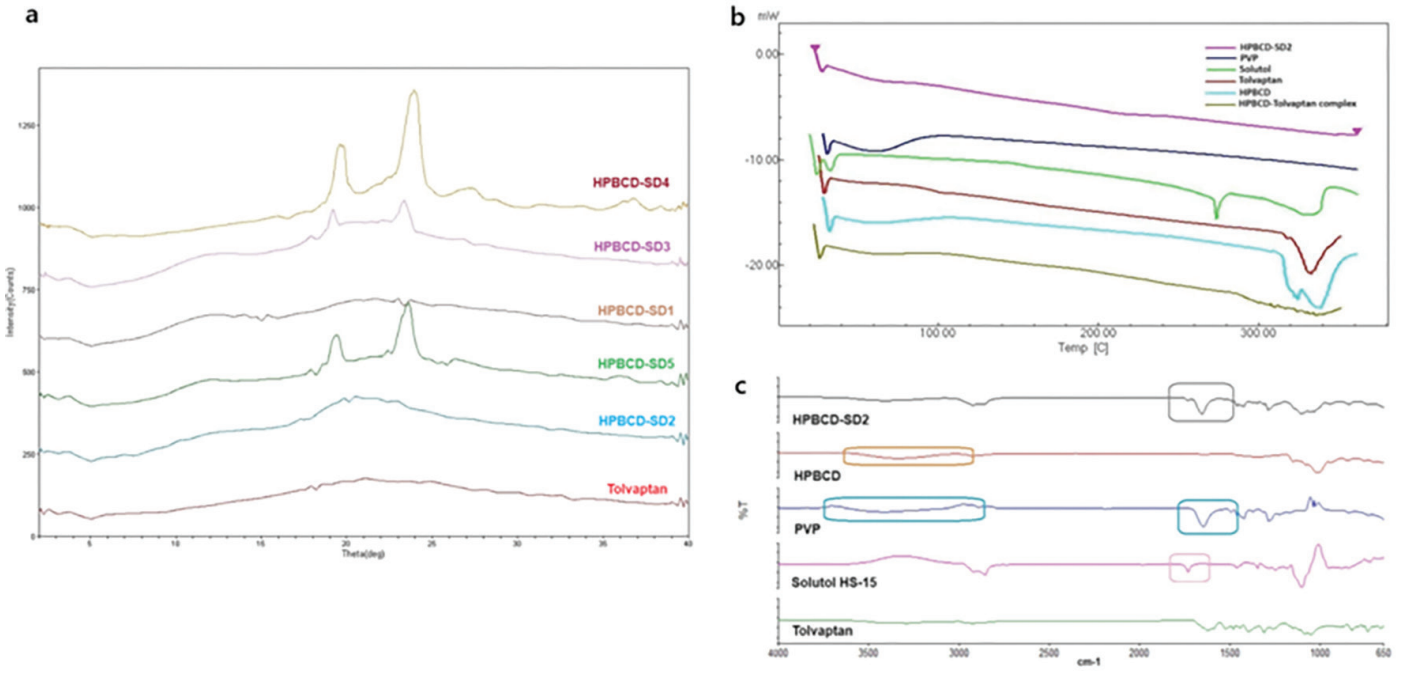

Figure 3. XRD diffractograms; (a) tolvaptan, HPβCD-SD1, HPβCD-SD2, HPβCD-SD3, HPβCD-SD4, HPβCD-SD5, and belonging to PVP, Solutol, tolvaptan, HPβCD, HPβCD-tolvaptan complex, and HPβCD-SD2; (b) DSC thermograms and (c) FTIR spectra.

DSC, differential scanning calorimetry; HPβCD, 2-hydroxypropyl-beta-cyclodextrin; PVP, polyvinylpyrrolidone; SD, solid dispersion; XRD, X-ray diffraction.

suitable kinetic model (Table 3). When the dissolution profiles of the HPβCD-SD2 formulation in buffers containing 0.22% SLS were evaluated based on r^2adj, the Korsmeyer–Peppas kinetic model was the most appropriate (Table 3).

In the Weibull model, β constants can provide information about the mechanisms underlying drug-release kinetics in SDs. It is predicted that when β ⟨ 0.75, Fickian diffusion is the dominant release mechanism; when 0.75 ⟨ ß ⟨ 1, Fickian diffusion and swelling are the dominant mechanisms; and when ß ⟩ 1, the release mechanism is complex.[41-43] The β values of the HPβCD-SD2 formulation in distilled water and in pH 1.2, pH 4.5, and pH 6.8 buffers were 0.7995, 0.6603, 0.7581, and 0.6975, respectively (Table 3).

Using the Korsmeyer-Peppas model, one can determine the type of diffusion by which the active substance is released from swelling and non-swelling polymeric drug carrier systems into the buffer. In the Korsmeyer-Peppas model, the exponent n was used to characterize the drug release mechanism. The release of the active substance is thought to occur via pseudo-Fickian diffusion when n ⟨ 0.5, via Fickian diffusion when n = 0.5, via anomalous diffusion when 0.5 ⟨ n ⟨ 1, and via non-Fickian diffusion when n = 1.[44,45] The n values in the 0.22% SLS buffers of the HPβCD-SD2 formulation were 0.3017, 0.2544, 0.2000, and 0.2330, respectively. Quantification was performed in the HPβCD-SD2 formulation and percent recovery was 97.95 ± 4.54%. This result indicates that almost all tolvaptan in the formulation was recovered, confirming successful loading.

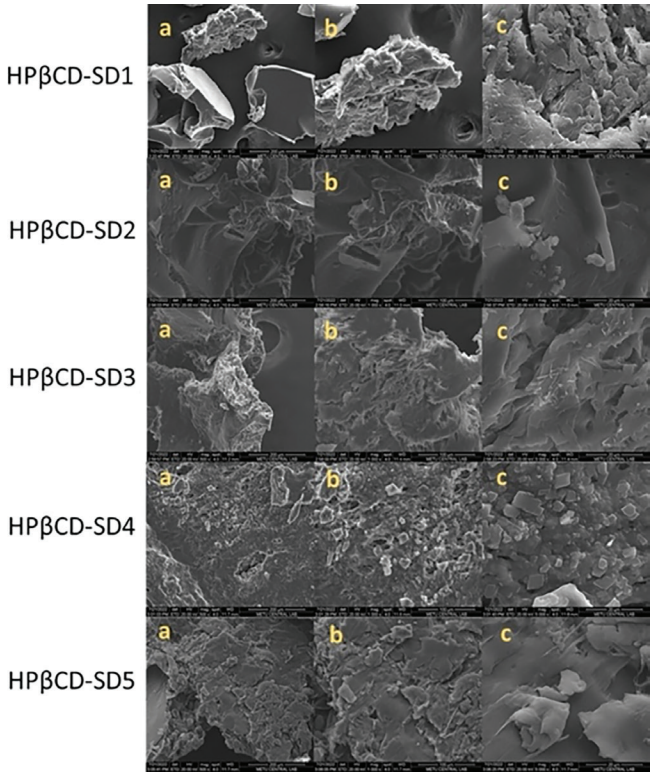

Figure 4. SEM images of HPβCD-SD1– HPβCD-SD5 [mag. (a) 500x, (b) 1000x, (c) 5000x].

HPβCD, 2-hydroxypropyl-beta-cyclodextrin; mag., magnification; SD, solid dispersion; SEM, scanning electron microscope.

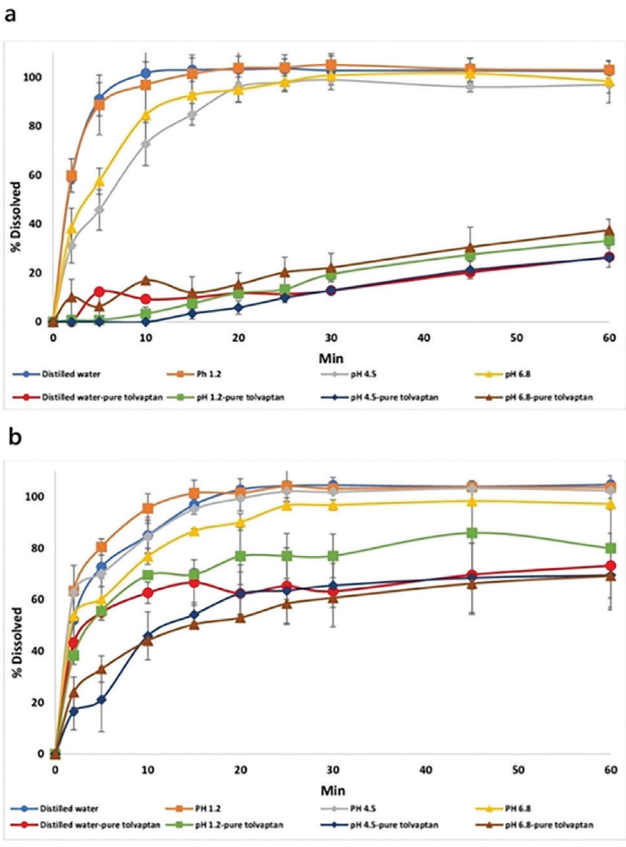

Figure 5. *In vitro* dissolution test of pure tolvaptan and HPβCD-SD2 formulation in (a) SLS-free buffers, (b) 0.22% SLS buffers.

HPβCD, 2-hydroxypropyl-beta-cyclodextrin; SD, solid dispersion; SLS, sodium lauryl sulfate.

Production of ODTs

The ODTs were pressed after adding superdispersing agents to the SDs (Tables 4 and 5). Based on comparisons of friability and disintegration time among the prepared ODTs, formulation 59, which showed ≤1% friability and a disintegration time ≤180 s, was selected as the optimal formulation (SD-ODT; Table 6).

Characterization studies of ODTs

The mean weight, diameter, and thickness of the prepared SD-ODT were 497.50 ± 0.53 mg, 3.99 ± 0.01 mm, and 12.13 ± 0.01 mm, respectively. The standard deviations of these parameters were small, indicating that the values were generally similar. The hardness of SD-ODT was 33.66 ± 2.94 n and did not prolong the disintegration time; SD-ODT dispersed within 94.00 ± 8.19. The friability was 0.88%.

DISCUSSION

This study aimed to increase the efficacy of tolvaptan by enhancing its water solubility and dissolution rate and improving patient compliance. For this purpose, SD formulations were prepared and ODTs were developed from them. During this process, characterization studies were performed, and the results were evaluated. The solvent evaporation method was preferred for SD preparation because it is a fast, inexpensive, and simple method for obtaining the product.

According to the XRD results, βCD was found in crystalline form.[46] Tolvaptan did not exhibit sharp peaks and was present in an amorphous form. The tolvaptan–βCD complex did not exhibit sharp peaks; the sharp peaks of βCD disappeared upon complex formation. In this case, the tolvaptan–βCD complex exhibited an amorphous structure. In the XRD analysis of pure 2-HPβCD, no sharp peaks corresponding to the crystal structure were observed (Figure 1A). Reported XRD analyses of pure HPβCD do not exhibit sharp peaks.[47] Similarly, the tolvaptan-HPβCD complex did not exhibit sharp peaks; instead, a peak pattern indicating formation of an amorphous complex was observed (Figure 1B).

The solubility study showed that preparing the HPβCD-SD2 formulation increased the solubility of tolvaptan compared with pure tolvaptan (Figure 2). Solubility results indicated that tolvaptan in the SDs of complexes prepared with HPβCD had higher solubility than in complexes prepared with CD-free βCD. The increase in the solubility of tolvaptan is thought to be due to the use of a hydrophilic polymer such as PVP K90, the use of a solubility enhancer such as Solutol HS-15, and the formation of an inclusion complex between tolvaptan and CD. Hydrophilic polymers, such as PVP K90, encapsulate active substances between polymer chains, thereby imparting hydrophilicity to the encapsulated substances.[48] Solutol HS-15 is a non-ionic surfactant.[49,50] Surfactants form micelles around active substances, thereby increasing their solubility. Active substances form complexes with the internal cavities of 2-HPβCD, increasing their solubility in water owing to the hydrophilic outer surface of 2-HPβCD. Additionally, the presence of surfactants, such as SLS, in the solubility medium increased dissolution. The solubility of tolvaptan in the HPβCD-SD2 formulation was higher in SLS-containing distilled water and pH 1.2 buffers than in SLS-containing pH 4.5 and 6.8 buffers. At pH 4.5 and 6.8, the sodium ions from disodium hydrogen phosphate and SLS produce a common-ion effect. Because of the common-ion effect, the solubility of active substances is lower than expected.[51] It is thought that the lower solubility of tolvaptan in the HPβCD-SD2 formulation in SLS-containing media at pH 4.5 and 6.8, compared with its solubility in SLS-containing distilled water and in pH 1.2 environments, is due to the common-ion effect. In a study, SD formulations of silnidipine were prepared. Solubility studies in SD formulations were carried out in distilled water and in a pH 6.8 medium containing 0.2% SLS. In SD containing a 1:3 silnidipine:PVP ratio, the solubilities of pure silnidipine were 0.6371 µg/mL in distilled water and 1.0051 µg/mL in a pH 6.8 medium containing 0.2% SLS. The solubility of silnidipine increased when SLS was added to the medium.[52]

DSC analysis showed no observable tolvaptan or HPβCD peaks in the HPβCD-SD2 formulation (Figure 3B). This may be due to the formation of an inclusion complex between tolvaptan and the CDs. Previous studies have reported that the DSC melting peak of the active substance disappears after the formation of the inclusion complex.[12,53]

Table 6. Friability and disintegration time results of tablets prepared with SD.

Number	Friability (%)	Disintegration time (s)	ODT weight (mg)	Number	Friability (%)	Disintegration time (s)	ODT weight (mg)
1	>1	>180	361.65	31	>1	>180	477.50
2	>1	>180	434.10	32	>1	>180	497.50
3	>1	>180	506.25	33	>1	145	487.50
4	>1	>180	433.80	34	>1	>180	487.50
5	>1	>180	577.50	35	>1	>180	487.50
6	>1	>180	506.25	36	>1	150	450
7	>1	>180	506.25	37	>1	>180	460
8	>1	>180	500	38	>1	>180	450
9	>1	>180	500	39	>1	>180	460
10	>1	>180	500	40	>1	>180	460
11	>1	>180	500	41	>1	>180	460
12	>1	>180	500	42	>1	90	460
13	>1	>60	500	43	>1	>180	400
14	>1	>60	500	44	>1	180	430
15	>1	>60	500	45	>1	>180	430
16	>1	150	470	46	>1	130	380
17	>1	>180	500	47	0.91	>180	400
18	>1	>180	492.50	48	>1	>180	450
19	>1	>180	500	49	>1	120	470
20	>1	>180	500	50	>1	>180	480
21	>1	180	497.50	51	>1	>180	500
22	>1	>180	450	52	>1	>180	600
23	>1	>180	450	53	>1	90	700
24	>1	>180	490	54	>1	175	700
25	>1	>180	500	55	>1	155	700
26	>1	>180	500	56	>1	165	700
27	>1	>180	490	57	>1	>180	500
28	>1	>180	490	58	0.43	>180	500
29	>1	>180	497.50	**59***	**0.88**	**94**	**500**
30	>1	>180	477.50				

ODT, orally disintegrating tablets; SD, standard deviation.

In the dissolution rate study of pure tolvaptan in buffer media tested (with or without 0.22% SLS), except in 0.22% SLS in distilled water, sink conditions could not be achieved in these media because of the low solubility of pure tolvaptan. Because sink conditions were not maintained, the dissolution rate was slow, and the percentage of tolvaptan dissolved did not reach 100% after 60 min. In 0.22% SLS in distilled water, tolvaptan dissolved rapidly during the second minute, reaching 43.19% dissolution, but the dissolution rate decreased thereafter. This is thought to be caused by the rapid dissolution and transformation of amorphous tolvaptan into a crystalline form. The dissolution rate study of the HPβCD-SD2 formulation was conducted in buffers with and without 0.22% SLS. At least 90% of tolvaptan in the formulation dissolved within 25 min in all buffers, both with and without 0.22% SLS (Figure 5). Rapid dissolution depends on the formulation containing a hydrophilic polymer with a large surface area, a solubility enhancer, and an inclusion complex with CDs.[54,55] Tolvaptan

was dispersed among the hydrophilic PVP K90 polymer chains, resulting in an increase in its hydrophilicity. Solutol HS-15 formed micelles with tolvaptan. The outer surfaces of the micelles formed by surrounding tolvaptan molecules are hydrophilic. In addition, tolvaptan formed an inclusion complex with 2-HPβCD, which exhibited hydrophilic properties. In our study, tolvaptan demonstrated hydrophilicity in three respects. Because tolvaptan is hydrophilic, it rapidly dissolves upon contact with the hydrophilic dissolution medium. In this case, dissolution occurred rapidly. The faster dissolution rate in buffers containing 0.22% SLS compared with buffers without SLS is thought to result from surfactants such as SLS reducing the surface tension between liquid and solid surfaces, thereby increasing the interaction between lipophilic drugs and the hydrophilic solvent medium.[56] The presence of surfactants, such as Solutol HS-15 in the formulation and SLS in the dissolution medium, accelerated the dissolution of tolvaptan from the HPβCD-SD2 formulation.

A study observed that SDs of indomethacin prepared with water-soluble carriers, such as PEG 4000 or Gelucire 50/13, alter its crystallinity depending on the carrier type and polymer amount. It has also been reported to contribute to an increase in the release rate of the drug, a decrease in the size and agglomeration of the particles, an increase in their wettability, and a decrease in the crystallinity of the drug.[57] In another study aimed at increasing the solubility and dissolution rate of itraconazole, a drug with low water solubility, researchers used hydrophilic polymers such as polyvinyl acetal diethylaminoacetate (AEA®) and Eudragit® E 100 with the SD method. The dissolution rate of itraconazole from the tablets obtained using SDs prepared by spray drying increased, with more than 90% of the drug released within 5 min. SDs prepared with AEA® or Eudragit® E 100 at a 1:1 (*w/w*) drug/hydrophilic polymer ratio showed approximately a 70-fold increase in dissolution rate, compared to the commercial product.[58]

The HPβCD-SD2 formulation released the drug into the buffer at pH 1.2 and 6.8 via Fickian diffusion. In contrast, drug release in distilled water and in pH 4.5 buffer proceeded via Fickian diffusion and swelling mechanisms (Table 3). Zhu et al.[59] prepared SDs of resveratrol, a compound with poor water solubility using hydrophilic polymers (Eudragit RS and polyethylene glycol 600). In the release study, the r^2adj values of the kinetic models were examined; the highest r^2adj was observed for the Weibull kinetic equation. Weibull kinetics is a model that describes the dissolution behavior of matrix systems.[60] They stated that the Weibull model is an empirical model used in rapid-release and SR drug-release systems, and that formulation[59] exhibits burst release of resveratrol. Tolvaptan in the HPβCD-SD2 formulation was released into buffers containing 0.22% SLS by pseudo-Fickian diffusion. In a study, SDs of gliclazide were prepared using PVP K90. By fitting the *in vitro* dissolution data to various release kinetic models, correlation coefficient (r) values were obtained, and it was determined that the Korsmeyer-Peppas kinetic model was the most suitable. The n-value was 0.7249, indicating that the release occurred via non-Fickian diffusion.[61] Tolvaptan was dissolved from the HPβCD-SD2 formulation by non-swelling-controlled matrix diffusion.

Formulations coded 13, 14, 15, 16, 33, 36, 42, 46, 49, 53, 54, 55, 56, and 59 met the European Pharmacopoeia Requirement for a disintegration time of <3 min. Formulations coded as 47, 58, and 59 had acceptable friability (<1%). In the preformulation study of ODTs, the following superdisintegrants were used (Table 5): Primogel, 30 mg in formulation coded 47; Pharmaburst 500, 357.50 mg in formulation coded 57; a mixture of Primogel (20 mg) and Pharmaburst 500 (337.50 mg) in formulation coded 58; and a mixture of sodium starch glycolate (25 mg) and Pharmaburst 500 (332.50 mg) in formulation coded 59. The additional use of sodium starch glycolate as a superdisintegrants in the 59-coded formulation, unlike in the 57-coded formulation, had a positive effect on disintegration time and friability. Although using Primogel as a superdisintegrants in formulation codes 47 and 58 improved friability, it did not improve disintegration time. After evaluating dispersion time and friability of the formulations, formulation code 59 was selected as the final ODT formulation (Table 6). The disintegration time of ODT formulations generally increases with hardness. As the compression force increased, powder particles slid past one another and formed a tablet with a denser structure, making it more difficult for water to penetrate the tablet and disperse within the medium. To ensure that the disintegration time was shorter by 3 min, a lower compressive force was applied. However, a low compression force resulted in loose structures and increased tablet friability (>1%). Preparing the optimal ODT that met the appropriate dispersion time, friability, and hardness criteria was challenging. To overcome this challenge, SD can be developed using the lower-molecular-weight polymer PVP K30 instead of PVP K90. In a study, tablet formulations were prepared using ibuprofen-containing pellets. Tablets were pressed by applying forces of 5, 10, and 15 kN to the mixtures, and the effects of these forces on the disintegration time and friability were examined. With increasing tablet compression force, disintegration time increased, whereas friability decreased. consequently, it was reported that, as the compression force increased, a more compact mass was formed.[62] In a study, SDs were prepared with meloxicam, PVP K30, crospovidone, and SLS, and ODT formulations were developed from the resulting solid mass. The optimized ODT showed a hardness of 48 ± 4.3 N. This formulation achieved rapid disintegration in 19 ± 2 s.[63] If the high-molecular-weight PVP K90 is used in SD-ODT, it may cause longer disintegration times than observed in this study. Moreover, this value is below 3 min, meeting the requirement for ODTs. in addition, the friability value was 0.88%, which is less than 1% and is in accordance with the pharmacopoeial standard.

CONCLUSION

In this study, SDs were prepared by the solvent evaporation method to improve the solubility and dissolution rate of tolvaptan, an active substance classified as BCS Class IV. solubility and dissolution rates of the resulting SD formulations were evaluated. After detailed characterization of these

formulations, several ODT formulations were developed from the selected optimum formulation (HPβCD-SD2) using different superdisintegrants. The characterization studies demonstrated that SD-ODT meets pharmacopeial standards for ODTs. For geriatric and pediatric patients who have difficulty swallowing or refuse to do so, a tolvaptan-containing dosage form has been developed that can be easily administered without water and has a faster onset of action. Further *in vivo* studies are needed to demonstrate the efficacy of the final formulation.

Ethics

Ethics Committee Approval: There is not required for ethical approval.

Informed Consent: There is not required for informed consent.

Footnotes

Authorship Contributions

Concept: A.A.K., S.T., F.A., Design: A.A.K., S.T., F.A., Data Collection or Processing: A.A.K., S.T., F.A., Analysis or Interpretation: A.A.K., S.T., F.A., Literature Search: A.A.K., S.T., F.A., Writing: A.A.K., S.T., F.A.

Conflict of Interest: The authors declare no conflicts of interest.

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