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Original Article

Formulation and Evaluation of HPMC Phthalate Succinate-based Tablets of Tolvaptan: *In vitro* Evaluation

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ABSTRACT

Aim: This study aimed to evaluate the performance of novel Hydroxy Propyl Methyl Cellulose Phthalate Succinate polymers (HPMCPS) as alternatives to Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS) and other polymers. **Background:** Tolvaptan, classified as a Biopharmaceutics Classification System (BCS) Class IV molecule, exhibits limited solubility and permeability, posing challenges for its formulation. Otsuka Pharmaceuticals addressed this by developing and patenting an amorphous solid dispersion using Hydroxypropyl Cellulose (HPC) as a carrier. In this study, a novel polymer, HPMCPS, was investigated with Tolvaptan as the model drug. Its *in vitro* performance was systematically compared to established polymers, including HPMCAS, to evaluate its potential as an alternative in enhancing drug solubility and delivery. **Materials and Methods:** Tolvaptan solid dispersions were prepared with Polyvinylpyrrolidone (PVP), HPC, Hydroxypropyl Methylcellulose (HPMC), HPMC succinate, HPMC phthalate, HPMCAS, and HPMCPS at the same drug-to-polymer ratio using the spray drying technique. **Results and Conclusion:** Tolvaptan and polymer Spray-Dried Solid Dispersions (SSD) were characterized by FTIR, DSC, SEM, and PXRD. Tablet formulations incorporating these SSDs were evaluated through *in vitro* dissolution and permeation studies. The shifting of peaks and reduction in peak intensities in FTIR spectroscopy indicated hydrogen bond interactions between the functional groups of the drug and the polymer. DSC studies showed higher glass transition temperatures and stability of SSDs. X-ray diffraction studies confirmed no evidence of crystalline form for all SSDs at the same polymer concentration, except for PVP 30, where some crystalline tolvaptan was observed, which in turn affected dissolution and release. Tolvaptan tablets prepared with novel polymer(s) (HPMCPS) solid dispersion demonstrated either the same or slightly faster dissolution and *in vitro* permeation behavior compared to the brand Tolvaptan tablets (Jinarc) and tablets prepared with HPC solid dispersion.

Keywords: Dissolution Enhancement, Alternate Polymer, Solid Dispersion, Solvent Evaporation Method, Spray Drying, HPMCAS.

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INTRODUCTION

Biopharmaceutical classification system Class IV molecules pose significant challenges from a formulation perspective because of their poor solubility and permeability. Researchers in academia and the pharmaceutical industry have explored several techniques to enhance drug solubility, improve absorption, and increase bioavailability.[1] Tolvaptan is a BCS Class IV molecule discovered by Otsuka Pharmaceutical Co. and approved by the US FDA in 2009 under the brand name Samsca®. Conventional diuretics, when used to treat edema, excrete both water and electrolytes, resulting in an electrolyte imbalance. Tolvaptan, a novel diuretic, solely excretes water. Tolvaptan is also approved for autosomal dominant polycystic kidney disease, a rare disease for which there was no known treatment until tolvaptan was approved under the brand name of Jinarc® in April 2018.[2,3] Tolvaptan is a selective vasopressin V2-receptor antagonist prescribed for the treatment of euvolemic and hypervolemic hyponatremia, including patients with heart failure, syndrome of inappropriate antidiuretic hormone, and cirrhosis. Tolvaptan is a white crystalline powder, non-hygroscopic, that melts at 227.5ºC. It is slightly soluble in ethyl acetate, practically insoluble in water over pH 2.0 to 12.0 (0.0005 w/v% at 25ºC), freely soluble in benzyl alcohol, soluble in methanol, and sparingly soluble in ethanol. At 25ºC, the octanol: water partition coefficient is more than 5000. The molecule has one chiral center, leading to two enantiomers.[4] The absolute oral bioavailability of jet-milled tolvaptan in rats and dogs was determined to be 0.63% and 2.0%, respectively. The absolute oral

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bioavailability of the modified tolvaptan in rats and dogs is 16.0% and 14.6%, respectively.[5]

Despite its excellent pharmacological activity, the poor solubility of tolvaptan limits its oral absorbability. To overcome this limitation, Otsuka Pharmaceuticals developed and patented an amorphous compound using the solid dispersion technique. By incorporating hydroxypropyl cellulose polymer, they enhanced tolvaptan's solubility, disintegration, dissolution, and consequently, its absorption. Tolvaptan amorphous solid dispersion was prepared using the spray drying process. Two parts of the Active Pharmaceutical Ingredient (API) were dissolved with one part of the polymer Hydroxypropyl Cellulose (HPC-SL) in an ethanol and dichloromethane mixture (20:80).[6] Self-micro-emulsifying systems are also explored to improve the dissolution behavior of tolvaptan.[7]

From a commercial point of view, the formation of solid dispersion involves intricate preparation methods. Achieving reproducible physicochemical properties and scalability for large-scale production can be challenging. It can be very challenging to stabilize solid dispersion formulations, as they are susceptible to physical changes over time, such as crystallization or phase separation, degradation during melt processes, or residual organic solvent during solvent-based processes.[8] Temperature fluctuations during manufacturing, storage, and transportation can affect the stability of solid dispersion. Ensuring excellent flow properties during tableting or capsule filling can be difficult, impacting production efficiency.[9] Different excipients or macromolecular carriers can facilitate the amorphization of drugs. But these polymers are often present in high concentrations, which makes the tablet harder and encourages the formation of a gelling polymer network. This slows down disintegration and requires more disintegrant.[10]

HPMCAS is widely utilized to enhance the solubility and bioavailability of poorly soluble drugs. By maintaining the drug in a supersaturated state, HPMCAS prevents precipitation and promotes dissolution in aqueous media. Additionally, HPMCAS possesses a high glass transition temperature (Tg), which stabilizes amorphous solid dispersions.[11] Consequently, this polymer has become the preferred choice for the preparation of amorphous solid dispersions. This has been evidenced by the launch of new products in the USA utilizing solid dispersion technology. Notably, six out of eight products introduced after 2010 have employed HPMCAS, and all these formulations are protected by patents, highlighting the need for the development of new polymers.

This study is a continuation of our previous work, where we synthesized and characterized novel Hydroxy Propyl Methyl Cellulose Phthalate Succinate polymers (HPMCPS) as potential alternatives to the patented HPMCAS used in solid dispersion. Using esterification, HPMC was modified with phthalic and succinic anhydrides. The synthesized polymers showed successful chemical modification confirmed by FTIR and NMR. Most derivatives were amorphous, had particle sizes <5 µm, and exhibited good film-forming ability. They remained intact in acidic (pH 1.2) and acetate buffer (pH 4.5) but dissolved in phosphate buffer (pH 6.8), indicating suitability for enteric coatings. These polymers required less solvent than HPMCAS, offering eco-friendlier processing. Their properties support application in pH-dependent and targeted drug delivery.[12] In this study we prepared tolvaptan tablets utilizing solid dispersion of novel HPMCPS. The numeric identifiers in HPMCPS41, HPMCPS73, and HPMCPS32 grades correspond to the concentrations of phthalate and succinate.

MATERIALS AND METHODS

Materials

Tolvaptan was purchased from Aurisco, India. Cornstarch was purchased from Roquette, Lestrem, France. Lactose monohydrate was purchased from Kerry, Tralee, Ireland. Microcrystalline Cellulose (MCC) was purchased from IFF Pharma Solutions, USA. Croscarmellose sodium was purchased from IFF Pharma Solutions, USA. Magnesium stearate was procured from Nitika Pharmaceutical Specialties Pvt. Ltd., Nagpur, India. HPMC was purchased from Colorcon Asia Private Limited, Goa, India. HPMCP and HPMCAS were purchased from ShinEtsu Chemical Co., Ltd., Japan. Povidone (Kollidon® 30) and Sodium Lauryl Sulfate (SLS) were purchased from BASF, Germany. All the chemicals and reagents used were of analytical grade.

Methods

Preparation of tolvaptan solid dispersion using spray drying technique

Spray Dried Solid Dispersions (SSD) were prepared by spray drying technique using solvent evaporation method. Selecting a common solvent system is very important for the preparation of solid dispersion. A mixture of solvents is used to accommodate the solubility of lipophilic API and hydrophilic polymer(s).[13-15] Carriers are hydrophilic in nature and not completely soluble in organic solvents alone. Tolvaptan and a carrier polymer were dissolved in a solvent system containing ethanol and Dichloromethane (DCM) at a ratio of 1:4, and then the solvent was spray dried. Despite the Class 2 solvent, dichloromethane was chosen for its low boiling point (39.8ºC), high volatility, and excellent solubilization power. Tolvaptan and polymer solutions were prepared separately and mixed before spray drying (sonication and heating applied as necessary) (Table 1A). The samples were spray dried in a Buchi mini spray dryer B290 (Buchi, Switzerland). The pump was set at 10%, the inlet temperature was set at 65ºC, the aspirator was set at 100%, and the outlet temperature varied between 40 to 50ºC.

Powder X-ray diffraction analysis

Powdered sample (50 mg) was packed in a 25 mm specimen ring and analyzed using an X-ray diffractometer (Bruker D8 Advance Diffractometer, Wisconsin, USA) at 22ºC. The X-ray source (Cu, λ=1.5418 Å) was operated at 40 kV voltage and 40 mA current. Samples were scanned from 5 to 35º (2θ) with a step size of 0.02º and a scan rate of 1 s/step.

FTIR analysis

The possible interaction between tolvaptan and polymers (HPC, HPMC, HPMCP, HPMCAS, HPMCPS41, HPMCPS73, HPMCPS32) was investigated by FT-IR (FTIR-7600, Lambda Scientific, Australia). Samples were prepared using KBr pellet method. An attenuated diamond crystal unit was used to obtain infrared spectra between 4000 to 400 cm^{-1}.[16]

Thermal analysis

Solid-state changes over time were assessed to elucidate the crystallization tendency of tolvaptan from SSDs fabricated from HPMCAS, HPMCPS 41, HPMCPS 73, and HPMCPS 32. Differential Scanning Calorimetry (DSC) studies were conducted by using a differential scanning calorimeter (DSC01, 200W, Mettler Toledo, Switzerland). Sample powder (about 5 mg) was weighed and sealed in an aluminum DSC pan. Samples were scanned from 25ºC to 300ºC at a heating rate of 10ºC/min under dry nitrogen purge. An empty pan served as a reference.

Morphological characterization

Morphological characterization of tolvaptan polymer-solid dispersion was done using a Scanning Electron Microscope (SEM) (Inspect F50, EFI Inspect, Netherlands) using a sputter coater (Emiteck K550K, Quorum technology). Powdered samples were spread with a spatula onto a carbon-conductive tap in the sample holder and then coated under platinum in an argon atmosphere using an Emiteck K550K sputter coater. Prepared samples were placed under a microscope and imaged using a secondary electron detector on a field emission gun SEM.[17]

Tablet preparation by direct compression method

A spray-dried solid dispersion (135 mg) was mixed with corn starch (150 mg), lactose monohydrate (160 mg), MCC PH 102 (25 mg), and croscarmellose sodium (25 mg). The mixture was blended thoroughly for 3 min, then lubricated with magnesium stearate (5 mg) for 2 min. The final blend was compressed using a tablet press (FA 10, Italy) with tooling dimensions of 10 mm round. The targeted hardness range of tablets was between 180 to 200 N for all formulations. The composition of various formulations is detailed in Table 1B.

In vitro release study

Dissolution tests were performed using the USP apparatus 2 apparatus (EDT-08Lx, Electro Lab, India) at 50 rpm. Dissolution medium (900 mL distilled water with 0.22% SLS) was maintained at 37.0±0.5ºC. The samples were analyzed by a High-Performance Liquid Chromatography (HPLC) system (Waters, Milford, USA) using a C-18 (2 µm) column. The solvent flow rate was maintained at 0.45 mL/min. The runtime was 4 min. For standard preparation, accurately weighed 3.2 mg of tolvaptan was transferred into a 10 mL volumetric flask. Methanol (6 mL) was added and sonicated thoroughly. The volume was maintained up to the mark with methanol, and 2.5 mL of this solution was transferred into a 50 mL volumetric flask and diluted up to the mark with the dissolution medium. The solution was filtered through a 0.22 µm syringe filter and analyzed at 240 nm.

The dissolution conditions adopted in this study were taken from the regulatory approval package, notably the chemistry reviews of Jynarque and Samsca-both USFDA-approved tolvaptan-containing formulations. Tolvaptan's physicochemical profile, particularly its poor aqueous solubility and pH-independent solubility across a wide range (pH 2-12), necessitates a dissolution medium capable of ensuring consistent and complete drug release. To address this, SLS was incorporated into the dissolution medium as a surfactant. This selection was substantiated by data provided by the sponsor, demonstrating that the chosen concentration of SLS effectively establishes sink conditions. Such conditions are essential for minimizing solubility limitations and promoting accurate assessment of release kinetics. Moreover, the dissolution method exhibited discriminatory capability, reliably differentiating between formulations with distinct release profiles. This feature is critical for method robustness, enabling its application in both quality control environments and regulatory evaluations. The combined scientific justification and regulatory precedent affirm the suitability of the proposed dissolution conditions for tolvaptan-containing formulations.

In vitro permeation studies

In vitro permeation study for tolvaptan-HPMCPS-SSD was performed using a vertical Hanson Automated Franz Diffusion cell (RDS, Teledyne Hanson, USA) and compared with tolvaptan-HPMCAS-SSD. This apparatus features automated sampling, media replacement, a single computer workstation, precision borosilicate glass, and mixer inserts. A synthetic membrane (Strat-M) was used to mimic the membrane and to avoid ethical issues.[18,19] The receiver compartment was filled with 12 mL of Phosphate Buffer Solution (PBS, pH 7.4) imitating the conditions of the blood, and a Strat-M membrane was sandwiched and fastened between the donor and receiver compartments.[20] The system was equilibrated at 37±1ºC for 1 h. At the beginning of the measurements, a 3 mg equivalent of the drug triturate dissolved in 2 mL of simulated gastric fluid (pH

1.2) was added to the donor compartment. The solution in the receptor was continuously stirred at 600 rpm during the study. At a predetermined time point, 0.75 mL sample was withdrawn using an autosampler and replaced with an equivalent volume. Collected samples were filtered through nylon membrane filters and subsequently analyzed using HPLC.

Stability study of solid dispersion and tablets

Stability studies were conducted at accelerated storage in open conditions by placing 1 g of solid dispersion in a petri dish. The samples were stored in an oven at 50±2ºC for one month. After this period, the samples were withdrawn and evaluated for physical description and subjected to powder X-ray diffraction analysis. For the stability study of tablets, tablets (T5, T6, T7) compressed with solid dispersions prepared with novel polymer(s) packed in PVC/Aclar packing and placed in stability chambers, according to the ICH Q1A (R2) guidelines at accelerated storage conditions (40±2ºC and 75±5% RH). The samples were taken at predetermined time intervals (3 months and 6 months) to determine appearance and drug release.

RESULTS

X-ray diffraction analysis

The X-ray Diffraction (XRD) patterns of pure tolvaptan and the initial diffraction pattern of the spray-dried amorphous solid dispersion are presented in Figure 1A. Pure tolvaptan exhibited prominent diffraction peaks at 1.6, 15.3, 16.4, and 21.9º 2θ, indicating its crystalline nature. However, the XRD patterns of tolvaptan solid dispersions with various polymers, including HPC, HPMC E5, HPMCP, HPMCAS, HPMCPS41, HPMCPS73, and HPMCPS32, demonstrated a diffuse halo pattern, characteristic of an amorphous structure.

Fourier transform infrared spectroscopy

Fourier Transform Infrared Spectroscopy (FTIR) serves as a crucial analytical technique for identifying molecular interactions. This study elaborates on the methodology of using FTIR to elucidate molecular interactions and their consequent effects on drug performance. Peak shifts or changes in intensities indicated molecular interactions such as hydrogen bonding, van der Waals forces, or ionic interactions. By analyzing FTIR stretching patterns, it is possible to easily distinguish between free and hydrogen-bonded functional groups, hence it can be used to identify molecular interactions in solid dispersions. Molecular interactions within solid dispersions play a pivotal role in influencing the performance of drugs, particularly in terms of dissolution, solubility, and stability. Results of FTIR analysis of tolvaptan solid dispersion with HPC, HPMC, HPMCP, HPMCAS, HPMCPS41, HPMCPS73, and HPMCPS32 are presented in Figure 2 and Table 2.

Thermal analysis

DSC analysis was employed to investigate the melting and crystalline profiles of spray-dried solid dispersions. The DSC thermograms further corroborated these findings, displaying similar patterns for the dispersions with HPMCAS and HPMCPS, which lacked distinct melting peaks typically associated with crystalline structures.

Morphological characterization

The amorphous form of tolvaptan exhibited flat and thin structures, often referred to as flakes Figure 3. This morphology is consistent with the physical observation of tolvaptan as a fluffy material. In contrast, the novel polymers HPMCPS grades 73 and 32 display dense, irregular structures. These polymers' distinct morphology highlights their unique physical properties and potential impact on the formulation's performance. The SEM images of the tolvaptan Spray-Dried Solid Dispersions (SSD) revealed a classical spherical shape with diameters less than 5 µm.

In vitro drug release

Amorphous materials, being high-energy substances, provide faster dissolution. However, rapid crystallization back to a more stable but less soluble crystalline form limits the benefit of increased drug absorption rate and extent. To enhance bioavailability, the supersaturation state needs to be prolonged. This prolongation can be achieved by using appropriate excipients. These excipients can be envisioned as 'parachutes,' slowing the descent from high to low energy forms of the drug. This concept is defined by the authors as the spring and parachute effect.[21] For generic development of solid dispersions formulation, *in vitro* mapping of Spring and Parachute effect is critical to meet bioequivalence criteria.

Considering that Jinarc® (the trade name for tolvaptan tablets) is formulated by spray-dried solid dispersion of API and HPC-SL in a 2:1 ratio, this study evaluates different formulations with various polymers and compares their efficiency with Jinarc. To evaluate the similarity of release profiles for test and reference (Jinarc) formulations, the similarity factor, f_2 was applied using the following equation.[22]

$$f_2 = 50 \times \log\left(\frac{100}{\sqrt{1+\frac{\sum_{t=1}^{n}(R_t - T_t)^2}{n}}}\right)$$

Except for PVP 30 and HPMCS (HPMC succinate), all other known polymers exhibited a profile comparable to the innovator product Jinarc as shown in Table 3A, along with the spring and parachute phenomena, up to 60 min. This similarity is reflected in their f_2 values, which are above 50. PVP 30 did not exhibit spring and parachute behavior like Jinarc and did not meet the f_2 value. If dosed, it might fail to meet the rate (C_{max}) and extent (AUC) criteria. HPMCS did show parachute behavior but failed to match the spring behavior, with more than 10% less release

until 30 min compared to the brand product and could not meet the f_2 value. This formulation may fail to meet the rate (C_{max}). Further investigation of PXRD for PVP revealed 25% crystalline Figure 1B, which reveals PVP may be needed higher percentage of polymer in comparison with others.

The dissolution behavior of novel polymer spray-dried solid dispersions was evaluated and compared with Jinarc and HPMCAS as shown in Table 3B. Although most of the drug was released by 30 min, the dissolution study continued until 60 min to understand the precipitation behavior of the drug with different polymers. All novel polymer solid dispersions exhibited spring and parachute behavior and had comparable f_2 values to the brand and HPMCAS polymer.

The release kinetics of tolvaptan were further evaluated and tabulated in Table 3C to determine the most appropriate kinetic model. The selection of the optimal model was based

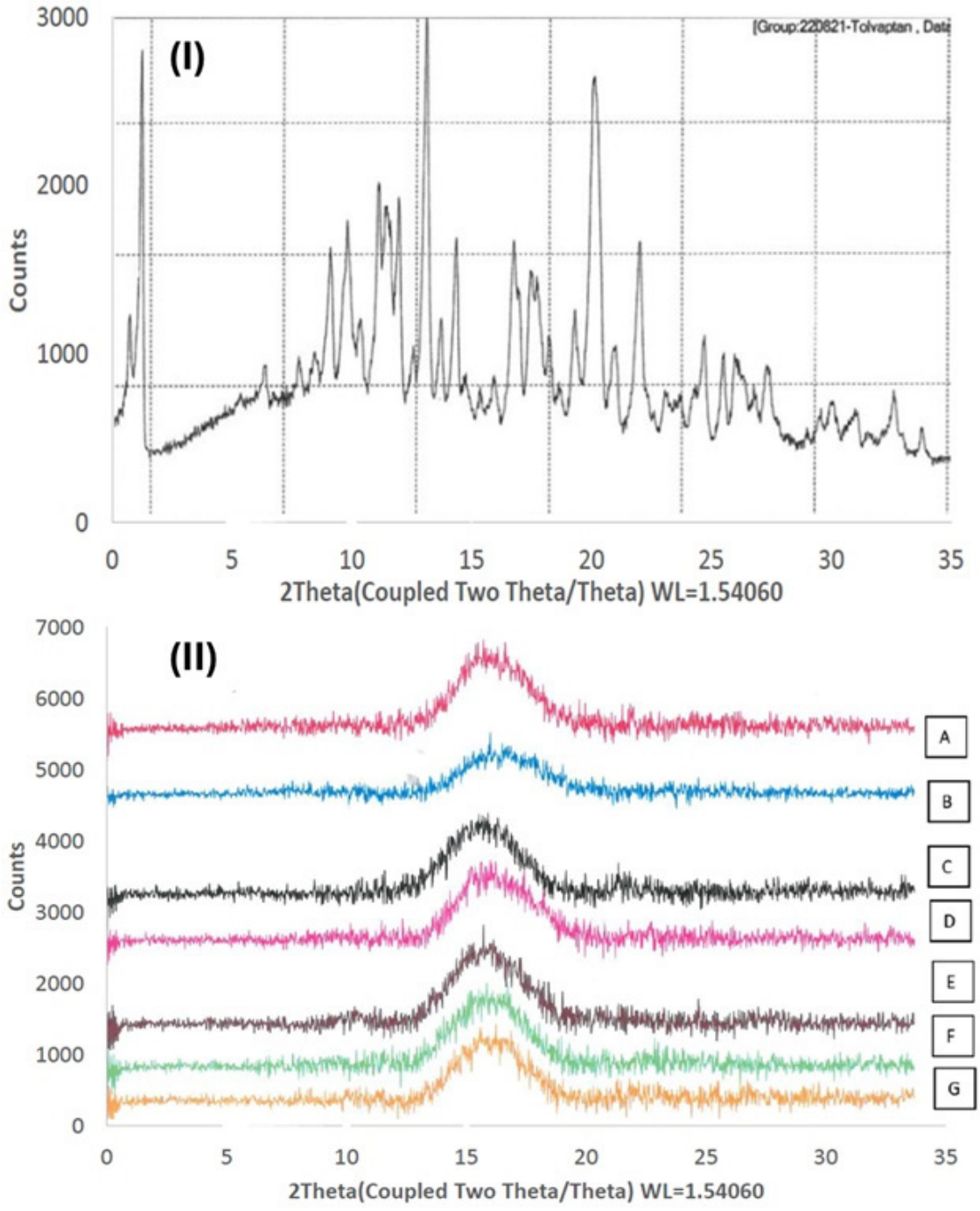

Figure 1A: X-ray diffraction spectrum of (I) Tolvaptan (API) and (II) Tolvaptan solid dispersion with different polymers by spray drying technique (Initial). (A) Tol-HPC SSD (B) Tol-HPMC SSD (C) Tol-HPMCP SSD (D) Tol-HPMCAS SSD (E) Tol-HPMCPS 41 SSD (F) Tol-HPMCPS 73 SSD (G) Tol-HPMCPS 32 SSD.

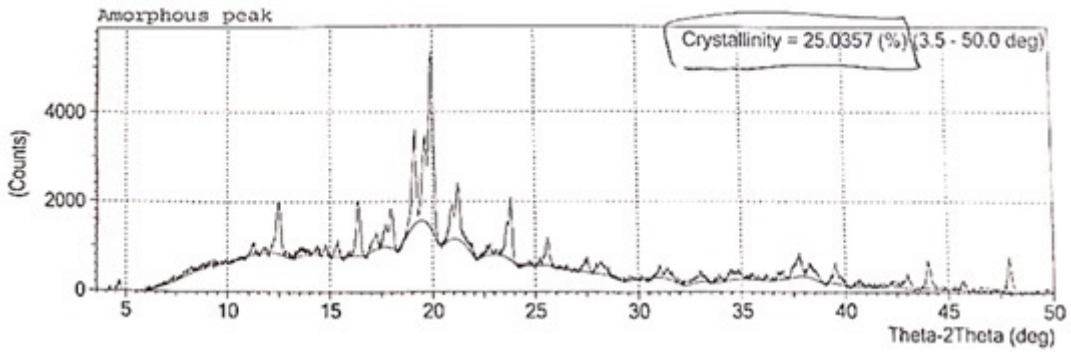

Figure 1B: X-ray diffraction spectrum of tolvaptan solid dispersion with PVP 30.

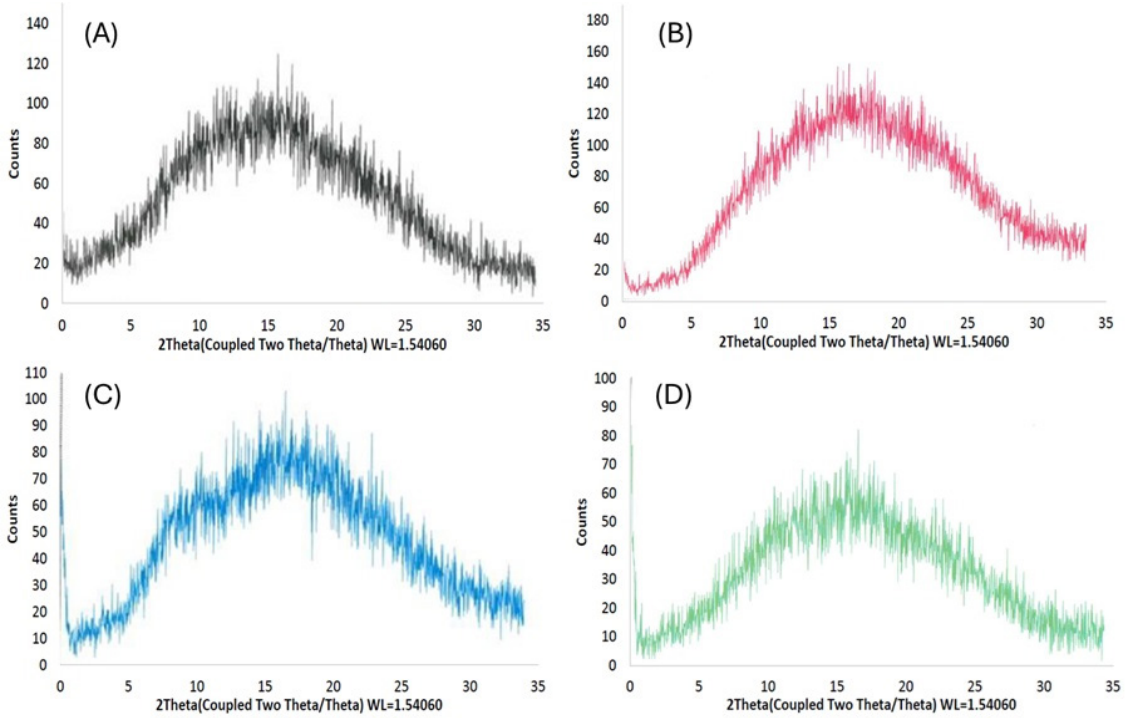

Figure 1C: X-ray diffraction spectrum of tolvaptan solid dispersion at accelerated condition: (A) HPMCAS, 50ºC open, 1M, (B) HPMCPS 41, 50ºC open, 1M, (C) HPMCPS 73, 50ºC open, 1M, and (D) HPMCPS 32, 50ºC open, 1M.

Table 1A: Composition of solid dispersion prepared by the solvent evaporation method using the spray drying technique.

Ingredients	F1	F 2	F 3	F 4	F 5	F 6	F 7	F8	F9
Tolvaptan crystals	5	5	5	5	5	5	4.5	4.5	4.5
HPC	2.5	-	-	-	-	-	-	-	-
HPMC E5	-	2.5	-	-	-	-	-	-	-
HPMCP	-	-	2.5	-	-	-	-	-	-
HPMCAS	-	-	-	2.5	-	-	-	-	-
HPMC Phthalate Succinate 41	-	-	-	-	2.5	-	-	-	-
HPMC Phthalate Succinate 73	-	-	-	-	-	2.5	-	-	-
HPMC Phthalate Succinate 32	-	-	-	-	-	-	2.25	-	-
HPMC Succinate	-	-	-	-	-	-	-	2.25	-
PVP 30	-	-	-	-	-	-	-	-	2.25
Dichloromethane (DCM)	69	69	69	69	69	69	101.1	361.8	69
Ethanol	17.25	17.25	17.25	17.25	17.25	17.25	25.3	90.45	17.25

Table 1B: Composition of tablets prepared by the solvent evaporation method using the spray drying technique.

Ingredients	T1	T2	T 3	T4	T5	T6	T7	T8	T9
Tolvaptan SSD	135 (F1)	135 (F2)	135 (F3)	135 (F4)	135 (F5)	135 (F6)	135 (F7)	135 (F8)	135 (F9)
Corn starch	150	150	150	150	150	150	150	150	150
Lactose monohydrate	160	160	160	160	160	160	160	160	160
MCC PH 102	25	25	25	25	25	25	25	25	25
Croscarmellose Sodium	25	25	25	25	25	25	25	25	25
Magnesium stearate	5	5	5	5	5	5	5	5	5
Tablet weight	500	500	500	500	500	500	500	500	500

on its goodness of fit, as determined by the highest coefficient of determination (r^2) value, the Akaike Information Criterion (AIC), and the Model Selection Criterion (MSC). For most of the formulations, the dissolution of tolvaptan was best represented by First-order kinetics and the Hixson-Crowell cube root model. The First-order kinetic model describes the drug release rate as being proportional to the concentration of the drug that remains within the dosage form. This model was found to provide a strong fit, indicating that the release rate of Tolvaptan decreases as the concentration within the dosage form diminishes. Hixson-Crowell cube root model was found to accurately describe the dissolution behavior of Tolvaptan. This model suggests that the drug release is influenced by the diminishing surface area available for dissolution as the drug particles erode over time. However, an exception was observed with the formulation containing PVP 30 (Polyvinylpyrrolidone). For this specific formulation, the release kinetics did not conform to the First-order kinetics or the Hixson-Crowell cube root model. Instead, alternative kinetic models may better describe the release behavior of Tolvaptan in the presence of PVP 30, which could be attributed to the unique properties and interactions of the polymer within the formulation.

Permeation study using Strat-M

Strat-M membrane used as a surrogate in assessing the permeation of drugs and cosmetics without the need for animal testing. Permeation studies were performed using Strat-M membrane using the Franz diffusion assembly for 24 hr. The cumulative drug permeation with novel polymers compared with HPMCAS in Figure 4A, and the Pharmacokinetic (PK) parameters are summarized in Table 4. The newly synthesized polymers, HPMCPS, were designed as potential alternatives to HPMCAS. Given this objective, HPMCAS was considered the reference standard in this study. The comparative analysis revealed that HPMCPS 32 demonstrated equivalent characteristics to HPMCAS, while the other two polymers, HPMCPS 41 and HPMCPS 73, exhibited superior properties. HPMCAS is widely recognized for its favorable characteristics in pharmaceutical formulations, including its ability to enhance the solubility and stability of poorly water-soluble drugs. The study aimed to investigate whether the novel HPMCPS polymers could not only match but also surpass these desirable traits.

HPMCPS 32 showed comparable performance to HPMCAS in terms of solubility enhancement, and overall formulation efficacy. This equivalence indicates that HPMCPS 32 can serve as a viable alternative to HPMCAS without compromising the formulation quality. In contrast, HPMCPS 41 and HPMCPS 73 displayed superior characteristics. These polymers demonstrated enhanced solubility, potentially offering greater efficacy in drug delivery applications. The superior performance of HPMCPS 41 and HPMCPS 73 suggests that they may provide additional benefits over HPMCAS, making them promising candidates for further development and utilization in pharmaceutical formulations.

Stability results

To evaluate the stability of the spray-dried amorphous solid dispersions, these dispersions were subjected to open exposure at 50°C for one month. The stability assessment revealed that the solid dispersions prepared with HPMCPS exhibited comparable behavior to those formulated with HPMCAS under both initial and accelerated stability conditions. This similarity in performance suggests that the newly synthesized HPMCPS polymers maintain the amorphous state and structural integrity of the dispersions, even under stressful conditions as depicted in Figure 1C.

The tablet formulations (T5, T6, T7) prepared with spray-dried solid dispersions using various grades of Hypromellose Phthalate Succinate (HPMCPS) were subjected to rigorous dissolution performance evaluation under accelerated stability conditions (40±2°C and 75±5% RH). The dissolution performance of these formulations in Figure 4B was compared with the initial dissolution profiles to ascertain any changes due to the stability testing. The dissolution studies indicated that there was no significant change in the dissolution performance of the tablet formulations over the stability testing period. This consistent dissolution behavior, observed at both the initial time point and after exposure to the accelerated stability conditions, suggests that the amorphous solid dispersions remain stable.

The stability of the amorphous solid dispersions within the tablet formulations is a critical factor, as it ensures the continued efficacy and bioavailability of the API throughout the product's shelf life. The findings from these dissolution studies provide strong evidence that the incorporation of various grades of HPMCPS in the spray-dried solid dispersions effectively maintains the amorphous state and prevents recrystallization of the API.

Table 2: Comparison of key functional group shifts in tolvaptan solid dispersion relative to pure tolvaptan and polymer.

Sample	Functional group	Tolvaptan	Polymer	Solid dispersion
Tolvaptan HPC-SSD	O-H stretching	Broad peak	3433 cm^{-1}	3410 cm^{-1}
	N-H stretching	3290 cm^{-1}	NA	3301 cm^{-1}
	C-H stretching	2932 cm^{-1}	2928 cm^{-1}	2925 cm^{-1}
	C=C stretching	1625 cm^{-1}	1622 cm^{-1}	1628 cm^{-1}
	C=O stretching	1738 cm^{-1}	1739 cm^{-1}	NA
Tolvaptan HPMC-SSD	O-H stretching	Broad peak	3422 cm^{-1}	3414 cm^{-1}
	N-H stretching	3290 cm^{-1}	NA	3301 cm^{-1}
	C-H stretching	2932 cm^{-1}	2921 cm^{-1}	2925 cm^{-1}
	C=C stretching	1625 cm^{-1}	1622 cm^{-1}	1629 cm^{-1}
	C=O stretching	1738 cm^{-1}	NA	NA
Tolvaptan HPMCP-SSD	O-H stretching	Broad peak	3448 cm^{-1}	3415 cm^{-1}
	N-H stretching	3290 cm^{-1}	NA	3301 cm^{-1}
	C-H stretching	2932 cm^{-1}	2926 cm^{-1}	2924 cm^{-1}
	C=O stretching	1738 cm^{-1}	1723 cm^{-1}	1725 cm^{-1}
	C=C stretching	1625 cm^{-1}	1600 cm^{-1}	1631 cm^{-1}
Tolvaptan HPMCAS-SSD	O-H stretching	Broad peak	3451 cm^{-1}	3427 cm^{-1}
	N-H stretching	3290 cm^{-1}	NA	3301 cm^{-1}
	C-H stretching	2932 cm^{-1}	2931 cm^{-1}	2927 cm^{-1}
	C=O stretching	1738 cm^{-1}	1737 cm^{-1}	1741 cm^{-1}
	C=C stretching	1625 cm^{-1}	1600 cm^{-1}	1631 cm^{-1}
Tolvaptan HPMCPS 41-SSD (0.75 phthalate)	O-H stretching	Broad peak	3457 cm^{-1}	3427 cm^{-1}
	N-H stretching	3290 cm^{-1}	NA	3293 cm^{-1}
	C-H stretching	2932 cm^{-1}	2929 cm^{-1}	2925 cm^{-1}
	C=O stretching	1738 cm^{-1}	1736 cm^{-1}	1727 cm^{-1}
	C=C stretching	1625 cm^{-1}	1600 cm^{-1}	1628 cm^{-1}
Tolvaptan HPMCPS 73-SSD (0.58 phthalate)	O-H stretching	Broad peak	3447 cm^{-1}	3416 cm^{-1}
	N-H stretching	3290 cm^{-1}	NA	3298 cm^{-1}
	C-H stretching	2932 cm^{-1}	2934 cm^{-1}	2925 cm^{-1}
	C=O stretching	1738 cm^{-1}	1736 cm^{-1}	1727 cm^{-1}
	C=C stretching	1625 cm^{-1}	1600 cm^{-1}	1628 cm^{-1}
Tolvaptan HPMCPS 32-SSD (0.44 phthalate)	O-H stretching	Broad peak	3450 cm^{-1}	3421 cm^{-1}
	N-H stretching	3290 cm^{-1}	NA	3297 cm^{-1}
	C-H stretching	2932 cm^{-1}	2928 cm^{-1}	2924 cm^{-1}
	C=O stretching	1738 cm^{-1}	1720 cm^{-1}	1729 cm^{-1}
	C=C stretching	1625 cm^{-1}	1600 cm^{-1}	1629 cm^{-1}

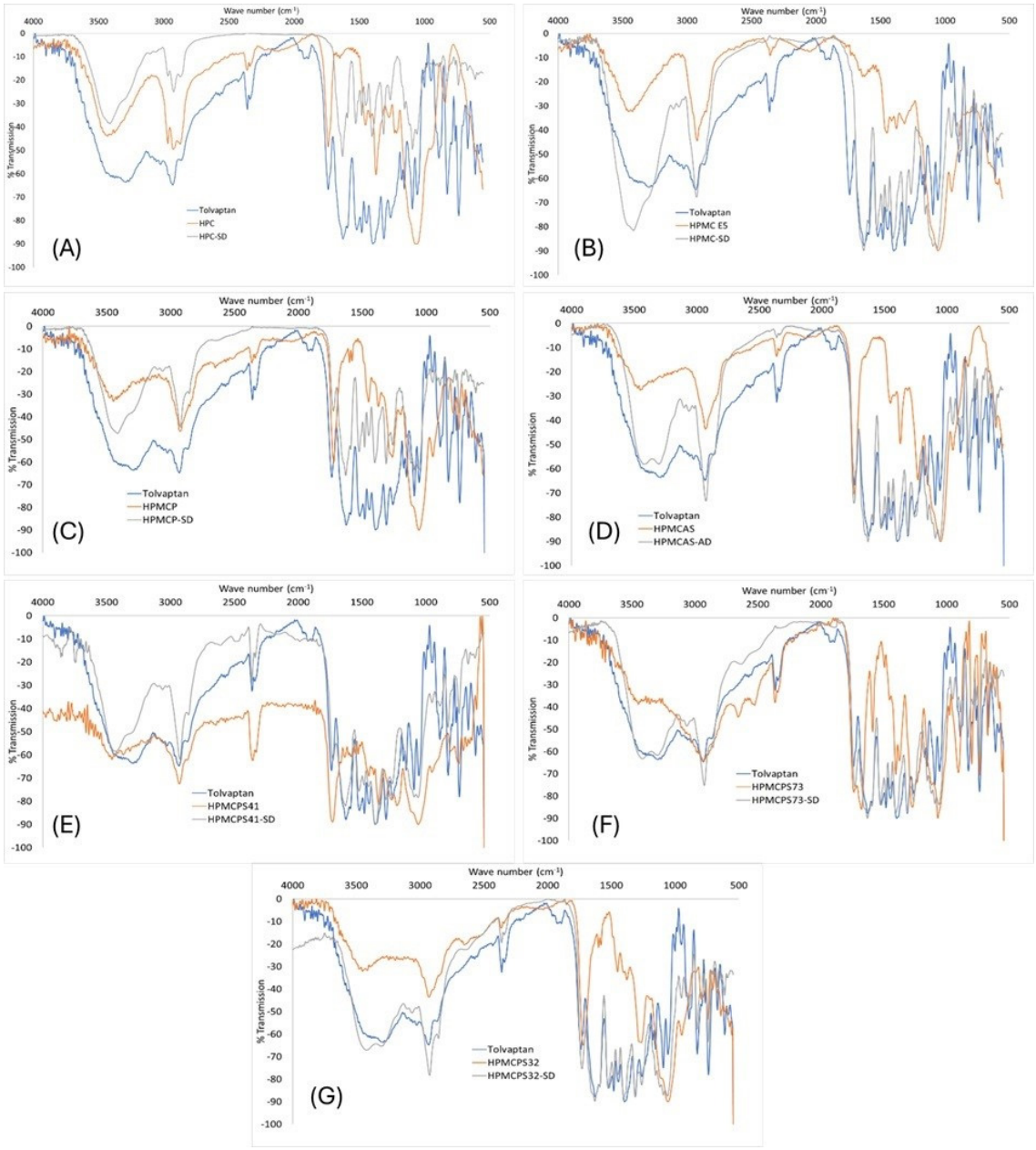

Figure 2: FTIR spectrum of Tolvaptan solid dispersion with different polymers: (A) HPC, (B) HPMC, (C) HPMCP, (D) HPMCAS, (E) HPMCPS41, (F) HPMCPS73, and (G) HPMCPS32.

DISCUSSION

The PXRD results of solid dispersions with various HPC and HPMC derivatives, including HPMC E5, HPMCP, HPMCAS, HPMCPS41, HPMCPS73, and HPMCPS32, demonstrate a significant transformation of the crystalline form of tolvaptan into an amorphous state. The observed halo patterns, characterized by the absence of sharp crystalline peaks, are indicative of the successful conversion. This transformation is crucial for enhancing the solubility and eventually bioavailability of tolvaptan. Crystalline forms often exhibit poor solubility due to their rigid and ordered lattice structures. In contrast, amorphous forms, with their disordered atomic arrangements, tend to dissolve more readily, thereby improving drug absorption and therapeutic efficacy.

Molecular interactions in FTIR are evidenced by the shifting, reduction, and disappearance of peak intensities for characteristic functional groups.

O-H Stretching shifting suggests the formation of hydrogen bonds between the hydroxyl groups of the drug and the polymer. This interaction is crucial as it can enhance the solubility and stability of the drug within the polymer matrix.

N-H Stretching shifting indicates a possible interaction between the amine groups of the drug and the polymer. This interaction

could lead to the formation of a more stable complex, potentially improving the drug's bioavailability.

C-H Stretching shifting suggests a reduction in the hydrophobic interactions within the solid dispersion. This reduction may facilitate better dispersion of the drug within the polymer, enhancing its dissolution rate.

C=C Stretching peak disappearance or significant reduction indicates a strong interaction between the drug and the polymer, possibly through π-π stacking interactions. These interactions can contribute to the stabilization of the drug in its amorphous form, preventing recrystallization.

C=O Stretching peak shifting/disappearance is indicative of strong interactions, such as hydrogen bonding or dipole-dipole interactions, between the carbonyl groups of the drug and the polymer. This interaction is essential for maintaining the drug in a dispersed state, thereby improving its therapeutic efficacy.

The DSC thermograms corroborated the findings of PXRD, displaying similar patterns for the dispersions with HPMCAS and HPMCPS, which lacked distinct melting peaks typically

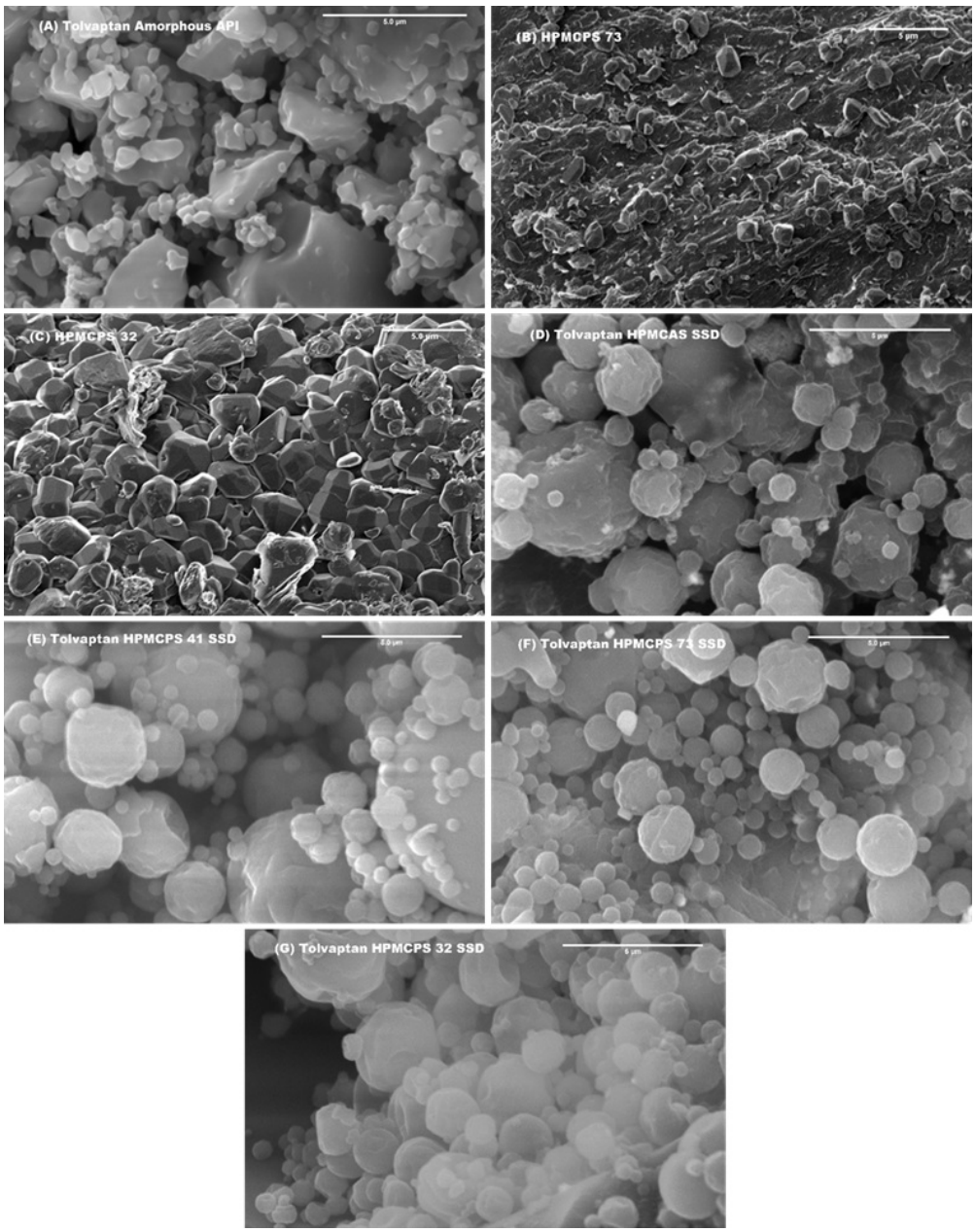

Figure 3: SEM images of amorphous pure drug, polymers, and spray-dried solid dispersions (A) Tolvaptan amorphous API, (B) HPMCPS73 Polymer, (C) HPMCPS32 Polymer, (D) Tolvaptan HPMCAS SSD, (E) Tolvaptan HPMCPS41 SSD, (F) Tolvaptan HPMCPS73 SSD, and (G) Tolvaptan HPMCPS32 SSD.

Table 3A: *In vitro* dissolution results of tolvaptan tablets.

Time (min)	Jinarc	T4 (HPMCAS)	T1 (HPC)	T2 (HPMC)	T3 (HPMCP)	T8 (HPMCS)	T9 (PVP 30)
0		0	0	0	0	0	0
5	36.21±3.1	25.32±4.4	42.41±3.8	31.30±3.1	28.46±2.5	20.53±2.5	17.32±2.6
10	71.43±2.5	65.80±4.6	63.05±3.6	68.08±3.6	67.19±2.5	54.37±3.1	51.95±3.1
15	85.11±1.0	75.91±3.1	74.05±2.0	75.80±2.6	78.46±1.5	70.73±3.6	55.12±2.5
20	91.36±1.0	83.51±1.5	82.27±3.1	81.23±3.1	85.17±2.1	76.06±2.1	53.14±1.5
30	97.09±1.2	91.17±1.2	90.14±2.0	87.55±2.0	92.09±2.5	84.42±2.6	44.91±1.5
45	100.01±2.1	97.51±2.1	95.09±2.1	95.81±2.0	98.27±1.5	93.81±2.5	36.44±1.5
60	101.24±0.6	98.72±3.0	100.10±1.5	100.20±1.7	100.05±1.5	100.03±1.5	30.63±2.1
F2		53	53	60	62	40	32

Table 3B: *In vitro* dissolution results of tolvaptan tablets prepared using novel polymer.

Time (min)	Jinarc	T4 (HPMCAS)	T5 (HPMCPS41)	T6 (HPMCPS73)	T7 (HPMCPS32)
0	0	0	0	0	0
5	36.22±3.1	25.30±4.4	24.23±3.5	40.37±3.1	31.14±3.5
10	71.41±2.5	65.81±4.6	64.51±2.6	68.71±2.6	66.17±3.2
15	85.13±1.0	75.92±3.1	72.62±1.5	77.06±1.5	74.05±1.2
20	91.30±1.0	83.54±1.5	82.32±1.5	85.15±0.6	78.40±2.1
30	97.05±1.2	91.11±1.2	90.31±1.2	92.54±1.7	86.31±1.0
45	100.06±2.1	97.50±2.1	98.45±1.5	100.20±0.6	96.14±2.0
60	101.02±0.6	98.71±3.0	101.06±1.5	103.10±1.2	100.05±1.5
F2		53	49	65	58

Table 3C: Release constant and efficient correlation of tolvaptan SSDs with different polymers.

	Jinarc	T1 (HPC)	T2 (HPMC)	T3 (HPMCP)	T4 (HPMCAS)	T5 (HPMCPS41)	T6 (HPMCPS73)	T7 (HPMCPS32)	T8 (HPMCS)	T9 (PVP 30)
k1	0.114	0.094	0.091	0.097	0.089	0.085	0.104	0.087	0.071	0.018
Rsqr_adj	0.9917	0.9927	0.9810	0.9855	0.9801	0.9801	0.9949	0.9794	0.9821	-0.6868
AIC	36.7547	34.4056	42.6124	41.0914	43.5959	43.7793	32.2942	43.0933	42.5459	69.3313
MSC	3.6956	3.7616	2.9323	3.2417	2.9845	3.0168	4.1405	2.8616	3.1969	-1.4337
kHC	0.025	0.023	0.023	0.024	0.023	0.023	0.024	0.023	0.020	0.005
Rsqr_adj	0.9549	0.9612	0.9570	0.9698	0.9701	0.9755	0.9655	0.9546	0.9736	-0.8528
AIC	50.2742	47.7584	49.1247	46.9482	46.8565	45.4429	47.5500	49.4127	45.6759	70.0822
MSC	2.0056	2.0925	2.1183	2.5095	2.5770	2.8088	2.2335	2.0717	2.8057	-1.5275

Table 4: Permeation parameter comparison using Strat-M.

	J_{max} (µg/cm²)	Total permeated amount (AMT) (µg. cm^{-2}. hr^{-1})	T/R J_{max}	T/R AMT
HPMCAS	41.39	349.45		
HPMCPS 41	58.94	447.61	142.40	128.09
HPMCPS 73	55.45	469.38	133.97	134.32
HPMCPS 32	41.02	408.97	99.12	117.03

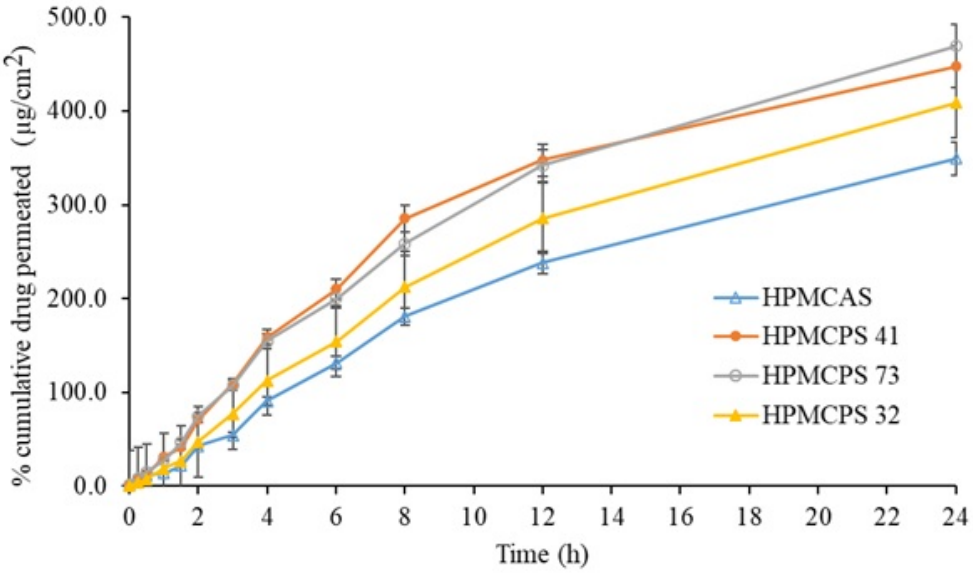

Figure 4A: *In vitro* permeation results of tolvaptan tablets prepared by the direct compression method.

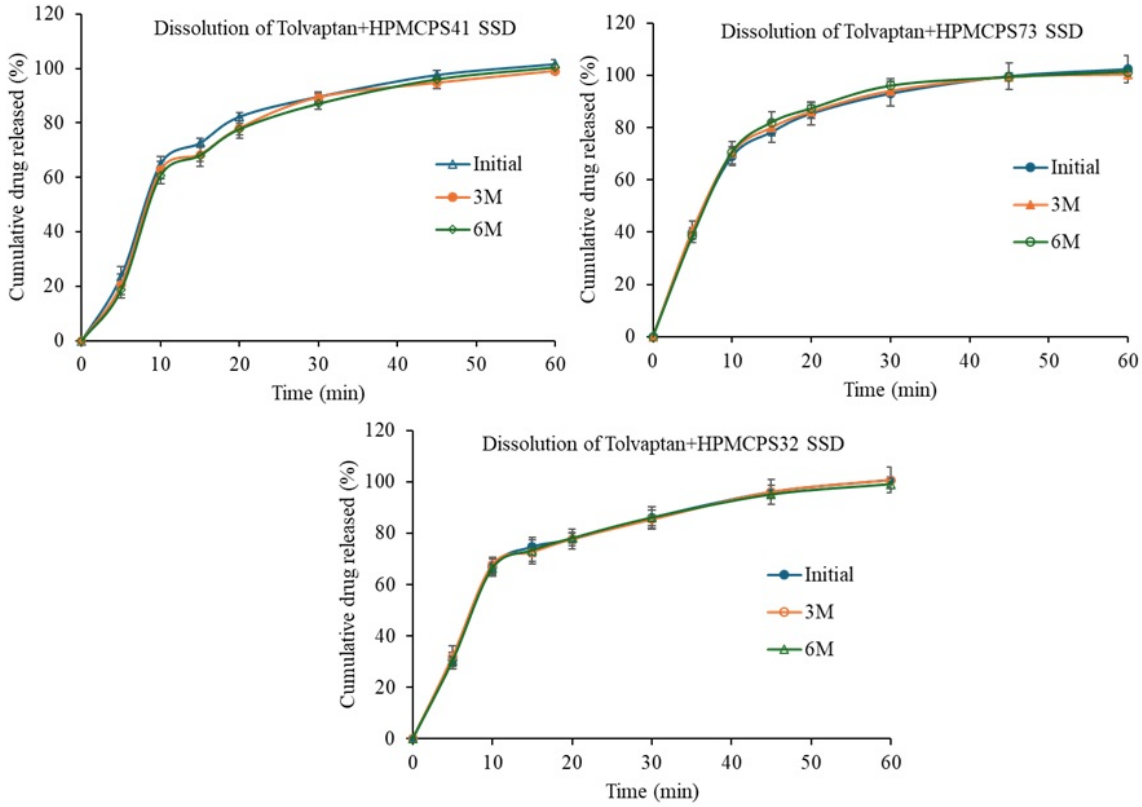

Figure 4B: Dissolution profile of tolvaptan tablets prepared with solid dispersions of novel polymers.

associated with crystalline structures. These results suggest that the incorporation of HPMCAS and HPMCPS effectively inhibited drug crystallization within solid dispersions. Consequently, the spray-drying process, in conjunction with these polymers, appears to enhance the amorphous state of the drug, potentially improving its solubility and bioavailability. The glass transition temperature (Tg) of amorphous solid dispersions plays a pivotal role in determining the molecular mobility of their constituents. An elevated Tg within the dispersion restricts drug mobility, thereby reducing its tendency to transition from an amorphous to crystalline state. This increase in Tg effectively raises the activation energy required for structural change, resulting in kinetically stable systems. These dispersions, while not necessarily thermodynamically favored, exhibit prolonged persistence due to the impeded pathway to transformation. As a result, increasing

Tg may inhibit the formation of phase-separated domains and support the long-term physical stability of the formulation.

This spherical morphology of SEM is indicative of a successful spray-drying process, which typically results in uniformly sized and shaped particles. These findings underscore the thorough mixing of the tolvaptan within the polymer carriers, HPMCPS 73 and HPMCPS 32, during the spray-drying process. The absence of crystalline structures in the SSDs, as evidenced by the SEM images, indicates a complete loss of API crystallinity.

The successful conversion of crystalline Tolvaptan to its amorphous form in the solid dispersion is evidenced by several key observations. The loss of crystallinity by PXRD, as indicated by the absence of sharp melting peaks in the DSC, and the presence of spherical particles in the SEM, highlight the transformation. Additionally, the FTIR spectra reveal molecular interactions, further supporting this conversion. This transformation is supported by *in vitro* dissolution tests, which show matching or superior dissolution profiles compared to the brand product Jinarc.

The comparative permeability assessment using the Strat-M membrane model demonstrates the superior performance of HPMCPS variants over the reference polymer HPMCAS, as evidenced by key pharmacokinetic parameters J_{max} and AMT. HPMCPS 41 and HPMCPS 73 exhibited significantly enhanced absorption profiles, with T/R ratios of J_{max} at 142.40% and 133.97%, respectively. These values represent a >40% and >33% improvement in flux compared to HPMCAS, highlighting a meaningful enhancement in permeability. Corresponding increases in AMT (447.61 and 469.38 $\mu g \cdot cm^{-2} \cdot hr^{-1}$), and a T/R AMT (128.09, 134.32) further confirm the improved diffusion potential and bioavailability of these novel polymeric systems in comparison with HPMCAS. Meanwhile, HPMCPS 32 displayed a J_{max} ratio of 99.12%, suggesting near equivalence to HPMCAS.

These findings highlight the unique qualities of the HPMCPS 41 and 73 grades, which have specific levels of succinyl and phthalyl substitutions and a balanced hydrophilic-lipophilic balance property. Such modifications contribute to enhanced drug transport across membrane models and support their utility in improving oral bioavailability. Accordingly, these polymers represent promising candidates for advanced drug delivery applications, reinforcing their novelty and relevance in contemporary pharmaceutical formulation.

CONCLUSION

Spray Dried solid Dispersions (SSDs) of tolvaptan using the novel polymers HPMCPS41, HPMCPS73, and HPMCPS32 have yielded promising results. The transformation of crystalline Tolvaptan into its amorphous form, confirmed by PXRD diffractograms, DSC, and SEM, indicates successful conversion. Additionally, FTIR spectroscopy has highlighted potential hydrogen-bonding interactions within the SSDs. Moreover, more transparent SEM images for various grades of HPMC Phthalate Succinate compared to HPMCAS suggest a possible higher drug loading capacity than HPMCAS. Tablet formulations incorporating these SSDs were rigorously evaluated through *in vitro* dissolution and permeation studies. When benchmarked against the reference formulation Jinarc (utilizing HPC polymer) and another formulation prepared with HPMCAS, the novel polymer formulations exhibited comparable dissolution profiles and demonstrated either similar or enhanced *in vitro* permeation characteristics. This suggests that novel polymers are viable alternatives to the existing ones. Further stability studies have underscored the robustness of these novel polymer formulations, demonstrating their stability under accelerated conditions. These findings collectively indicate that the use of novel polymers HPMCPS41, HPMCPS73, and HPMCPS32 offers a promising approach for the effective formulation of Tolvaptan, providing potential advantages over traditional polymers. Therefore, these novel polymers represent a significant advancement in the field of pharmaceutical formulation, with the potential for improved drug delivery and efficacy. The novel HPMCPS polymers explored in this study demonstrated promising *in vitro* performance when incorporated into solid dispersion-based tablet formulations, particularly in enhancing the solubility and dissolution rate of poorly water-soluble drug. Future investigations should prioritize preclinical *in vivo* evaluations to substantiate these findings. Comprehensive pharmacokinetic and pharmacodynamic studies in appropriate animal models will be critical to elucidate its potential in improving systemic bioavailability, achieving targeted drug release, and maintaining biocompatibility and safety. Following successful preclinical validation, the polymers can be advanced to clinical trials in human subjects to assess their therapeutic efficacy, safety, and tolerability, thereby establishing their translational potential for pharmaceutical applications.

ABBREVIATIONS

HPMC: Hydroxypropyl methylcellulose; **HPMCAS:** Hydroxypropyl methylcellulose acetate succinate; **HPMCPS:** Hydroxypropyl methylcellulose phthalate succinate; **FTIR:** Fourier transform infrared spectroscopy; **SEM:** Scanning electron microscope; **DSC:** Differential scanning calorimetry.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

HPMCAS is a widely used carrier molecule in solid dispersion technology for poorly soluble drugs, but its patent restrictions necessitate alternatives for generic companies. In this study, the authors synthesized an alternative polymer, HPMCPS, by substituting the acetyl group in HPMCAS with a more

hydrophobic phthalic group to enhance molecular dispersibility. The *in vitro* performance of this novel polymer was evaluated alongside existing polymers using Tolvaptan as a model drug, employing spray drying techniques. The solid dispersions prepared with various polymers were characterized using PXRD, FTIR, DSC, SEM, dissolution, and *in vitro* permeability tests. The results indicate that the novel synthesized polymer, HPMCPS, shows promising potential as an alternative to HPMCAS.

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