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Improvement of *in vitro* dissolution profile of poorly aqueous soluble anti-parasitic agent ivermectin using novel hydrophilic polymeric carriers

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ABSTRACT

Ivermectin (IVM), a BCS Class II drug with weak water solubility, has minimal oral absorption and dissolution. This study aims to enhance the dissolution profile of IVM by performing solid dispersion methods using four hydrophilic polymers: Kollicoat IR, Kollidon 90F, poloxamer 407, and hydroxypropyl methylcellulose (HPMC). The solid dispersion formulations (SDF) were made through physical mixing, solvent evaporation, and melt solvent/fusion. Using three ratios of IVM and hydrophilic carriers (1:1, 1:2, and 1:3), the cumulative release rate of IVM from formulations formed by physical mixing, solvent evaporation, and fusing was much larger than pure IVM (10%). IVM release rates from formulations including Poloxamer 407, Kollicoat IR, and HPMC polymers were 76% (fusion technique), 69% (physical mixing), and 47% (solvent evaporation method). The research demonstrated that fusion optimized drug solubility better than physical mixing and solvent evaporation. The research found that SD of weakly water-soluble IVM with Kollicoat IR/Poloxamer 407 improves its *in vitro* dissolving profile much better.

Keywords: Ivermectin; BCS Class II; Solid dispersion; Solvent evaporation; Fusion; Polymers

Introduction

Ivermectin is an antiparasitic drug (Johnson-Arbor, 2022; Laing *et al.* 2017; Tang *et al.* 2021) that belongs to the avermectin (Buonfrate *et al.* 2022) family of medications. Following its innovation in 1975 (Crump, 2017a), its earliest applications were in veterinary medicine to inhibit and treat acariasis and heartworm (Quang *et al.* 2022). It was approved for human use in 1987 (Crump, 2017b) and is now widely used to treat infestations such as scabies, river blindness, head lice, onchocerciasis, trichuriasis, strongyloidiasis, lymphatic filariasis, and ascariasis (Batiha *et al.* 2019; Crump, 2017b; Krotneva *et al.* 2015).

Ivermectin belongs to the Biopharmaceutics Classification System (BCS) Class II category (Das *et al.* 2020; del Moral Sanchez *et al.* 2018; Rowland and Wesche, 2023). The Biopharmaceutics Classification System (BCS) categorizes drugs into different classes based on their biopharmaceutical properties. One such class is Class II, which comprises drugs with low water solubility, a low dissolution rate (%), and high permeability (Hastedt *et al.* 2022; Samineni *et al.* 2022). Ivermectin has a water solubility of approximately 4mg/L (Diagboya *et al.* 2021). It is spontaneously soluble in methanol and ethanol (95%) (Campbell and Marchant, 2018).

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The substance in question has a coloration ranging from white to yellowish-white. It possesses a crystalline structure and does not readily absorb moisture from the surrounding environment. Its physical state is that of a powder, characterized by a melting temperature of approximately 155°C (Abbas, 2013; Suvarna, 2023). The partition co-efficient of Ivermectin in an octanol/water system was reported to be approximately 1.651×10^3 at pH 7. The high partition co-efficient reflects its hydrophobicity, which indicates low aqueous solubility, resulting in lower bioavailability (Abbas, 2013). So, improving this drug's water solubility is a useful way to enhance therapeutic efficacy.

A poorly water-soluble drug's oral absorption, solubility, and dissolution rate may all be improved by using Solid Dispersion Formulation (SDF) (Choi *et al.* 2022; Xiong *et al.* 2019). The dissolution rate can be enhanced by the following factors: (1) the decrease of drug particle size to its molecular level; (2) the solubilizing behavior of a water-soluble carrier on the drug; and (3) an improvement of drug wettability and dispersibility through the use of a carrier material (Aparna and District, 2021; Mishra and Kulkarni, 2021). To facilitate the preparation of SDF, it is necessary to achieve complete dissolution of both the drug and carrier using either the solvent evaporation method, whereby an organic solvent is employed, or the fusion method, which involves heating the components together (Yamashita *et al.* 2003). Numerous carriers for solid dispersion formulations (SDF) have been shown to be effective in enhancing the solubility and bioavailability of pharmaceuticals with limited water solubility. These carriers encompass polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), eudragits, and chitosans, among others (Bhujbal *et al.* 2021; Yadav *et al.* 2022).

The objective of the current investigation was to formulate SDFs of Ivermectin with different hydrophilic carriers such as Kollicoat IR, Kollidon 90F, HPMC, and Poloxamer 407; evaluate physicochemical properties of those formulations; and identify the most suitable solid dispersion formulation. The aqueous solubility and drug release rates *in vitro* were enhanced through the utilization of physical mixing, solvent evaporation, and melt solvent fusion techniques. We assumed that the drug's crystalline structure would be modified into an amorphous form via chemical interaction between Ivermectin and hydrophilic carriers, improving both drug water solubility and *in vitro* drug dissolution rate.

Materials and methods

Ivermectin, poloxamer, Kollicoat IR, Kollidon 90F, Copovidone High-grade hydroxypropyl methyl cellulose, Lutrol, Soluplus, Na-CMC, Polyethylene glycol, Ethylene oxide/propylene oxide, PEG-200, methanol, ethanol, HCl, Monobasic Potassium Phosphate, Potassium di-hydrogen phosphate, Ethanol, Acetronitrile, KOH, Mili Q water, NaOH, Isopropyl alcohol, a small mortar and pestle, syringes, filter papers, tissue, funnels, membrane filters, pipettes, a cuvette cell for UV spectrometer, pipette filler, and volumetric flask were bought from local vendors.

Solvent evaporation method

Several mixes of Ivermectin and polymers, namely in ratios of 1:1, 1:2, and 1:3 (w/w), were solubilized in 15 mL of methanol. Subsequently, the solvent was subjected to controlled evaporation through gentle heating in a water bath maintained at a temperature of 50°C, while continuous agitation was maintained. After evaporating the solvent, a uniform solid mass was obtained and pulverized using a mortar and pestle. The mixtures were labeled (Table I) and stored in a desiccator maintained at approximately 25°C (Mikrani and Sharmin 2022; Sarkar *et al.* 2020).

Fusion/ melt solvent method

An accurate amount of polyethylene glycol (PEG-200) was weighed in a ratio of 1:5 (drug: PEG-200) and melted in a water bath at 55–60°C. To the molten PEG-200, Ivermectin and polymers were mixed homogeneously at 1:1, 1:2, and 1:3 ratios and cooled to room temperature. A dried solid mass was obtained that was pulverized with a mortar and pestle. The dried mixtures were sieved through No. 30 mesh, labeled (Table I), and kept in desiccators at room temperature until further evaluation (Mikrani *et al.* 2022; Sarkar and Sharmin 2020).

Preparation of physical mixture

Pure Ivermectin (IVM) and polymers were measured accurately, and three distinct physical mixtures of Ivermectin with each polymer (at 1:1, 1:2, and 1:3) were produced. The ivermectin and polymer combinations

were ground in a mortar and pestle and thoroughly combined to achieve uniformity. All binary physical mixtures (PM) are given a code name (Table I) and kept in desiccators at room temperature (Mikrani *et al.* 2022; Sarkar and Sharmin 2020).

PHM: Physical HPMC; PPM: Physical Poloxamer; PKI: Physical Kollicoat IR; PKN: Physical Kollidon 90F; EHM: Evaporation method HPMC; EPM: Evaporation method Poloxamer; EKI: Evaporation method Kollicoat IR; EKN: Evaporation method Kollidon 90F; FHM: Fusion method HPMC; FPM: Fusion method Poloxamer; FKI: Fusion method Kollicoat IR; FKN: Fusion method Kollidon 90F; PHM1=Drug : HPMC = 1 : 1; PHM2= Drug : HPMC = 1 : 2; PHME= Drug: HPMC = 1:3

Table. Ivermectin (IVM) formulations by physical mixing, solvent evaporation, and fusion method

Formulation code	Ingredients					
	IVM (mg)	Kollidon 90F(mg)	Kollicoat IR (mg)	HPMC (mg)	Poloxamer 407(mg)	PEG-200 (mg)
PKN1	12	12	-	-	-	-
PKN2	12	24	-	-	-	-
PKN3	12	36	-	-	-	-
PKI1	12	-	12	-	-	-
PKI2	12	-	24	-	-	-
PKI3	12	-	36	-	-	-
PHM1	12	-	-	12	-	-
PHM2	12	-	-	24	-	-
PHM3	12	-	-	36	-	-
PPM1	12	-	-	-	12	-
PPM2	12	-	-	-	24	-
PPM3	12	-	-	-	36	-
EKN1	12	12	-	-	-	-
EKN2	12	24	-	-	-	-
EKN3	12	36	-	-	-	-
EKI1	12	-	12	-	-	-
EKI2	12	-	24	-	-	-
EKI3	12	-	36	-	-	-
EHM1	12	-	-	12	-	-
EHM2	12	-	-	24	-	-
EHM3	12	-	-	36	-	-
EPM1	12	-	-	-	12	-
EPM2	12	-	-	-	24	-
EPM3	12	-	-	-	36	-
FKN1	12	12	-	-	-	60
FKN2	12	24	-	-	-	60
FKN3	12	36	-	-	-	60
FKI1	12	-	12	-	-	60
FKI2	12	-	24	-	-	60
FKI3	12	-	36	-	-	60
FHM1	12	-	-	12	-	60
FHM2	12	-	-	24	-	60
FHM3	12	-	-	36	-	60
FPM1	12	-	-	-	12	60
FPM2	12	-	-	-	24	60
FPM3	12	-	-	-	36	60

Optimization of solid dispersions

In-vitro dissolving studies of prepared SDs were performed to decipher the rate of IVM mass conversion from solid to solution. A total of 900 mL of 0.1 N HCl dissolving medium (DM) was used to dissolve the sample (10 mg of IVM in SDs). The dissolution process was carried out in a controlled environment using a USP-II paddle dissolution device (Erweka DT 600, Heusnstamm, Germany) at 37 ± 0.5°C and 50 rpm. There was a 60-minute run time, during which five milliliters of DM samples were taken and discarded at regular intervals. Samples were diluted appropriately, filtered through No. 41 filter paper (Whatman plc, UK), and spectrophotometrically examined at λmax 245 nm using a UV-Visible Spectrophotometer (V630; Jasco, Japan). The data shown is the average of three independent measurements.

Physicochemical properties

The physicochemical properties of unformulated IVM, PM, and SD were characterized by DSC, FTIR, and SEM.

FTIR (Fourier transform infrared spectroscopy)

The IFS-55 equipment manufactured by Bruker Corporation in Switzerland was used to obtain the Fourier transform infrared spectroscopy (FTIR) spectra of the pure drug, excipients, and samples. The KBr disc method was employed, where a 2 mg sample was mixed with 200 mg of KBr. The instrument was operated using a dry air purge, within the wave number range of 4000–400 cm^{-1}, and with a resolution of 2 cm^{-1}.

DSC (*Differential Scanning Calorimetry*)

The DSC-60 thermal analyzer (Shimadzu Corporation, Japan) was used to obtain the DSC thermograms of the IVM and poloxamer, as well as their best PM and SD formulations. 2.28 to 2.95 mg of suitable samples were used for the analysis, and heating was conducted at a rate of 5°C per minute from 30.5 to 165.5°C.

SEM (Scanning electron microscopic)

SEM was used to characterize the SD and PM formulations physiologically. The scanning electron microscopic research was carried out using a scanning electron microscope (JSM-7610F, Japan). The IVM and SD samples were mounted to the stubs using double-sided adhesive. For the SEM investigation, the samples of this formulation were subsequently thinly coated with platinum (JEC-3000FC Auto Fine Coater, Japan).

Results and discussion

Optimization of solid dispersions

The study of dissolution behavior plays a crucial role in informing the advancement of novel formulations and can serve as a critical criterion for distinguishing between various newly produced formulations. Formulations prepared by physical mixing, solvent evaporation, and the fusion method showed a considerably improved rate and efficiency of IVM dissolution than pure IVM alone. Among the formulations made by the physical mixing method, PPM3 and PKI3 showed enhanced drug release after 60 minutes. Increasing the concentration of polymers (Kollicoat IR, HPMC, Poloxamer) improves the drug release from the physical mixing formulation. However, formulations prepared by the physical mixing method exhibited a decreasing release rate with a higher concentration of kollidon 90F. Formulations containing a high amount of polymer demonstrated a better release rate of IVM prepared by both the solvent evaporation and fusion methods after the first 60 minutes, and FPM3 provided the highest cumulative percent of API release after 1 hour (Table II & Table III). This formulation also demonstrated a higher dissolution rate (76%) than pure IVM (26%) and three commercial IVM products designated by A 51% (Std. dev. = 0.53), B 56% (Std. dev. = 1.71), and C 60% (Std. dev. = 0.0039) in distilled water after 60 minutes (Fig. 1).

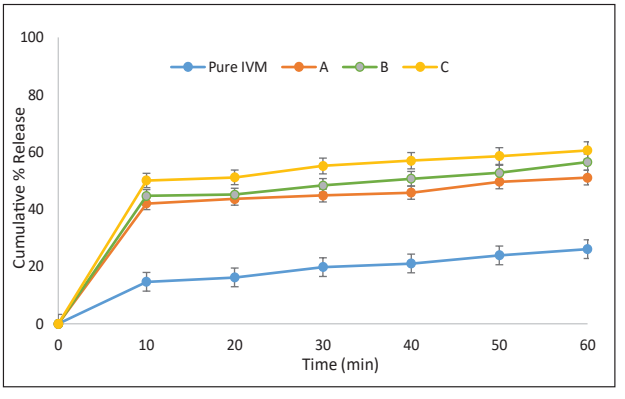

Fig. 1. Dissolution profile of pure IVM and comparison with three commercial products designated as A, B, and C in distilled water

The solid dispersion technique involves incorporating a drugwith limited water solubility into one or more hydrophilic carriers, resulting in the entanglement of the drug within the carrier matrix (Mikrani *et al.* 2022). Hydrophilic polymers like kollidon 90F, kollicoat IR can improve the dissolution profile of poor aqueous soluble drug lovastatin (Sarkar and Sharmin 2020). A higher release rate was observed for pitavastatin using poloxamer 407 and HPMC

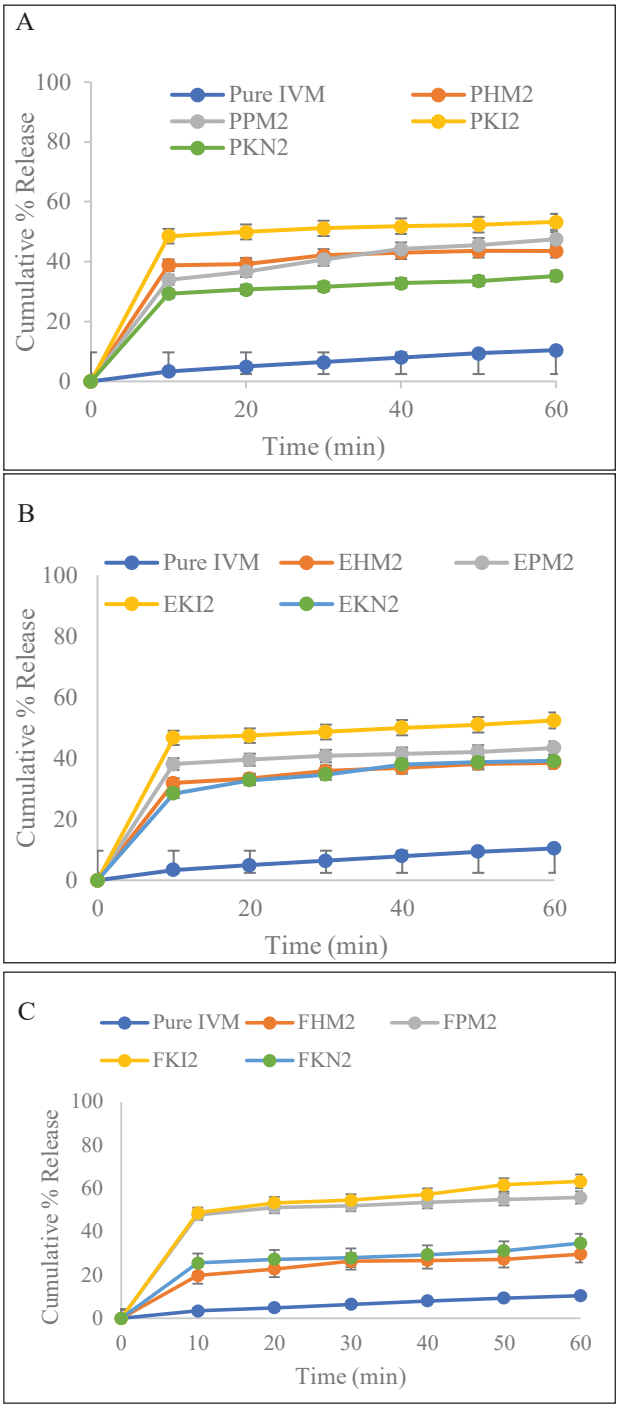

Fig. 2. Dissolution profiles of different methods (A) physical mixing (B) SDs by solvent evaporation (C) SDs by fusion method of different polymers at drug-polymer ratio 1:2. Each value represents the mean ±SD (n = 3)

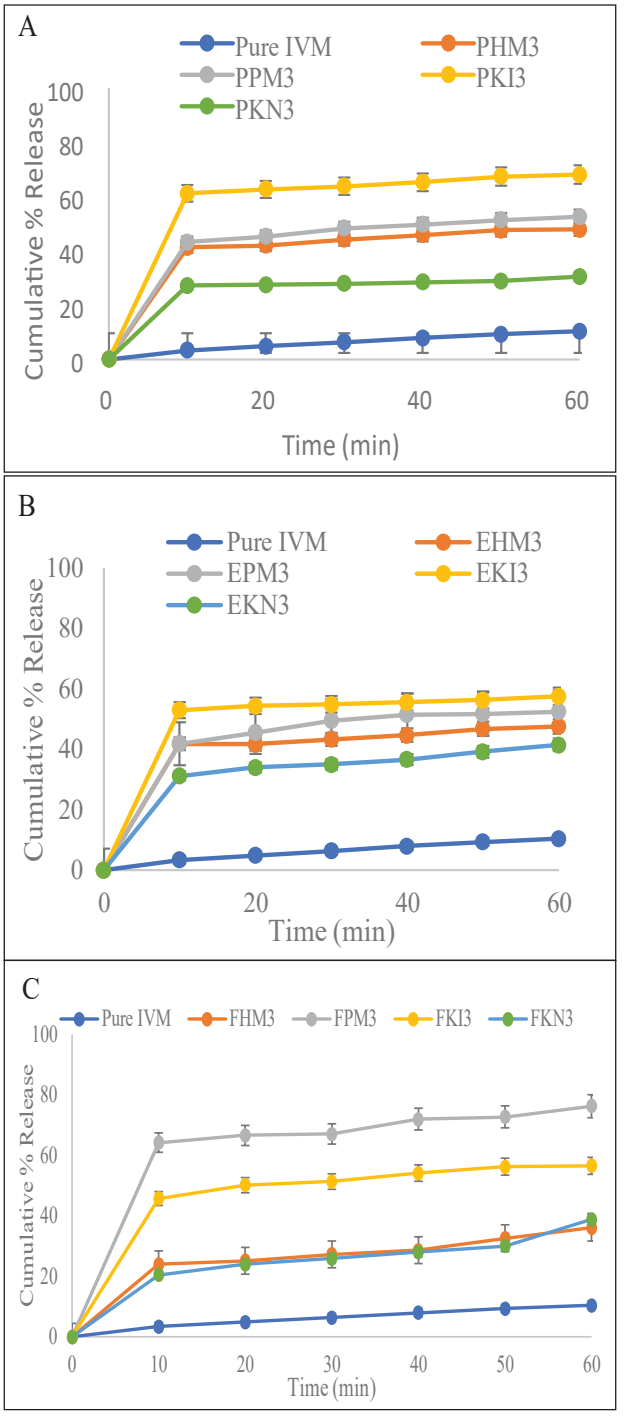

Fig. 3. Dissolution profiles of different methods (A) physical mixing (B) SDs by solvent evaporation (C) SDs by fusion method of different polymers at drug-polymer ratio 1:3. Each value represents the mean ±SD (n = 3)

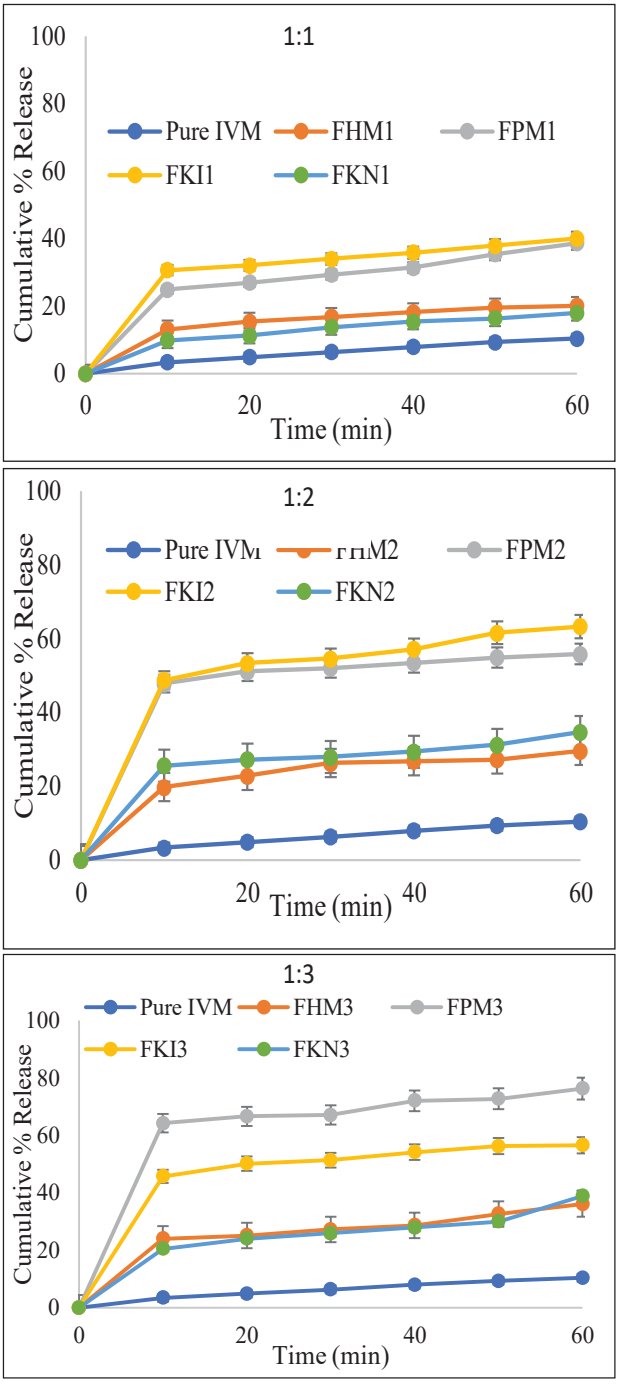

Fig. 4. Dissolution profiles of different weight ratios (1:1, 1:2, 1:3) of drug: poloxamer manufactured by fusion method in 0.1 N HCl. Each value represents the mean ±SD (n = 3)

(Mikrani *et al.* 2022). Several variables can contribute to the enhanced dissolution of pharmaceuticals from drug carrier systems. Higher wettability and dispersibility might be attributed to improvement, as suggested by the dissolving data of physical mixture. When a hydrophobic medicine is dry-mixed with a hydrophilic carrier, the available surface area for dissolution increases, leading to a decrease in the interfacial tension between the hydrophobic drugs and the dissolving media (Modi and Tayade, 2006).

These findings of the study suggest that the improved SD dissolution may be attributed to improved wettability of the drug by the carrier, drug particle size reduction during the preparation of the solid dispersion, improvement in surface area, higher degree of porosity, and polymorphic transformation of the drug to amorphous form (Saffoon *et al.* 2011; Vasconcelos *et al.* 2007).

Release kinetics

Drug release from IVM: Poloxamer 407 (1:3) fusion method SD follows zero order kinetics. n Value from Krosmeyer Peppas model is less than 0.45 indicates that the drug release mechanism is Quasi Fickian diffusion (Table II).

Physicochemical properties

Fourier transform infrared (FTIR) spectroscopy

An FTIR spectroscopy study was done to find out if there were any physical or chemical interactions between IVM and polymers in solid dispersion formulations. The prominent peaks of Ivermectin were observed at 3477 cm^{-1} due to (-OH stretching), a peak at 2938 cm^{-1} due to (C-H stretching), and a peak at 1734 cm^{-1} due to (C=O stretching) to the carbonyl group (Fig. 7), which is almost similar to the previous FTIR study of Ivermectin conducted (Dos Santos Moreira *et al.* 2018). The physical mixture of the drug and poloxamer showed that the major peaks at higher frequencies had no significant changes (Fig. 7A). This indicates that the overall symmetry of the structure of the formulation might not be significantly changed. In the case of the fusion method formulation, FPM3 broadening of the peak was observed in the (C-H stretching) region (Fig. 7B), which may be due to the presence of a greater number of (C-H) groups in the PEG. However, other peaks related to (-OH stretching) and (C=O stretching) remain unchanged (Fig. 7B). This also indicates that the overall symmetry of the structure of the formulation remained the same; no major additional reactions or bindings between functional groups occurred.

DSC analysis

Fig. 8 represents differential scanning calorimetry of pure IVM, Poloxamer 407, PM, and SD. The DSC curve of pure IVM displayed an endothermic peak at 150.5°C–155.5°C

Table II. Release kinetics of (Drug: Poloxamer=1:3) Fusion method

Name of Polymer (Fusion Method)	Ratio	Zero Order		First Order		Higuchi Model		Hixson Crowell Model		Korsmeyer Peppas Model		
		R^2	K_0	R^2	K_1	R^2	K_h	R^2	K_{HC}	R^2	n	k
HPMC	1:1	0.9679	0.1400	0.9716	-0.0016	0.9941	1.5612	0.9704	-0.0025	0.9825	0.2567	0.0676
	1:2	0.9111	0.1796	0.9166	-0.0023	0.9530	2.0209	0.9155	-0.0034	0.9901	0.2501	0.1067
	1:3	0.9540	0.2412	0.9444	-0.0035	0.8941	2.5699	0.9477	-0.0047	0.9058	0.1946	0.1511
Poloxamer	1:1	0.9837	0.2745	0.9763	-0.0039	0.9421	2.9554	0.9789	-0.0055	0.9402	0.2839	0.1121
	1:2	0.9554	0.1516	0.9649	-0.0032	0.9852	1.6941	0.9619	-0.0038	0.9467	0.0890	0.3894
	1:3	0.9592	0.2387	0.9501	-0.0081	0.9269	2.5819	0.9538	-0.0083	0.9229	0.1053	0.4883
Kallicoat	1:1	0.9959	0.1894	0.9931	-0.0030	0.9653	2.0522	0.9942	-0.0039	0.9088	0.1398	0.2225
	1:2	0.9767	0.2854	0.9767	-0.0067	0.9694	3.1288	0.9773	-0.0077	0.9315	0.1460	0.3461
	1:3	0.9414	0.2151	0.9520	-0.0044	0.9758	2.4096	0.9487	-0.0054	0.9793	0.1740	0.2811
Kollidon	1:1	0.9838	0.1649	0.9859	-0.0018	0.9865	1.8172	0.9852	-0.0028	0.9769	0.3867	0.0378
	1:2	0.9403	0.1685	0.9310	-0.0023	0.8842	1.7985	0.9342	-0.0033	0.9004	0.1587	0.1756
	1:3	0.9019	0.3205	0.8782	-0.0046	0.8500	3.4237	0.8864	-0.0063	0.8177	0.2937	0.1027

Table III. Release kinetics of Solvent Evaporation

Name of Polymer (Solvent Evaporation)	Ratio	Zero Order		First Order		Higuchi Model		Hixson Crowell Model		Korsmeyer Peppas Model		
		R^2	K_0	R^2	K_1	R^2	K_h	R^2	K_{HC}	R^2	n	k
HPMC	1:1	0.9559	0.0857	0.9549	-0.0012	0.9330	0.9755	0.9035	-0.0011	0.9006	0.0907	0.1986
	1:2	0.9501	0.1393	0.9541	-0.0021	0.9764	1.5533	0.9395	-0.0026	0.9708	0.1132	0.2426
	1:3	0.9471	0.1299	0.9459	-0.0023	0.8942	1.3886	0.9685	-0.0018	0.8125	0.0764	0.3410
Poloxamer	1:1	0.9538	0.1329	0.9491	-0.0018	0.9194	1.4363	0.9585	-0.0019	0.8844	0.1165	0.2063
	1:2	0.9853	0.0993	0.9873	-0.0016	0.9930	1.0964	0.9943	-0.0017	0.9761	0.0687	0.3234
	1:3	0.8710	0.2089	0.8829	-0.0039	0.9371	2.3844	0.865	-0.0023	0.9714	0.1325	0.3095
Kallicoat	1:1	0.9859	0.0888	0.9851	-0.0014	0.9630	0.9654	0.9907	-0.0016	0.9182	0.0746	0.2512
	1:2	0.9930	0.1163	0.9911	-0.0023	0.9620	1.2601	0.9745	-0.0015	0.9058	0.0635	0.3973
	1:3	0.9802	0.0843	0.9805	-0.0018	0.9740	0.9251	0.9428	-0.0012	0.9459	0.0424	0.4782
Kallidon	1:1	0.9953	0.2036	0.9942	-0.0025	0.9796	2.2226	0.9898	-0.0053	0.967	0.2984	0.0691
	1:2	0.9098	0.2133	0.9192	-0.0032	0.9622	2.4136	0.9441	-0.0032	0.9838	0.1859	0.1863
	1:3	0.9835	0.1961	0.9806	-0.0030	0.9603	2.1326	0.9632	-0.0026	0.9316	0.1490	0.2172

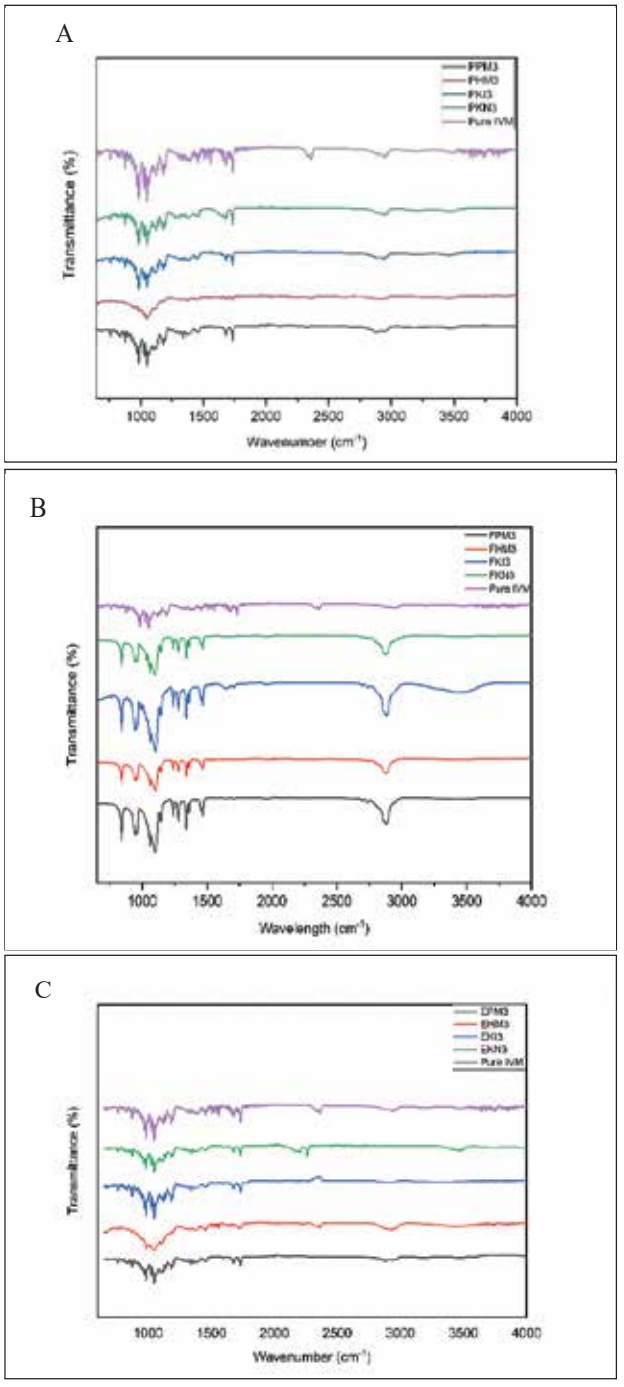

Fig. 5. FTIR analysis of IVM with polymers Poloxamer 407, HPMC, Kollicoat IR, Kollidon 90F by Physical mixing method (A), IVM with polymers Poloxamer 407, HPMC, Kollicoat IR, Kollidon 90F by Fusion method (B), IVM with polymers Poloxamer 407, HPMC, Kollicoat IR, Kollidon 90F by Solvent evaporation method (C)

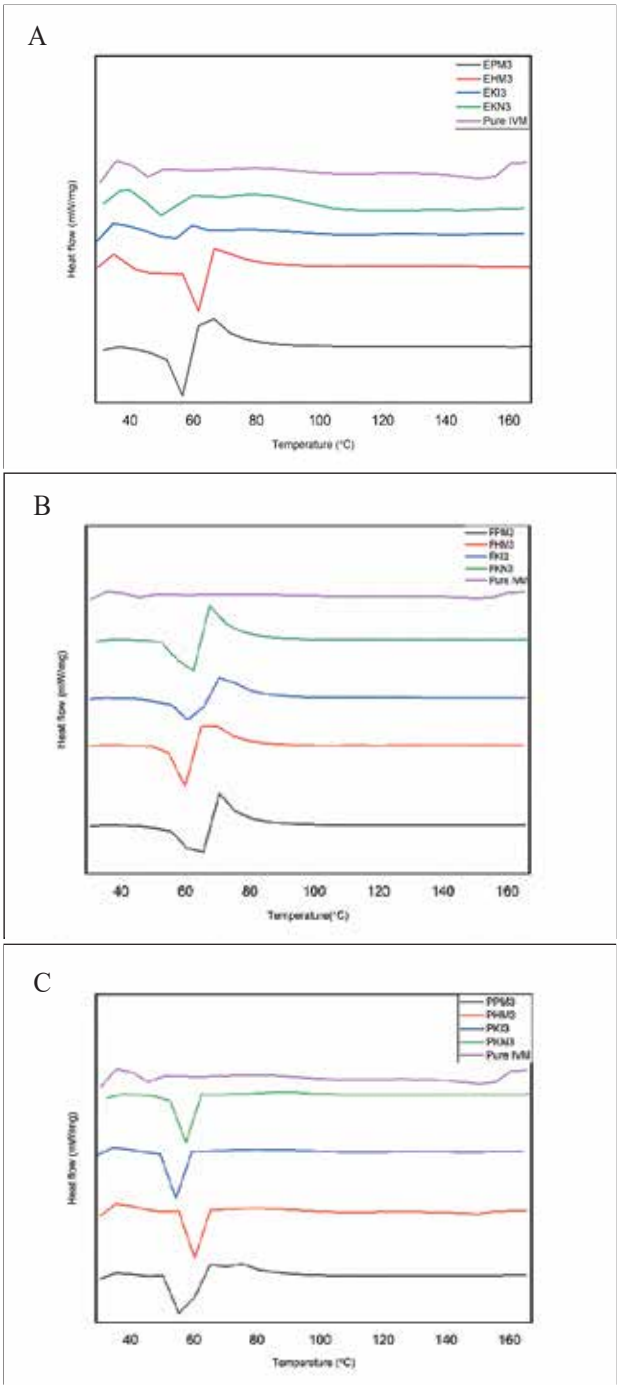

Fig. 6. DSC analysis of IVM with polymers Poloxamer 407, HPMC, Kollicoat IR, Kollidon 90F by Physical mixing method (A), IVM with polymers Poloxamer 407, HPMC, Kollicoat IR, Kollidon 90F by Fusion method (B). IVM with polymers Poloxamer 407, HPMC, Kollicoat IR by solvent evaporation method (C)

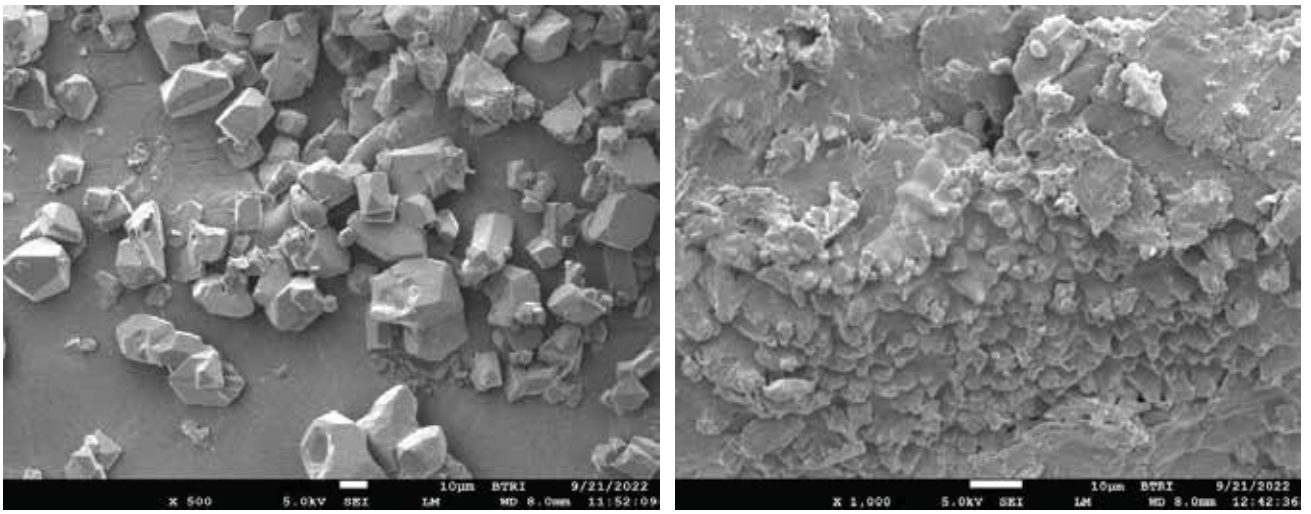

Fig. 7. Scanning electron microscopic analysis of (A) pure IVM, (B) IVM with poloxamer prepared by fusion method (FPM3)

due to its melting point. The DSC curve of a previous study showed that the melting point of the polymer Poloxamer 407 is 149.5°C (Rani *et al.* 2015; Sikdar *et al.* 2021). Endothermic peak of FPM3 in the range of 55.5-60.5°C indicates that the melting point decreased compared to pure IVM. The endothermic peak of FPM3 in the range of 55.5°C to 60.5°C indicates that the melting point decreased compared to pure IVM. The decreasing melting point compared to pure IVM indicates that the crystallinity form of the formulation may be changed. As a result of the transition of the IVM crystal structure to an amorphous state, the peaks of pure IVM in the DSC curve of the SD formulation dissipated (Verma *et al.* 2021).

Fig 6. DSC analysis of IVM with polymers Poloxamer 407, HPMC, Kollicoat IR, Kollidon 90F by Physical mixing method (A), IVM with polymers Poloxamer 407, HPMC, Kollicoat IR, Kollidon 90F by Fusion method (B). IVM with polymers Poloxamer 407, HPMC, Kollicoat IR by solvent evaporation method (C)

Scanning Electron Microscopy:

SEM analysis has been used to investigate the morphological characteristics of the pure IVM, PMs, and SDs. The SEM study showed that the API (Pure IVM) particle shape is crystal-like (Fig. 9A). The uniform dispersion of the FPM3 formulation of IVM with poloxamer produced using the fusion process revealed that the API molecules were evenly distributed in the carrier (Fig. 9B). In this solid dispersion, formulation decreased crystallinity and transformed into an amorphous state.

Conclusion

The study performed here revealed that the crystallinity of water-insoluble IVM can be modified by dispersing the drug into hydrophilic carriers such as Kollidon 90F, Kollicoat IR, poloxamer 407, and HPMC. This study also showed that using the SD approach, especially the fusion method with various hydrophilic polymers, the dissolution rate of poorly soluble IVM could be significantly improved. The optimal IVM to polymer ratio was determined to be 1:3, and the study revealed that poloxamer is a possible drug carrier for the IVM SD method to enhance the dissolution of pure IVM (Table II). Data from FTIR, DSC, and SEM further validated these formulations' physicochemical stability and amorphous properties. These results may help to develop more sophisticated and efficient methods to boost the release of IVM and other drugs with poor water solubility. To validate the outcomes of an enhanced *in vitro* dissolution rate of IVM as well as the oral bioavailability of IVM SD formulations, *in vivo* studies will be essential to be conducted in the future.

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