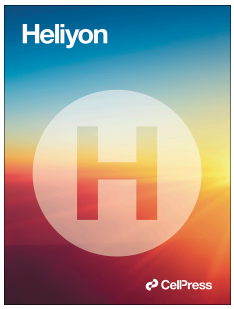

Deciphering the Role of Plasticizers and Solvent Systems in Hydrophobic polymer coating on Hydrophilic core

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Title

Deciphering the Role of Plasticizers and Solvent Systems in Hydrophobic polymer coating on Hydrophilic core

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Abstract

The type of plasticizer and the choice of solvent or co-solvents used for coating of a hydrophilic core can greatly impact the permeability, porosity, and mechanical strength of the polymer film. Although, Ethylcellulose (EC) is an old polymer, it is a polymer of choice for modifying the drug release due to its inherent properties. The ability of polymers like EC alone to form a diffusion-controlling membrane with good mechanical properties is limited. To modulate the drug release as per the desired profile and modify the film properties, ethylcellulose is often used with hydrophilic hypromellose (HPMC) along with plasticizers. The main focus of the current study was the identification of an appropriate solvent system and plasticizer for the ethylcellulose-hypromellose polymer combination. The study evaluated the coating solution properties, the feasibility and efficiency of the process, the physical attributes of the tablet, the surface properties of the polymer film, the in-vitro drug release and behavior, and the impact of curing time on surface properties and drug release, among other factors.

The isopropyl alcohol-water mixture (9:1) produced a homogeneous film in comparison to films produced by other solvents. Although both hydrophilic and hydrophobic plasticizers produce homogeneous films, hydrophilic plasticizers have a higher rate of drug diffusion than hydrophobic plasticizers. During the tablet curing and stability study, the drug release from the polymeric film coating with triethyl citrate decreased moderately and with polyethylene glycol decreased significantly. The presence of hydrophobic plasticizers, viz., dibutyl sebacate and acetyl tributyl citrate, in the polymeric film coating does not impact drug release. For the combination of ethylcellulose and hypromellose, it was found that a mixture of isopropyl alcohol and water (9:1) worked better as a solvent for coating solutions, and hydrophobic plasticizers lower the risk associated with coating ethylcellulose and hypromellose together.

Keywords

Ethylcellulose, hypromellose, controlled-release; reservoir system, plasticizer, polymer coating, dibutyl sebacate, acetyl tributyl citrate, triethyl citrate, polyethylene glycol

1. Introduction

2. The discovery of a new chemical entity (NCE) has become more difficult in recent scenarios due to its complexity, stringent regulations, and lack of financing. Pharmaceutical companies target the development of new dosage forms for existing molecules depending on the scope of the development, like improving the bioavailability, delivery system, fixed-dose combinations, etc. Due to this, pharmaceutical companies have taken a strong interest in the controlled-release (CR) dosage formulations due to their potential clinical benefits (1). It also has commercial and industrial advantages like the illustration of innovative and technological leadership, product life-cycle extension, product differentiation, market expansion, patent extension, etc. (2).
3. Polymer coating (reservoir system) is commonly used for developing solid oral CR dosage forms containing hydrophilic cores. In these systems, a thin polymer film coat is formed on the surface of a solid dosage form (3). By selecting a suitable polymer and making an optimal choice of pore former, the rate, extent, and site of the gastrointestinal drug release can be influenced (4). Many polymers with different characteristics are available to select for the development of reservoir-controlled release dosage forms of the desired drug release profile. Amongst them, ethyl-cellulose (EC), though old, is an ideal polymer for modifying the drug release due to its inherent properties. The polymer has to form a uniform, continuous film on the surface of the core. It is practically insoluble in water at any pH that occurs in the gastrointestinal tract and is generally used with organic solvents for coating. As the ability of ethyl-cellulose alone to form a diffusion-controlling membrane with good mechanical properties is limited, it is rarely used alone for controlling the drug release, and it is often used along with the hydrophilic polymers like hypromellose (HPMC) to enhance the permeability of the films or form the pores needed to modulate and to achieve the desired drug release (5). The selection of solvent system and the plasticizer are equally important to achieve the appropriate, robust and stable polymeric film for the CR dosage forms (6).
4. Suitable solvent system is most important for polymer coating. The selection of the solvent system for the single polymer is comparatively easy as compared to the selection for the combination of polymers with different solubility like EC and HPMC. EC and HPMC have different properties, including solubility. Ethylcellulose is hydrophobic, and hypromellose is a hydrophilic polymer (7, 8). EC is insoluble in water, soluble in ethanol (EOH), acetone, isopropanol (IPA), methanol (MeOH), and combinations of all (5). HPMC

is insoluble in chloroform, EOH and ether and soluble in cold water, in mixtures of EOH and dichloromethane (DCM), mixtures of MeOH and DCM, and mixtures of water and alcohol (8, 9).

5. The polymer or combinations thereof has to form a continuous and uniform coat over the tablet surface, which is based on their film forming properties. The polymer alone generally forms rigid, brittle and inflexible films. Plasticizers are added to the polymers to improve the film flexibility and plasticity. The plasticizers have the ability to interact with polymer chains and provide the desired flexibility (10). The mechanical properties, the surface characteristics, the minimal film forming temperature (MFT) can be altered with the use of different plasticizers (6, 11). The MFT is the lowest temperature required for film formation where coalescence of particles occurs on a core as a thin film. Polymer dispersions form an opaque, discontinuous film below MFT while, a clear homogeneous film at temperature above the MFT. However, polymer solutions can form a thin film even at room temperature (1, 12). They also play an important role in modulating drug release profiles due to their plasticizing effect. The selection of a plasticizer is critical for the stability of the dosage form, processing, and in vivo performance. There are several plasticizers which are used traditionally in ethylcellulose or hypromellose coating. Depending on the application it may not be the critical for the product performance for example the barrier coatings, seal coating or color film coatings (13). However, it plays significant role in the functional polymer coating as it is not only sufficient to form a good film but also yield a robust and stable formulation.
6. Factors such as plasticizer type and solvent or co-solvents may have a significant impact on the film permeability, porosity, and mechanical strength of the polymer film (14, 15). The proposed work was targeted to the coating of ethylcellulose-hypromellose polymer combination, the suitable solvent system for this combination, and the plasticizer suitable for coating of this polymer combination. Though there are several ways of classifying the plasticizers based on the physical nature, chemical structures, properties, etc. here, the plasticizers were selected based on their hydrophilic and hydrophobic nature for evaluation of their effect on coating. Polyethylene Glycol (PEG) and TEC were evaluated as hydrophilic plasticizers and DBS and Acetyltributylcitrate (ATBC) as hydrophobic plasticizers (16). Metformin Hydrochloride, a highly soluble drug as per the biopharmaceutical classification system (BCS) was selected as a model drug candidate. Thus the study evaluated effect of solvent system and type of plasticizer on coating of ethylcellulose-hypromellose polymer combination on metformin tablets.

7. Materials and Methods

2.1 Materials

Metformin HCl (grade: USP; manufacturer: USV), lactose monohydrate (grade: Pharmatose® 200M; manufacturer: DFE), povidone (grade: Kollidon® 30; manufacturer: BASF), colloidal silicon dioxide (grade: Aerosil 200 pharma; manufacturer: Evonik), magnesium stearate (grade: Ligamed MF-2-V; manufacturer: Petergreven), hypromellose (grade: AnycoatC AN-5; manufacturer: Lotte), ethylcellulose (grade: Ethocel Standard 10 Premium; manufacturer: Dupont), TEC (manufacturer: Vertellus), PEG (grade: Kollisolv® PEG 400; manufacturer: BASF), DBS (manufacturer: Vertellus), ATBC (manufacturer: Vertellus) was obtained from Centaur Pharmaceuticals. Hydrochloric acid (37 %), sodium hydroxide, potassium dihydrogen phosphate, disodium hydrogen phosphate, sodium acetate, glacial acetic acid of analytical grade (Emparta®; manufacturer: Merck).

2.2 Methods

2.2.1 Evaluation of solvent system for ethylcellulose and hypromellose

Although the solubility information is available as per the literature for the individual components, testing is performed to ensure which solvents are capable of yielding the polymer solution with the desired solid contents and a viscosity feasible for the tablet coating process.

- Solubility study:

For solubility evaluation, the below common procedure was used for each solvent or their combination.

Hypromellose: The solvent (95 g) was kept under stirring using a mechanical stirrer; hypromellose (5 g) was added to the solvent under stirring, which continued for 15 min. The resulting solution or dispersion (5% w/w) was observed physically (17).

Ethylcellulose: The solvent (95 g) was kept under stirring using a mechanical stirrer; ethylcellulose (5 g) was added to the solvent under stirring, which continued for 15 min. The resulting solution or dispersion (5% w/w) was observed physically.

Ethylcellulose and hypromellose: The solvent (95 g) was kept under stirring using a mechanical stirrer; ethylcellulose (2.5 g) and hypromellose (2.5 g) were added to the solvent under stirring, which continued for 15 min. The resulting solution or dispersion (5% w/w) was observed physically.

The proposed studies are targeted at the CR polymer coating stage. A constant core formulation was used throughout the study. The formulation was designed to contain the hydrophilic core containing the drug, the seal coating, and later the CR polymer coating. The process was developed as presented in Figure 1. Drug product development is discussed in the subsequent section.

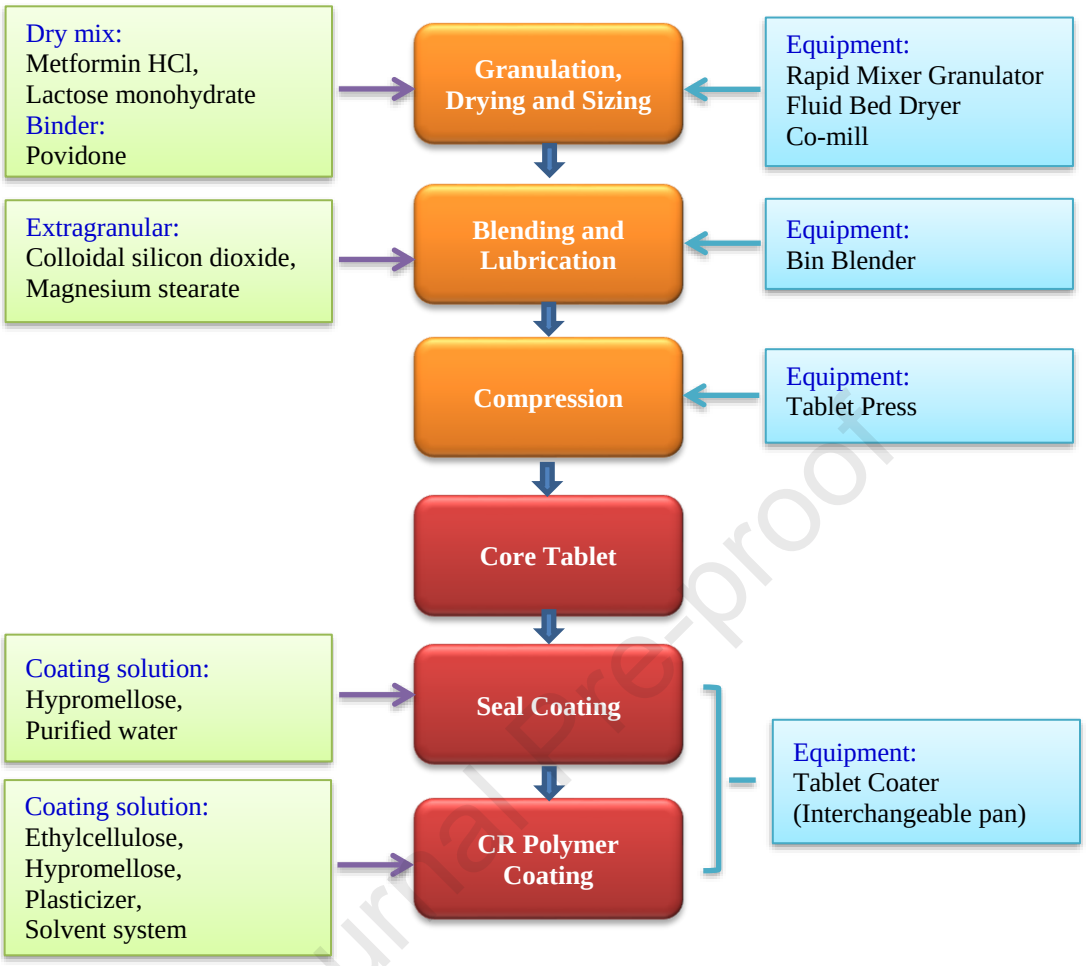

Figure 1. Process map

- Core development:

Tablet core contains Metformin HCl 50 mg per tablet. The dry mix comprising Metformin HCl (20% w/w) and lactose monohydrate (75% w/w) was granulated using an aqueous binder solution of povidone K30 (4% w/w) using a high shear rapid mixer granulator (model: lab-scale; capacity: 10 litres; make: Bectochem, India). Granules were dried in a fluid bed dryer (model: GPCG 1.1; capacity: 4.7 litres; make: ACG, India) at inlet temperature (55±5°C) till the moisture content of the granules reached below 1% using a moisture analyser (model: HB43-S; make: Mettler Toledo) at 105°C for 5 min. Dried granules were passed through a co-mill (model: lab-scale; make: Bectochem, India) fitted with a 1 mm grated screen at 1200 RPM, followed by the mixing with the glidant-colloidal silicon dioxide (0.5% w/w), and the lubricant- magnesium stearate (0.5% w/w) in a cage blender (model: lab-scale; capacity: 10 litres; make: Bectochem, India). Tablets were compressed using 8.2 mm round punches, and B-tooling tablet press (model: CMD4;

stations: 16; make: Cadmach, India) at a target tablet weight of 250 mg and a hardness 90±20 Newtons ensuring the friability below 1% w/w. The core tablet batch size was 10,000 units (18).

- Seal coating development:

The purpose of the seal coating was to smooth the core tablet surface and to act as a barrier between the drug core and the CR polymer coating. Core tablets from a batch size of 10,000 units were divided into 2 parts and the seal coating was carried out in 2 lots. Core tablets were loaded into the tablet coater (model: Quest TC; capacity: 2.5 liters; ACG, India) having perforated pan and the core tablets were seal coated with an 8% w/w aqueous solution of hypromellose (viscosity grade - 5 cps) up to 3±0.5% w/w weight gain. Process parameters for the seal coating were inlet temperature (60±10°C), exhaust temperature (45±5°C), pan speed (4 – 13 rpm), atomization air pressure (1.0 Kg/cm^2), spray rate (6 – 11 g/min.), nozzle diameter (0.8 mm), differential pressure (-5 to -10 mm of water), and the drying temperature (50°C) for 15 min. Seal-coated tablets obtained from the 2 lots were mixed together and used further (19, 20).

- Dissolution method development:

The dissolution method was developed in parallel with the prototype formulation development to achieve the most discriminatory dissolution method. It started with the determination of drug solubility studies and solution stability at 37 ± 1°C in aqueous media with a pH in the range of 1 - 6.8 using the shake-flask method. Depending on the solubility, the solution stability, and the ability to maintain the sink condition, the dissolution medium and volume were selected. The dissolution apparatus and the agitation speed with discriminatory power were selected for evaluating the *in vitro* drug release profile (16).

- CR polymer coating: effect of solvent system:

Solubility of the polymers is depending on the ratio of the polymers, the ratio of solvents, and the solid contents. As four solvent mixtures were found suitable to dissolve the polymers, four different trials were taken with these mixtures while keeping the polymer and plasticizer type and level constant, refer Table 1.

Table 1. Formulations with different solvent system

Ingredients	Formulation No.			
	F1 [MET/040]	F2 [MET/045]	F3 [MET/050]	F4 [MET/051]
	Quantity (mg/tablet)			
Seal-coated tablet	257.500	257.50	257.50	257.50
Ethylcellulose (viscosity grade – 10 cps)	17.961	17.961	17.961	17.961
Hypromellose (viscosity grade – 5 cps)	17.961	17.961	17.961	17.961
Dibutyl Sebacate	2.704	2.704	2.704	2.704
Isopropyl Alcohol	Q.S.	Q.S.	--	--
Ethanol	--	--	Q.S.	--.
Methanol	--	--	--	Q.S.
Dichloromethane	--	Q.S.	Q.S.	Q.S.
Purified water	Q.S.	--	--	--
CR polymer-coated tablet weight	296.125	296.125	296.125	296.125
% Coating	15% w/w	15% w/w	15% w/w	15% w/w

Solvent ratio and % solution:
F1:- Isopropanol: Water in 90:10 ratio to prepare 5% solution.
F2:- Isopropanol: Dichloromethane in 50:50 ratio to prepare 5% solution.
F3:- Ethanol: Dichloromethane in 50:50 ratio to prepare 5% solution.
F4:- Methanol: Dichloromethane in 50:50 ratio to prepare 5% solution.

Coating solution preparation (5% w/w): Dispensing of all the raw materials was done considering the batch size 1300 units with 50% w/w excess quantity to compensate process losses.

Trial F1 (MET/040): IPA was kept under constant stirring to form a vortex. Hypromellose was added to the IPA while stirring to form a uniform dispersion. Purified water was added immediately to the hypromellose dispersion to get a clear solution. Ethylcellulose, followed by DBS, was added to the hypromellose solution and stirred for a minimum of 60 min. before going for the tablet coating. It forms a clear solution.

Trial F2 – F4 (MET/045, MET/050, and MET/051): The solvent mixture was kept under constant stirring to form a vortex. Ethylcellulose and hypromellose were added to the solvent while stirring to form a clear solution. DBS was added to the solution and stirred for a minimum of 60 min. before going for the tablet coating. It forms a clear solution. The sub-coated tablets were loaded in coating pan by keeping inlet damper 'Off' and exhaust blower 'On'. Tablets were pre-warmed followed by the spraying of coating dispersion on the rolling tablets with the coating parameters tabulated below till required weight gain is achieved. After target weight gain achieved, drying was done at inlet

temperature of 45 ºC and pan running at 4 rpm for 15 min. At the end, tablets were allowed to cool with inlet blower 'Off' and exhaust blower 'On' with pan speed 4 rpm. Process parameters for the CR polymer coatings are presented in Table 2.

Table 2. CR polymer coating process parameters

-	**F1 [MET/040]**	**F2 [MET/045]**	**F3 [MET/050]**	**F4 [MET/051]**
Equipment	Tablet coater			
Model	Quest TC			
Make	ACG, India			
Capacity	0.8 Liters			
Pan load	1300 units (335 g)			
Parameters	Limits			
Preheating:				
Inlet temperature	45±5°C	33±3°C	33±3°C	33±3°C
Exhaust temperature	33±3°C	28±2°C	28±2°C	28±2°C
Pan speed	3 rpm	3 rpm	3 rpm	3 rpm
Spraying:				
Inlet temperature	45±5°C	33±3°C	33±3°C	33±3°C
Exhaust temperature	33±3°C	28±2°C	28±2°C	28±2°C
Pan speed	3 – 24 rpm	3 – 24 rpm	3 – 24 rpm	3 – 24 rpm
No. of spray guns	1 No.	1 No.	1 No.	1 No.
Spray rate	5 – 8 g/min.	5 – 8 g/min.	5 – 8 g/min.	5 – 8 g/min.
Atomization air pressure	0.8 Kg/cm^2	0.8 Kg/cm^2	0.8 Kg/cm^2	0.8 Kg/cm^2
Spray nozzle diameter	0.5 mm	0.5 mm	0.5 mm	0.5 mm
Pan differential pressure (ΔP)	-5 to -10 mm of water	-5 to -10 mm of water	-5 to -10 mm of water	-5 to -10 mm of water
Drying:				
Inlet temperature	45°C	45°C	45°C	45°C
Pan speed	3 rpm	3 rpm	3 rpm	3 rpm
Time	15 min.	15 min.	15 min.	15 min.

After completion of the coating, coating efficiency was calculated using the equation below.

$$\text{Coating efficiency } (\%) = \frac{\text{a } x \text{ b}}{\text{c } x \text{ d}} \; x \; 100$$

Where, a is the theoretical quantity of solution to be sprayed to achieve the target weight gain, b is the actual weight gain achieved, c is the actual quantity of solution sprayed to achieve the target weight gain and d is the theoretical target weight gain.

Coated tablets were evaluated for the physical attributes, film surface properties through SEM followed by the in vitro drug release using the discriminatory dissolution method.

2.2.2 Evaluation of plasticizer for ethylcellulose-hypromellose combination:

PEG is soluble in water, acetone, DCM, EOH and MeOH. TEC is soluble in water, miscible in acetone, alcohols and EOH. DBS is insoluble in water, soluble in EOH and IPA. ATBC is insoluble in water, miscible with acetone and EOH.

To evaluate the effect of plasticizer, different trials were taken with changing only plasticizers and keeping the polymer and solvent system constant. The plasticizer level was 7% in the total weight build-up, remaining ethylcellulose and hypromellose polymer with 50:50 ratios in the IPA-water with 90:10 solvent ratios. Composition is given in Table 3.

Table 3. CR-polymer coating composition with different plasticizers

Ingredients	**Formulation No.**			
	F5 [MET/040]	**F6 [MET/041]**	**F7 [MET/042]**	**F8 [MET/043]**
	Quantity (mg/tablet)			
Seal-coated tablet	257.500	257.50	257.50	257.50
Ethylcellulose (viscosity grade – 10 cps)	17.961	17.961	17.961	17.961
Hypromellose (viscosity grade – 5 cps)	17.961	17.961	17.961	17.961
Dibutyl sebacate	2.704	--	--	--
Polyethylene glycol 400	--	2.704	--	--
Acetyl tributyl citrate	--	--	2.704	--
Triethyl citrate	--	--		2.704
Isopropanol	Q.S.	Q.S.	Q.S.	Q.S.
Purified water	Q.S.	Q.S.	Q.S.	Q.S.
CR polymer-coated tablet weight	296.125	296.125	296.125	296.125

Dispensing of all the raw materials was done considering the batch size 1300 units with 50% w/w excess quantity to compensate process losses and to achieve 5% w/w coating solution. IPA was kept under constant stirring to form a vortex. Hypromellose was added to the IPA while stirring to form a uniform dispersion. Purified water was added immediately to the hypromellose dispersion to get a clear solution. Ethylcellulose, followed by plasticizer (different in each trial), was added to the hypromellose solution and stirred for a minimum of 60 min. before going for the tablet coating. It forms a clear solution. Sub-coated tablets were loaded in coating pan by keeping inlet damper 'Off' and

exhaust blower 'On'. Tablets were pre-warmed followed by the spraying of coating dispersion on the rolling tablets with the coating parameters tabulated below till required weight gain is achieved. After target weight gain achieved, drying was done at inlet temperature of 45 ºC and pan running at 4 rpm for 15 min. At the end, tablets were allowed to cool with inlet blower 'Off' and exhaust blower 'On' with pan speed 4 rpm. Process parameters for the CR polymer coatings are presented in Table 4.

Table 4. CR polymer coating process parameters

Equipment	Tablet coater
Model	Quest TC
Make:	ACG, India
Capacity	0.8 Liters
Pan load	1300 units (335 g)
Parameters	Limits
Preheating:	
Inlet temperature	45±5℃
Exhaust temperature	33±3℃
Pan speed	3 rpm
Spraying:	
Inlet temperature	45±5℃
Exhaust temperature	33±3℃
Pan speed	3 – 24 rpm
No. of spray guns	1 No.
Spray rate	5 – 8 g/min.
Atomization air pressure	0.6 Kg/cm^2
Spray nozzle diameter	0.5 mm
Pan differential pressure (ΔP)	-5 to -10 mm of water
Drying:	
Inlet temperature	45℃
Pan speed	3 rpm
Time	15 min.

After completion of the coating, coating efficiency was calculated using the equation discussed in previous section. Coated tablets were evaluated for the physical attributes, film surface properties through SEM followed by the in vitro drug release using the discriminatory dissolution method.

- Curing of the CR polymer-coated tablets comprising different plasticizers:

The curing of the CR polymer-coated tablets from each trial was performed in the dynamic conditions using the same perforated pan tablet coater (model: Quest TC; capacity: 0.8 liters; ACG, India). In experiment 1, the tablets were cured in tablet coater at 50℃ inlet temperature for 60 min. In experiment 2, tablets were cured at 60℃ inlet temperature and the sampling was done with the frequency of 60 min, 120 min, 180 min, and 240 min, respectively. All the samples were subjected for the drug release (21, 22).

- Stability study:

Batches with different plasticizer were packed in the blister using the polyvinyl chloride foil (250 µ) as a base and cold forming aluminium (25 µ) as the lidding foil using a blister packing machine (model: Ezee Blist; make: Mechtek, India). A sufficient number of blisters were loaded into the stability chambers at accelerated storage conditions (40 ± 2°C temperature and 75 ± 5% relative humidity) for up to 6 months. Dissolution testing was performed with a frequency of initial, 3 months, and 6 months, respectively (23).

8. Results and discussion

3.1 Solubility study

The observations from the solubility study were recorded as per the solubility classification in Indian Pharmacopoeia and are given in Table 5 below.

Table 5. Solubility of polymers in solvents (5% w/w concentration)

Sr. No.	Solvent system	Hypromellose	Ethyl cellulose	Ethylcellulose and Hypromellose
1	Ethanol	Insoluble	Soluble (Clear solution)	Insoluble
2	Methanol	Partially soluble	Soluble (Clear solution)	Insoluble
3	Acetone	Insoluble	Soluble (Clear solution)	Insoluble
4	Dichloromethane	Insoluble	Insoluble	Insoluble
5	Isopropanol	Insoluble	Soluble (Clear solution)	Insoluble
6	Water	Soluble (Clear solution)	Insoluble	Insoluble
7	Ethanol: Dichloromethane (50:50)	Soluble (Clear solution)	Soluble (Clear solution)	Soluble (Hazy Solution)
8	Methanol: Dichloromethane (50:50)	Soluble (Clear solution)	Soluble (Clear solution)	Soluble (Clear solution compare to Sr. No. 5 solution)
9	Isopropanol: Dichloromethane (50:50)	Soluble (Clear solution)	Soluble (Clear solution)	Soluble (Clear solution)

Sr. No.	Solvent system	Hypromellose	Ethyl cellulose	Ethylcellulose and Hypromellose
10	Isopropanol: Water (50:50)	Soluble (Clear solution)	Partially soluble	Insoluble
11	Isopropanol: Water (90:10)	Soluble (Clear solution)	Soluble (Clear solution)	Soluble (Clear solution)

Although ethylcellulose alone was soluble in many of the solvents, limited options were available for the ethylcellulose-hypromellose combination. There was no single solvent in which both ethylcellulose and hypromellose can be soluble. The polymer combination in the 50:50 ratio was soluble in the mixture of DCM with MeOH, EOH, and IPA in the 50:50 ratio. It was insoluble in the IPA and water mixture at a 50:50 ratio, but soluble at a 90:10 ratio.

3.2 Discriminatory dissolution method

Mean solubility of the Metformin HCl at 37 ± 1°C temperature was found to be 199 mg/ml in 0.1 N HCl, 167 mg/ml in pH 4.5 acetate buffer, 250 mg/ml in pH 6.8 phosphate buffer, and 200 mg/ml in purified water. The drug has high solubility; the sink condition can be maintained in 500 ml volume, allowing 3 times the unit dose (150 mg) to be comfortably dissolved in any medium. After evaluation of the analytical method, medium, apparatus, and agitation speed, a finalized discriminatory dissolution method was a type 2 (paddle) apparatus rotating at 50 rpm with 500 ml purified water. The drug release estimation method was UV spectrophotometry at λmax 233 nm (16).

3.3 Effect of solvent system:

The physical attributes of the CR polymer coating trials with different solvent system are tabulated in Table 6.

Table 6. Physical attributes of the CR polymer coating trials with different solvent system

Attributes	Formulation No.			
	F1 [MET/040]	F2 [MET/045]	F3 [MET/050]	F4 [MET/051]
Solution properties	Clear	Clear	Hazy	Clear
Processing feasibility	Feasible	Feasible	Feasible	Feasible
Process efficiency	84%	76%	67%	63%
Weight gain	14.6%	15.0%	14.8%	15.1%
Tablet physical properties	Smooth without defects	Smooth without defects	Smooth without defects	Smooth without defects
Average weight	293.9 mg	295.5 mg	296.3 mg	296.7 mg
Thickness	5.22 – 5.29 mm	5.27 – 5.32 mm	5.26 – 5.35 mm	5.24 – 5.32 mm

Coating process was feasible with all the solvent combinations studied. The coating efficiency was higher in formulation F1 (IPA-water) followed by the F2 (IPA-DCM) and lowest in F4 (IPA-MeOH). It could be due to the rapid evaporation of the solvent (DCM > MeOH > EOH) as compare to the IPA and water which results in the spray drying and poor efficiency.

All of the coated tablets from the trials were defect-free and had smooth surfaces. The drug release profile of the seal coated tablets was evaluated. It gives more than 85% drug release within 30 min time point and didn't had significant impact on the drug release. The results for drug release from subsequent coating s was also studied. The drug release results of all coating trials are given in Figure 2.

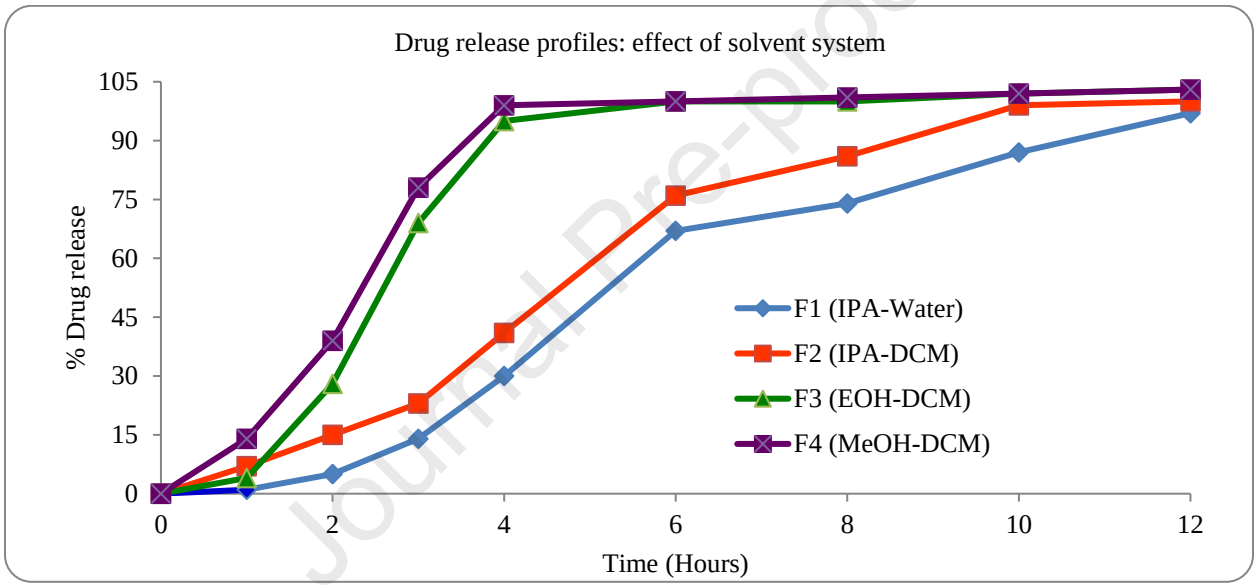

Figure 2. Drug release: CR polymer coating trials with different solvent system

There was significant difference in the drug release between the batches manufacturing using different solvent system. The formulation F1 (IPA-water) shown slowest drug release followed by the by the F2 (IPA-DCM). The formulation F3 (EOH-DCM) and F4 (MeOH-DCM) shown rapid and erratic drug release. Figure 3 showing the tablets before and after the dissolution study.

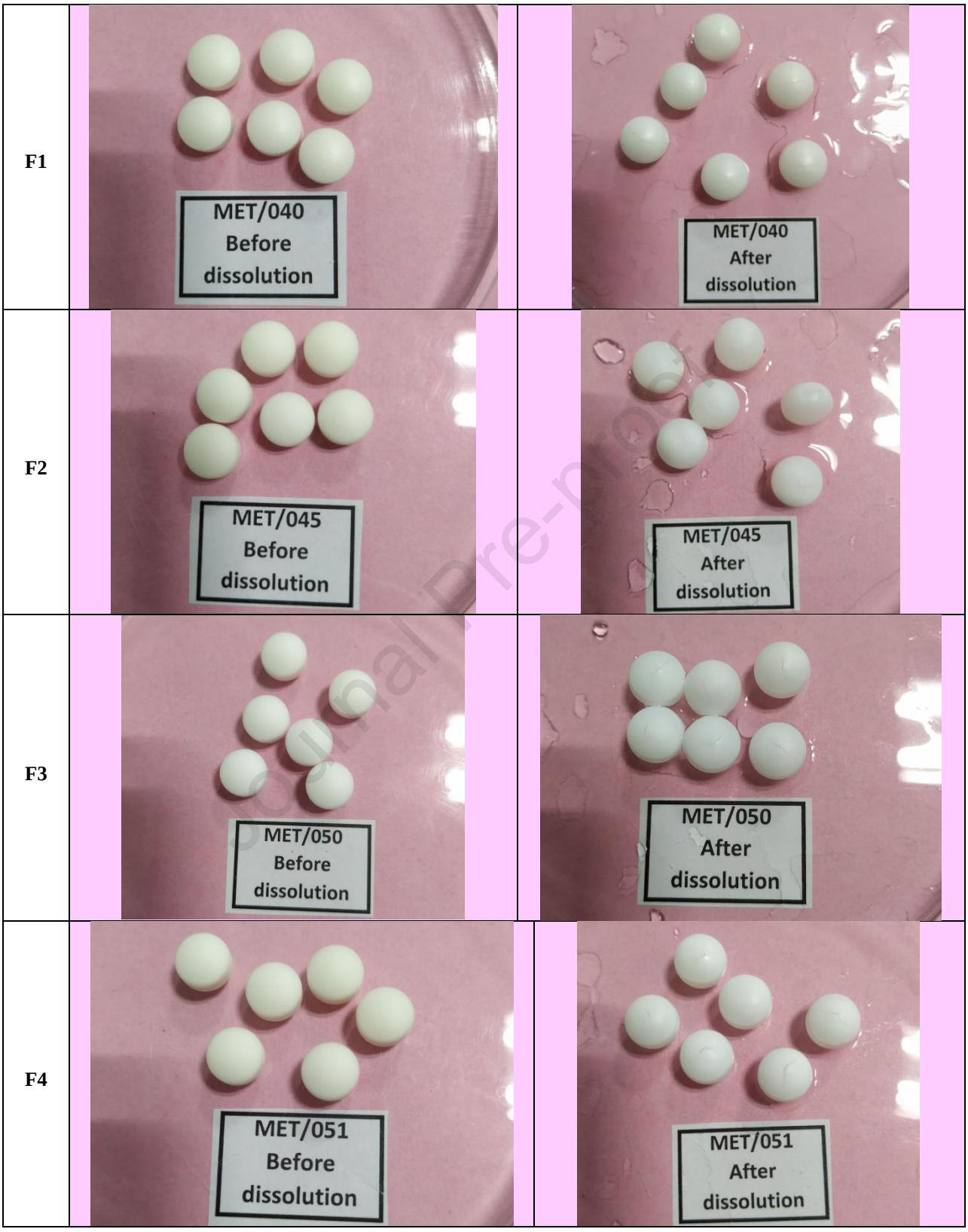

Figure 3. CR polymer coated tablets manufactured with different solvent system

The tablets from all the trials retained their shape and film until the end of the dissolution test. In all trials until the middle time points, the mechanism of drug release was diffusion, and later, from the ruptured film at the concave surface of the tablet.

To understand the difference in the film properties formed by the use of different solvent mixtures, coated tablets were analyzed by scanning electron microscopy (SEM). Figure 4 presents the SEM of the coated tablets.

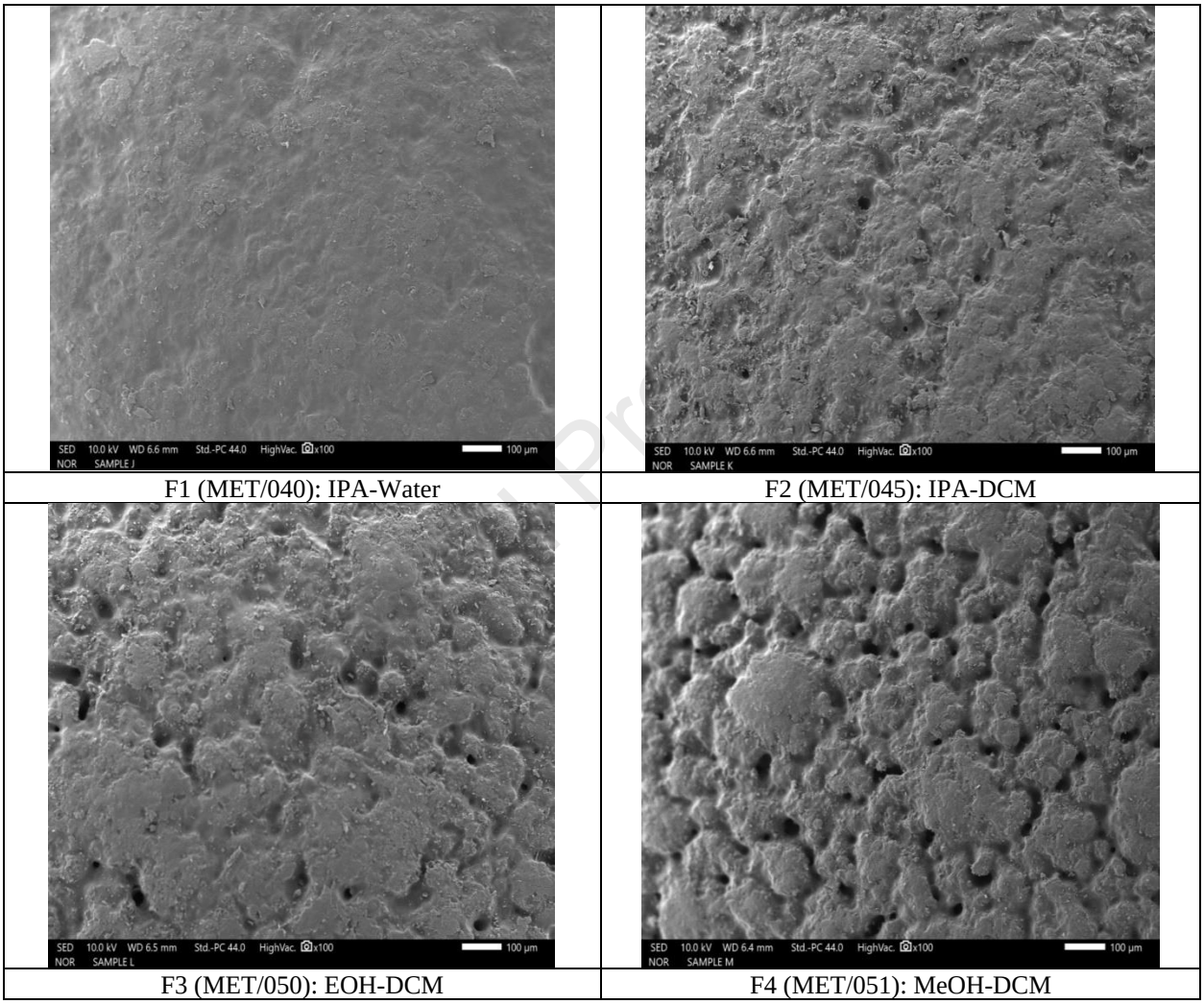

Figure 4. SEM of the CR polymer coating manufactured with different solvent system

There was a clear difference in the film properties as per the SEM analysis. The film formed by the use of the IPA-water mixture was homogeneous and without pores. The film formed by the other solvent combination had significant roughness and pores. It indicates the solvent system can alter the microstructure of the film, the mechanical strength, and the diffusivity. The stronger films are more uniform, have better mechanical properties, and have better control

over the drug release. The solvent system is presented below in terms of its performance in ethylcellulose-hypromellose polymer coating based on physical observations after dissolution, SEM, and drug release.

Table 8. Outcome of the evaluation of solvent system

Attributes	Solvent system			
	IPA-water	**IPA-DCM**	**EOH-DCM**	**MeOH-DCM**
Solution properties	*****	*****	*****	****
Processing feasibility	*****	*****	*****	*****
Process efficiency	*****	****	***	***
Film property	*****	****	***	**
Drug release control	*****	****	**	**

Based on the above evaluation, IPA-water was considered the best choice of solvent system for the ethylcellulose-hypromellose polymer coating intended for the tablet pan coating.

3.4 Evaluation of plasticizer for ethylcellulose and hypromellose

The physical attributes of the CR polymer coating trials with different plasticizers are tabulated in Table 9.

Table 9. Physical attributes of the CR polymer coating trials with different plasticizers

Attributes	Formulation No.			
	F5 [MET/040]	**F6 [MET/041]**	**F7 [MET/042]**	**F8 [MET/043]**
Solution properties	Clear	Clear	Clear	Clear
Processing feasibility	Feasible	Feasible	Feasible	Feasible
Process efficiency	84%	84%	86%	83%
Weight gain	15.6%	15.4%	15.1%	15.1%
Tablet physical properties	Smooth without defects	Smooth without defects	Smooth without defects	Smooth without defects
Average weight	293.9 mg	296.2 mg	296.0 mg	296.9 mg
Thickness	5.22 – 5.29 mm	5.25 – 5.34 mm	5.26 – 5.31 mm	5.22 – 5.33 mm

Coating process was feasible with all the plasticizers studied. The coating efficiency was almost comparable in all the trials. Coated tablets from all the trials were without any defects having the smooth surface. The coated tablets were analyzed for the drug release, results of all coating trials are given in Figure 5.

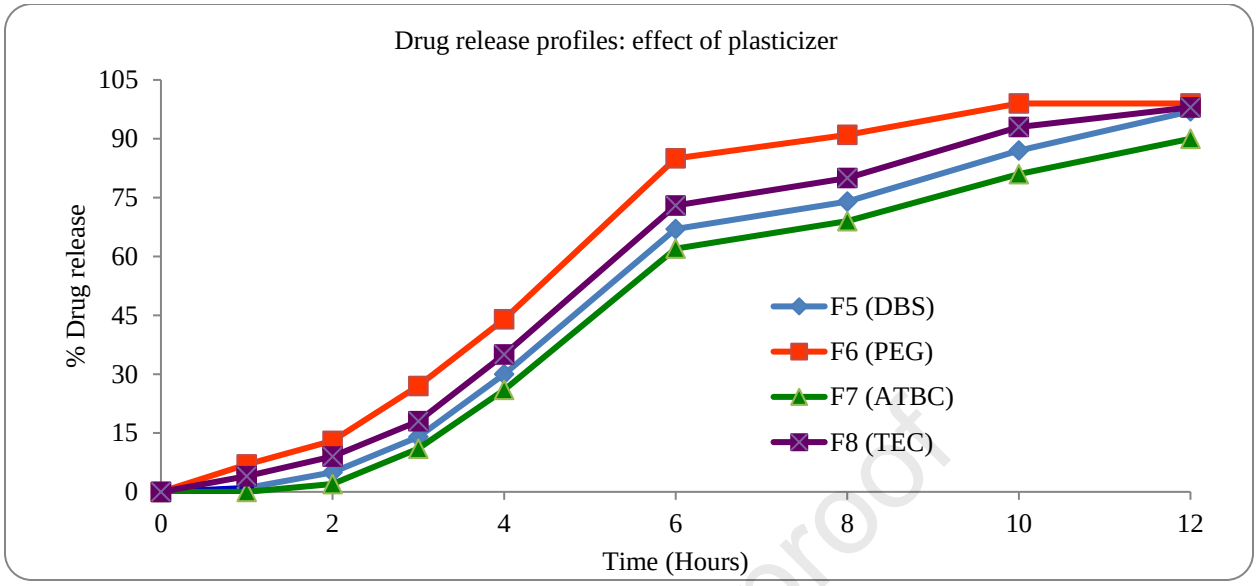

Figure 5. Drug release: CR polymer coating trials with different plasticizers

There was significant difference in the drug release between the batch with PEG as a plasticizer and other three (24). The formulation F6 (PEG) shown faster drug release. Figure 6 showing the tablets before and after the dissolution study.

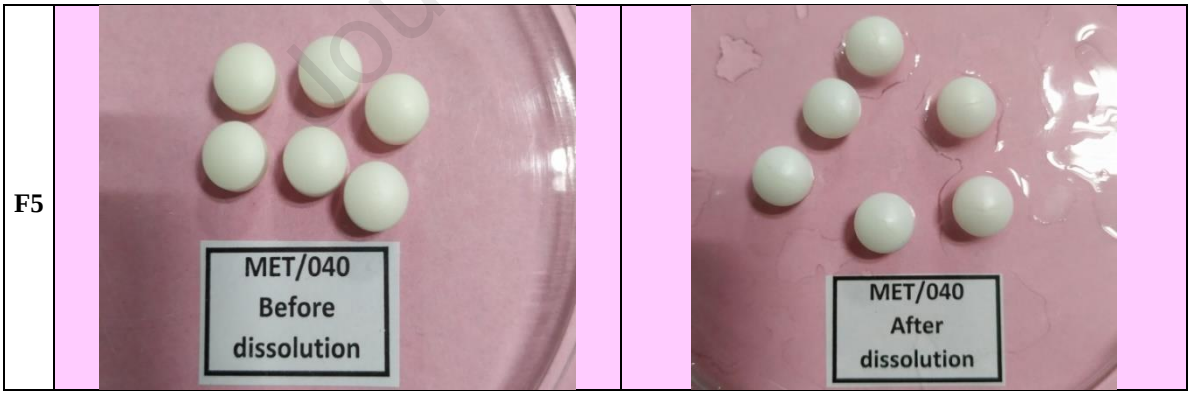

Figure 6. CR polymer coated tablets manufactured with different plasticizers

The formulations with hydrophobic plasticizers retain their shape and film till the end of dissolution test. The films were ruptured at the edges with the formulations with hydrophilic plasticizers at the end of dissolution test (25). The mechanism of drug release was diffusion in the trials with hydrophobic plasticizers; in the trials with hydrophilic plasticizers initially it was diffusion and later erosion of the core through the ruptured polymer film.

To understand the difference in the film properties formed by the use of different plasticizers, coated tablets were analyzed by scanning electron microscopy (SEM). Figure 7 presents the SEM of the coated tablets.

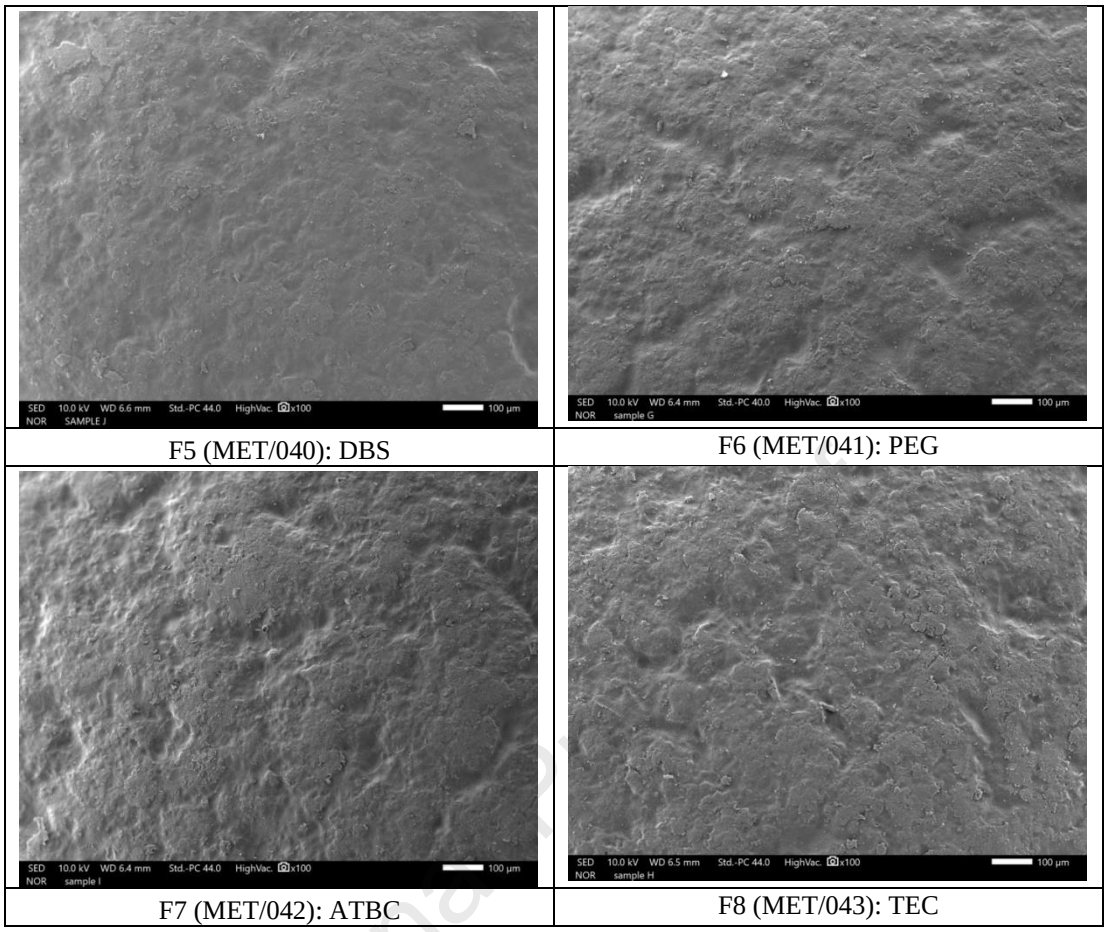

Figure 7. SEM of the CR polymer coating manufactured with different plasticizers

There was no significant difference in the film properties as per the SEM analysis. The film formed by the use of all plasticizers was homogeneous and without pores initially. The difference in the drug release is due to the water soluble plasticizers which enhance the permeability of the film to the solvent and accelerate the rate of diffusion (26). Generally, curing step is critical for the film coating with aqueous dispersion that involves the coalescence of colloidal particles to form a thin homogeneous film at suitable temperature conditions (27). Non-aqueous coatings with organic solvents contains the polymers in solution form which forms the film above MFT and considered the curing step is not required only the drying to remove the organic solvents is sufficient. However, it is assumed that the performance of the film in presence of the different plasticizers can change with the curing or aging of the formulation which later affects the in-vitro drug release. To study the effect of curing on the drug release, the batches with different plasticizers subjected to the different temperature and time period.

3.5 Effect of curing:

The drug release of the cured tablets comprising different plasticizers is presented in the tables and figures below. DBS (Figure 8A), PEG (Figure 8B), ATBC (Figure 8C) and TEC (Figure 8D).

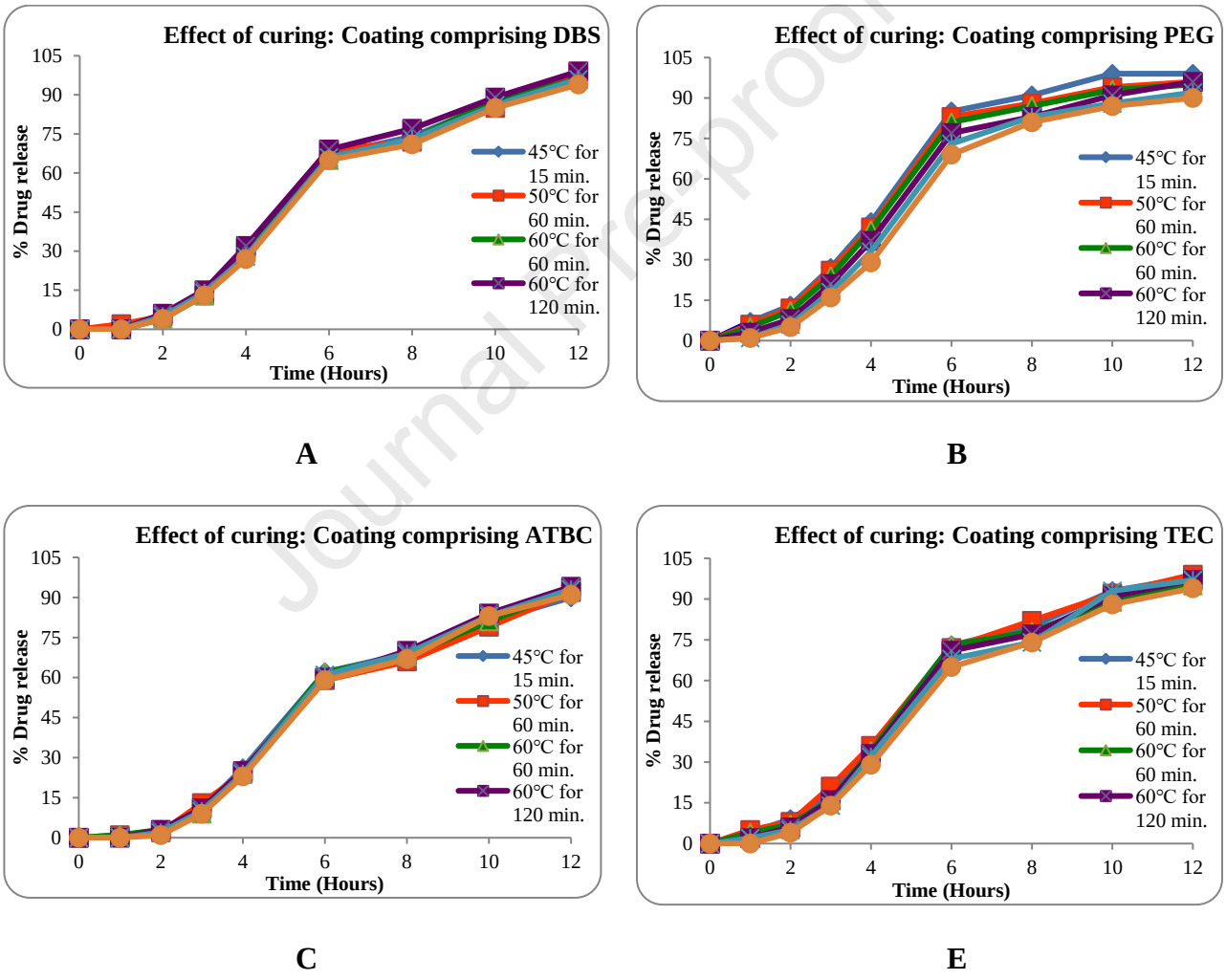

Figure 8. Drug release: CR polymer coating with A) DBS B) PEG C) ATBC and D) TEC as plasticizer

There was no significant effect of the curing over the drug release from the formulations containing DBS as a plasticizer. There was significant effect of the curing over the drug release from the formulations containing PEG as

a plasticizer. The rate of drug release was gradually decreased with increase in the curing temperature and the time (28-30). There was no significant effect of the curing over the drug release from the formulations containing ATBC as a plasticizer. There was moderate effect of the curing over the drug release from the formulations containing TEC as a plasticizer. The rate of drug release was gradually decreased with increase in the curing temperature and the time.

3.6 Stability study:

The dissolution results of the batches with different plasticizers during stability are presented in fig 12 (DBS), fig13 (PEG), fig. 14 (ATBC) and fig 15 (TEC).

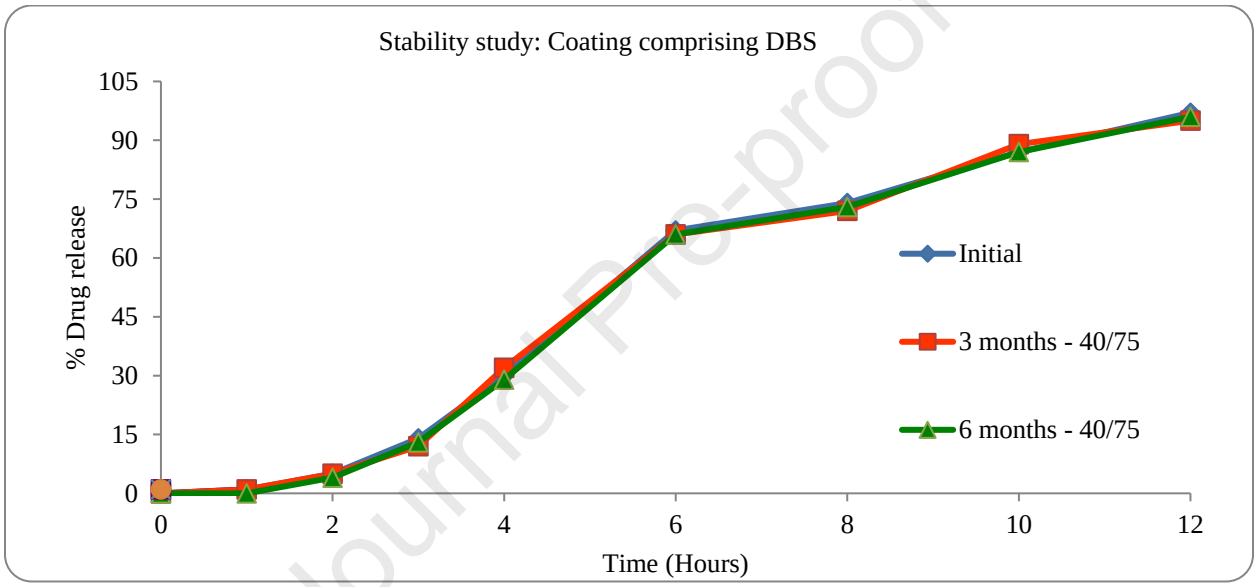

Figure 12. Drug release during stability study: Coating comprising DBS as plasticizer

There was no significant impact of the accelerated storage condition on the drug release profile of the batches comprising DBS as a plasticizer. The batch has been shown no effect of the extra curing or the stability study on the drug release profile.

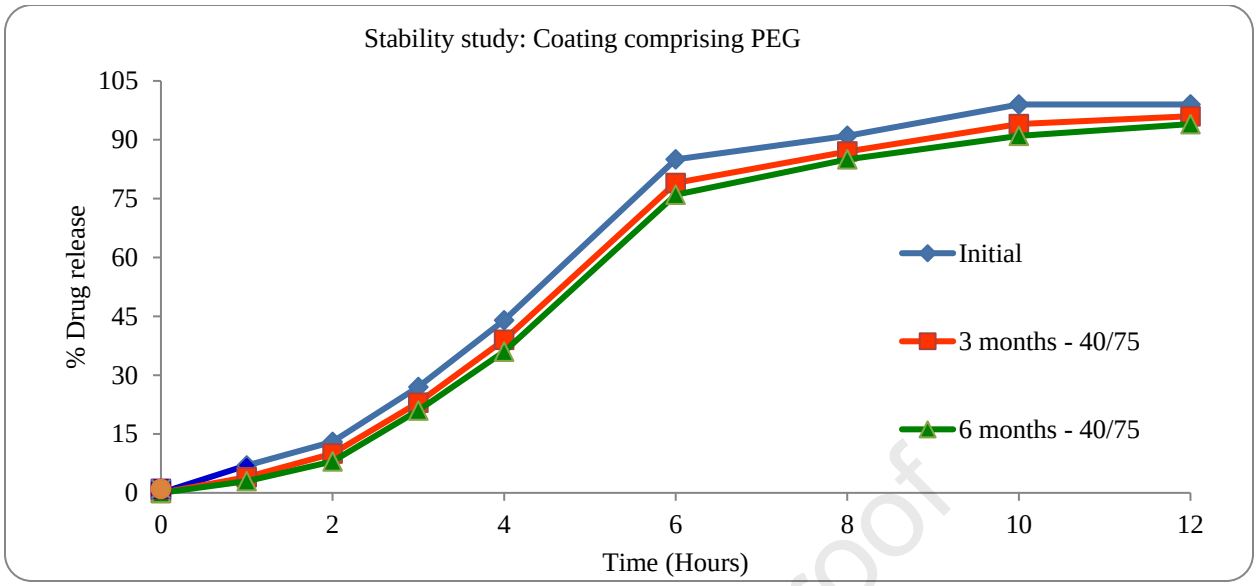

Figure 13. Drug release during stability study: Coating comprising PEG as plasticizer

There was moderate impact of the accelerated storage condition on the drug release profile of the batches comprising PEG as a plasticizer. The batch has been shown significant effect of the extra curing and the moderate impact of the stability study on the drug release profile.

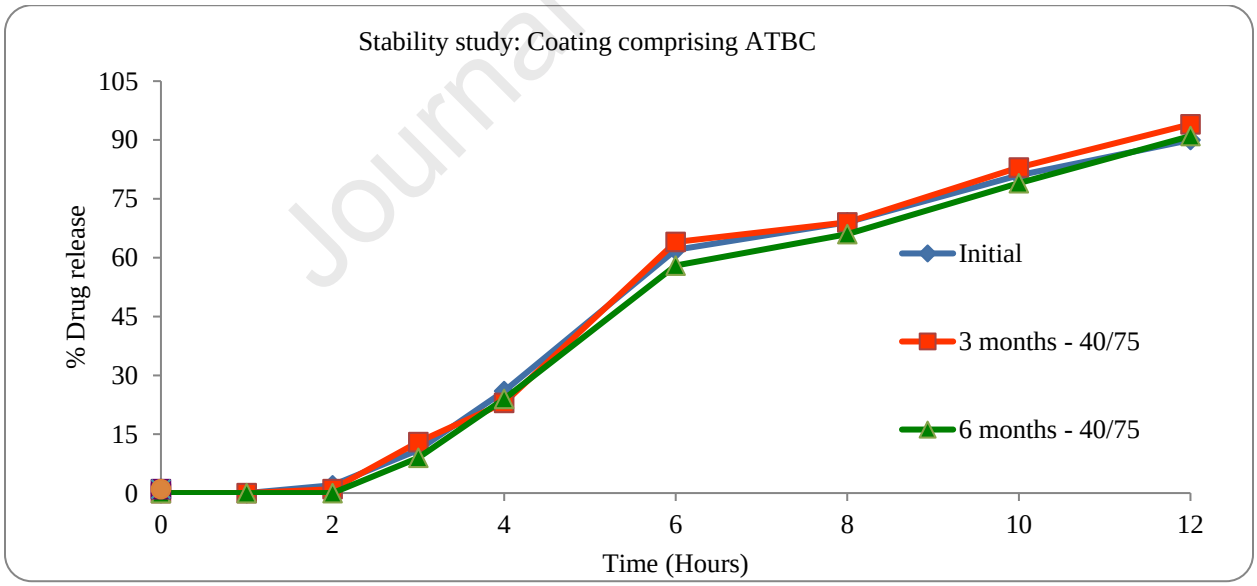

Figure 14. Drug release during stability study: Coating comprising ATBC as plasticizer

There was no significant impact of the accelerated storage condition on the drug release profile of the batches comprising ATBC as a plasticizer. The batch has been shown no effect of the extra curing or the stability study on the drug release profile.

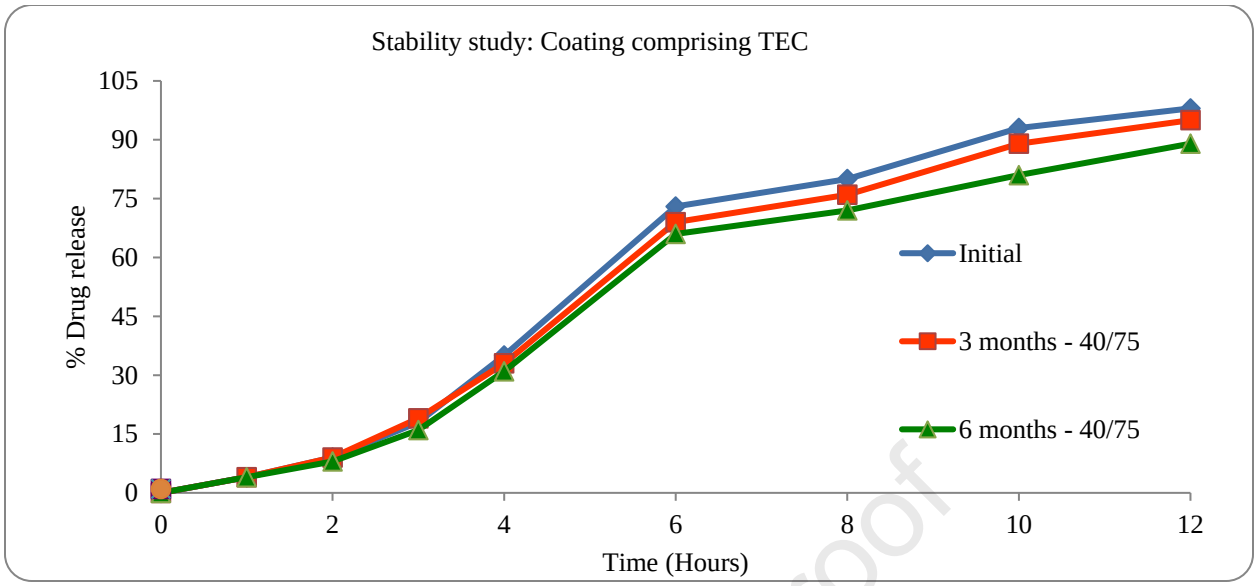

Figure 15. Drug release during stability study: coating comprising TEC as plasticizer

There was moderate impact of the accelerated storage condition on the drug release profile of the batches comprising TEC as a plasticizer. The batch has been shown moderate effect of the extra curing and the moderate impact of the stability study on the drug release profile.

It was observed that the composition which shown impact on drug release by the curing, similarly shown during the accelerated stability condition. This could be due to the progressive coalescence or due to the loss of plasticizer from the film during storage or curing at higher temperature. However, this phenomenon has been seen only with the hydrophilic plasticizers and there was no risk associated with the use of hydrophobic plasticizers. The hydrophilic plasticizers can be effectively used with the ethylcellulose- hypromellose polymer combination with prior and sufficient curing to eliminate prospective effect on the drug release during storage. It was derived that that curing for 120 min at 60°C was found to have an effect on drug release profile similar to that after six months accelerated storage condition. To reduce the risk during ethylcellulose- hypromellose polymer combination coating, use of hydrophobic plasticizers (DBS/ATBC) and the IPA-water solvent system shall be preferred (6, 31).

Conclusion

Ethylcellulose and hypromellose require a combination of the solvents to form a clear solution. A single solvent cannot dissolve both EC and HPMC for tablet coating. The coating efficiency was higher with the IPA-water solvent system. The film formed using the IPA-water mixture was homogeneous as compare to the other solvents. Any change in the

polymer ratio necessitates the evaluation and optimization of solvent ratios. The EC-HPMC polymeric film with all the plasticizers was homogeneous. The drug release was comparatively faster with the hydrophilic plasticizers compared to the hydrophobic plasticizers because the water-soluble plasticizers enhance the permeability and accelerate the diffusion rate. Tablet curing affects the drug release from the polymeric film containing hydrophilic plasticizers. Drug release moderately decreased with the TEC and significantly decreased with the PEG during the curing process and also during the stability study. It could be due to the progressive coalescence or the loss of plasticizer from the film during storage or curing at a higher temperature. The drug release remains unaffected by the polymeric film containing hydrophobic plasticizers.

Supplementary Materials

Not applicable.

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Conflict of Interest

The authors disclosed no conflicts of interest related to this article.

Author Contributions

All authors contributed to the study conception and design. Dr. Deepak Khobragade conceptualise the experiment and design and approved the final manuscript. Pramod Parshuramkar performed experimentation, data collection, and analysis. The first draft of the manuscript was written by Dr. Surendra Agrawal and reviewed and commented by. Dr. Rahul Ingale and Mrunali Potbhare.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used grammarly in order to check the grammer of text. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: