ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

REVIEW ARTICLE

# The Use of Various Polymers with Solid Dispersion Application of Hot Melt Extrusion (HME) Preparing New Delivery Drug System

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## Abstract

*Hot Melt Extrusion* (HME) at the beginning appeared widely used in the plastic industry and food industry, but in the last few decades, many researchers have succeeded in applying the HME method as a drug delivery system and determining various dosage forms in the pharmaceutical industry. The challenges that arise in the pharmaceutical are related to the solubility, dissolution rate, and bioavailability of drugs, especially for drugs that have low solubility in water. The low solubility and bioavailability will reduce the pharmacological effect of a drug. Solid dispersion using HME method succeeded in answering this challenge by distributing the drug evenly in the hydrophilic polymer during the extrusion process and changing the crystalline form to the amorphous form while maintaining drug stability. This review will examine the polymers are suitable for the HME method, Mechanism for solid dispersion using HME method, Steps must be taken to prepare solid dispersions using HME and characterization of solid dispersion resulting from HME and determinants of success of solid dispersions

**Keywords:** *Polymer, Solid Dispersion, hot-melt extrusion, Mechanism of solid dispersion, Step HME.*

## Introduction

*Hot Melt Extrusion* (HME) in the pharmaceutical world was introduced in the 1970s [1], this method is used in the pharmaceutical world to prepare solid dispersions. HME processing by mixing API (Active Pharmaceutical Ingredient), polymer, and if necessary plasticizers, surfactants, or others can be added to the screw extruder by adjusting the temperature and extruder rotation so that the API dissolves in amorphous polymers because there is a melting process, mixing, and homogenous, at the end it comes out through the die and there is a cooling and pelletizing process [2].

The HME method is a method that is more suitable than spray dry to prepare solid dispersions of drugs that have high crystallinity [3]. HME is a promising technology in the pharmaceutical industry, because it will not cause a problem with the toxicity of the residual solvent, does not require a solvent in the manufacture of solid dispersions. Besides, this method is also environmentally friendly [4], reduces process stages, does not require compressibility of active substances [5] and has been shown to disperse drug molecules with difficult solubility in polymer-carriers as well as to increase dissolution rates and bioavailability [6].

Several researchers have provided numerous reports on the use of polymers to disperse the active substances molecularly, help stabilize solid preparations, prevent crystallization, and maintain supersaturation during dissolution [7]. The following are some studies on the use of polymers in the pharmaceutical field in the last 10 years:

**Table 2: Use of HME Application Polymers**

| No | Year | Active Pharmaceutical Ingredient | Polymer and plasticizer | Drug to polymer ratio | Tg ($^0$C) | Tm($^0$C) | Dosage Form | Result | Ref |
|---|---|---|---|---|---|---|---|---|---|
| 1. | 2013 | Carbamazepine | Soluplus | 1:9<br>2,5:7,5<br>3:7<br>5:5 | 75,6$^0$C soluplus | 193,7$^0$C CBZ in soluplus | Extrudate | Crystallinity is reduced at 15% w / w CBZ compared to 25% immiscibility occurs at 30% CBZ and 50% w / w | [8] |
| 2 | 2019 | Glyburide | Soluplus Kollidon VA 64 added PEG 4000 as a plasticizer | 1:1<br>1:2 | 107$^0$C kollidon | 175$^0$C glyburide | Extrudate | More molecularly dispersed in soluplus polymer than PVP VA 64, however, X-ray microtomography showed an increase in polymer, decreased porosity of HME dispersion with PVP VA 64 potentially makes the product solid. | [9]; [10] |
| 3. | 2018 | Meloxicam (MLX) | Kollidon VA 64 with meglumine (MGL) and Eudragit® EPO as a plasticizer | 1:0 MLX:MGL<br>0,5:1 MLX:MGL<br>1:1 MLX:MGL<br>3:1 MLX:MGL<br>1:1 MLX:EPO<br>3:1 MLX:EPO<br>5:1 MLX:EPO | 106 °C Kollidon; MLX 17 °C and meglumine 18 °C | - | Extudate | Meloxicam concentration 10% (w / w) with the same amount of melumin which has the optimum result | [11] |
| 4. | 2014 | Osthole Derivative coumarine | Plasdone S-630, HPMC-E5, Eudragit EPO, and Soluplus | 1:3<br>1:6<br>1:9 | 1:3 SD Soluplus 75,9 °C Eudragit EPO 77,6°C HPMC 79,6 °C | Osthole 86,5 °C | Extrudate | Plasdone S-630 or HPMC-E5 (drug/polymer: 1:6) significantly increased the dissolution rate (3 fold D30) | [12] |
| 5. | 2018 | Itraconazole | Kollidon®VA64 with acid glutaric as an acid for pH decreases and solubility increases | 1:4:1 Itra:acid:koli | 90°C | Itraconazole 168°C; acid glutaric 98°C | Fast Dissolving Tablets | Itraconazole solid dispersion is physically stable in combination acid glutaric | [13] |
| 6. | 2019 | Acetaminophen or APAP (amorphous N-acetyl-para-aminopheno | HPMC | 30:70 b/b | - | Acetaminophen 169–170°C | Extrudate | APAP solid dispersion with HPMC is best in high spatial | [14] |

 

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| | | l) | | | | | | resolution (~ µm) capture images at 1700C and 200rpm | |
| 7. | 2018 | Itraconazole | Copovidone | 1:1<br>1:3<br>1:4<br>dan 1:9 | - | Itraconazole 166°C | Extrudate | The dissolution test results of SD Itraconazole increased 18 times compared to the original Itraconazole | [15] |
| 8 | 2019 | Indomethacin (IND) and Fenofibrate (FEN) | Soluplus | 1:4 | Around 80$^0$C | Indomethacin160,43°C Fenofibrate 82,6 6 °C | self-micellizing solid dispersions | Selfmicelizing Soluplus carrier is capable of dissolving IND or FEN and suppressing drug crystallization from a saturated state. | [16] |
| 9. | 2017 | Indomethacin (IMC) | Soluplus and Mannitol as an excipient | 50:50<br>15:85<br>IMC:SOL:MAN<br>50:50:25<br>IMC:SOL:MAN<br>15:85:15 | SOL 71,1°C<br>IMC 42°C<br>MAN 13°C | IMC 165°C | Extrudate | IMC extrudate was stable over 2 weeks | [17] |
| 10 | 2019 | Fenofibrate (FNB) | PVP VA64 | 2:8 | FNB °C 85,5<br>PVP VA64 106°C | - | Extrudate | Compared with the commercial lypanthil product, the bioavailability of the HME solid dispersion increased 2.45fold | [18] |
| 11 | 2015 | Artemether (ARTM) and lumefantrine (LUMF) | Soluplus added surfactant PEG 400, LF 127, LF 68 | 1:1<br>1:2<br>1:3 | 89,8 °C<br>70,7°C<br>67,2°C | - | Extrudate | Solubility test, dissolution significantly increased compared to pure drug and pharmacokinetic studies SDAL1 (sol: PEG4000) 1: 1, namely 44.12–65.24 fold increase AUC (0–72) and 42.87–172.61 fold increase Cmax | [19] |
| 12 | 2018 | Indomethacin (IMC) | Partially hydrolyzed polyvinyl alcohol (PVOH) | 3:7<br>5:5<br>7:3 | Tg PVOH 60,8°C<br>Tg PVOH HME (170°C)= | Tm PVOH 150 - 200°C | Extrudate | HME succeeded in amorphizing IMC with | [20] |

 

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| | | | | | 59,8°C<br>Tg PVOH HME (190°C)=60, 4°C<br>Tg γ-IMC = 160,3°C | | | the inter-molecular interaction between the IMC carboxylic acid and the hydroxy PVOH group and resulted in a stable solid dispersion. | |
| 13 | 2020 | Curcumin | Eudragit RSPO(hypotonicity) and Eudragit RLPO(hypertonicity) | 1:3<br>1:6 with a certain amount of porogen for sustained release | Tg curcumin 170°C | - | Sustained release solid dispersion | The effect of solid dispersion curcumin is significant when compared to physical mixtures and pure curcumin. | [21] |
| 14 | 2018 | Tamoxifen dan Resveratrol | Soluplus, Eudagit EPO, dan Kollidon VA64 | 1:2<br>1:5 | Tg 144 °C Eudragit EPO and Kollidon VA64 at D:P ratio 1:2 | Tm tam = 266°C | Film | HME significantly increased the bioavailability of tamoxifen | [22] |
| 15 | 2018 | Lacidipine | Soluplus, PVP K30, and PVP VA64) | 1:5<br>1:10<br>1:15 | Soluplus (Tg 70°C), PVP VA64 (Tg 101°C), and PVP K30 (Tg 149°C)<br>Tg SD 66°C soluplus, Tg SD 81°C PVP VA64 | Tm= lacidipine = 183°C | Extrudate | The optimum result is 1:10 with soluplus polymer and PVP VA64 | [23] |
| 16 | 2019 | Itraconazole | HPMCAS and surfactant | Polymer: drug:surfactant 70:20:10 dan 65:20:15 | Tg film contain-ing 30% P407 155°C | Tm itra Cona zole = 165°C | Extrudate | HME improves drug stability and release | [24] |
| 17 | 2014 | Sulindac | SUL:PPP:PEG1000<br>SUL:HPMC:TEC<br>SUL:HPC:PEG1000 | drug:polymer: plasticizer 1:5:1 | Tg PPP 70°C | Tm Sulindac 188°C | Film | The combination of SUL + PPP + PEG1000 which provides the best and stable results | [25] |
| 18 | 2017 | Artemisinin | Soluplus and acid citric as an acidifier | 1:1<br>1:0,95:0,5 Drug:polymer: citric acid | Tg soluplus 70°C | Tm artemisinin 154,81 °C | Extrudate | SD stabilized at 12 months | [26] |
| 19 | 2019 | Aripirazole (ARI) | Kollidon® 12 PF (PVP) and succinic acid (SA) | Drug:polymer:acidifier<br>10:70:10<br>40:50:10<br>30:65:5 | - | Tm ARI 140°C<br>Tm SA 190°C | Tablet | HME results were able to increase the solubility, dissolution and oral bioavai-lability | [27] |
| 20 | 2019 | Tacrolimus | Polyvinylpyrrolidone vinyl acetate (PVP VA64), Soluplus® | 10:10 | Tg TAC= 78,8°C<br>Tg PVPVA64= 101°C | Tm TAC above 130°C | oral Disintegration tablet | ODT tablets were stable for 3 months | [28] |

 

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| | | | and Hydroxypropyl Cellulose (HPC), at a drug loading of 10% w/w | | Tg Soluplus=70 °C Tg HPC=105°C | | | and increased their dissolution rate | |
| 21 | 2017 | Felodipine | Hydroxypropyl cellulose (Klucel™ MF) and hypromellose (Benecel™ K15M) | 1:1 | - | Tm Felodipine 146°C | Bioadhesive floating pellets | pellets can serve as a platform for creating gastroretentive controlled-release DDS | [29] |
| 22 | 2018 | ibuprofen (IBU) and isonicotinamide (INA) | xylitol , PVP K15 Soluplus | Drug:polymer 90:10 | Tg polymer Xylitol 84,95 and Tg co crystal 115, 28°C Tg soluplus dan Tg co crystal 118, 30°C 65,81 Tg PVP k-15 139,22 °C dan Tg co crystal 114, 31°C | - | Co crystal | spray drying showed better than HME in making Co Crystal without excipient carrier. | [30] |
| 23 | 2019 | Mefenamic acid | Eudragit® EPO | Drug:polymer 1:3 and 1:4 | - | Tm Mefenamic acid 230 °C | Tablet | Mefenamic acid tablets were successful with Eudragit® EPO polymer to increase the solubility of materials with high melting point and low solubility. | [31] |
| 24 | 2015 | Valsartan (VST) | Soluplus® (SP) and d-alpha-tocopherol polyethylene glycol 1000 succinate (TPGS) as a plasticizer | Polymer:drug 9:1, 7:3, and 5:5 VST:SP 30%:70% VST:SP:TPGS 30%:60%:10% | Tg soluplus 70°C | Tm TPGS 40°C; Tm VST 104,6°C | Extrudate | Formula developed 7: 3; the addition of a plasticizer decreases Tg and the melting viscosity of polymers during extrusion processing; HME successfully improves oral bioavailability | [32] |
| 25 | 2017 | Gliclazide (GLZ) | Affinisol, Soluplus®, Kollidon VA64® | 10:90 | - | - | Extrudate | Misscibility affinisol is better than Soluplus®, Kollidon VA64® and degradation does not | [33] |

 

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| | | | | | | | | depend on the polymer | |
| 26 | 2016 | Oleanolic acid (OA) | Soluplus®, PVP VA64 and PEG 6000 | 1:3; 1:5; 1:7; 1:10; 1:15 | - | Tm OA 320°C | Ekstru date | PVP VA64 with 1:10 which was amorphous and homogeneous and increased bioavailability | [34] |
| 27 | 2018 | Efavirenz (EFV) | Soluplus® (SOL) and Kollidon® VA 64 (KVA64) | 70:30; 50:50; 30:70 | Tg EV 139.60 °C | - | tablet | The maximum solubility and dissolution rates are in the 30% EFV formula with both SOL and KVA64 alone. | [35] |
| 28 | 2016 | Felodipine (FEL) | Soluplus® (SOL) | 1:1; 1:9;3:7 | Tg SOL 70°C | - | Extru date | The dissolution is increased through solid amorphous dispersions and encapsulation of SOL micelles | [36] |
| 29 | 2015 | Felodipine (FEL) | PEG 4000; polyox WSR 1105; Tween 80 | FEL:PEG:POL: TWEEN 10% 36% 27%27% 20% 32% 24%24% 30% 28% 21%21% | Tg FEL 45°C Tg PEG -61°C; Tg PEO-56°C; Tg tween -65°C | Tm FEL 144,39°C Tm PEG 59,13°C; Tm PEO 70,64°C | Buccal Patches | FEL Crystals have good solubility in tween 80 | [37] |
| 30 | 2017 | Naproxen | Meglumine (acidifier) Soluplus Kollidon VA 64<br><br>PVPK30 | NPX:Meg:polymer 48.7:41.3:10.0 48.7:51.3:31.63 48.7:41.3:10.0 48.7:51.3:43.70 48.7:41.3:10.0 48.7:51.3:49.00 | Tg Nap 5°C Tg meg 17°C Tg Kollidon K30 149°C | Tm Nap 155°C Tm meglumin 129°C | Extru date | The acid-base reaction between NPX and MEG during melt extrusion significantly improved the physical stability and the dissolution rate of NPX ASDs. | [38] |
| 31 | 2016 | Ibuprofen (IBU) | Eudragit RS PO (EU)<br>EU/Sucrose<br><br>EU/Methylcellulose<br>EU/Xanthan gum<br>EU/Poloxamer<br>EU/Gelucire 44/14 | 30%:70%<br><br>60:10<br><br>60:10 & 10:60<br><br>60:10 & 10:60<br><br>60:10<br><br>60:10 | Tg Ibu -43,4°C; Eudragit 53,3°C; metil selulosa 103° | Tm ibu 75,7°C; sukrosa Tm 175,2°C; Gelucire39,5°C | Transdermal Film | The best film on Gelucire 44/14 polymer | [39] |
| 32 | 2012 | Bifendate (BFN) | Plasdone ® S-630 Eudragit ® | 10:90<br><br>20:80 | - | Tm BFN 179,16°C; Tm PEG 6000 | Extru date | Kollidon® VA 64 is the optimal | [5] |

 

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| | | | EPO Kollidon ® VA 64 | 10:90 | | 63,12°C | | polymer in HME bifendate | |
| 33 | 2016 | Albendazole (ALB) | PVP K12 | 10:90 w/w | Tg PVP K12 90°C | ALB Tm 208°C; TM PVP K12 145°C | Extru date | Significant ly increased dissolution and was stable at 6 months of storage | [40] |
| 34 | 2018 | Phenytoin (PHT) Griseofulvin (GSF) Ibuprofen (IBU) Loratadine (LOR) | Poloxamer 338 (PLX) and dendrimer-like biopolymer (DLB) | API:DLB: PLX 3:1:1 | - | Tm PHT 296,23°C GSF 216,86°C IBU 74,79°C, LOR 134,06°C | Nano Partikel Edible | Increases solubility and dissolution rate. Solubility in water PHT <GSF <MOTHER <LOR. | [41] |
| 35 | 2015 | Carbamazep ine | Soluplus® and hypromellos e acetate succinate (HPMCAS-HF) | API: HPM-HF:solu 20:8:72 20:64:16 20:24:56 20:32:48 20:40:40 | - | Tm 191,01°C | Ekstru date | Soluplus increases the dissolution rate, the addition of HPMCAS HF increases stability for up to 12 months due to its high Tg and low hygroscopi c properties | [42] |
| 36 | 2017 | Mefenamic Acid (MA) | Kollidon Kollidon 12PF and Kollidon 17PF, added MgO as alkalizer) and PEG 3350 as a plasticizer | 20:80 20:70:10 (PEG) 20:75:5 (MgO) 20:65:5(MgO):1 0 (PEG) | Tg 12PF 90°C; Tg 17PF 138°C | Tm PEG53-59°C Tm MgO 2852°C Tm 230°C | Ekstru date | Penambah an alkalizer with plasticizer in the formula has a significant effect on the release of API from the kollidon matrix | [43] |
| 37 | 2018 | CuSO4 | (CuSO4:Spa n 80:Tween 80:PEG 6000) | 20:12:4:64 | - | - | Nanocom posites (NCs) from CuSO4 | CuSO4 NCs are successful photother mal candidates for colon cancer therapy | [44] |
| 38 | 2018 | Ketokonazol e (KNZ) | PVP-VA64 | 40:60 | Tg PVP-VA64 103,6°C Tg SD 69,3°C | Tm KNZ 149°C | Ekstru date | The polymer aids in supersatur ated and inhibits API deposition in the amorphous solid dispersion | [45] |
| 40 | 2020 | Quersetin | PEG 6000, F68, Soluplus | Drug-polymer(s) system w:w | - | Tm Que 326°C, HPMC 225°C, F68 is 57°C, | Ekstru date | The best excipient F68 | [46] |

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| | | | and PVP VA64 | Que:F68 1:7 Que:PEG 6000 1:7 Que:PVP VA64 1:7 Que:Soluplus 1:7 Que:F68 1:3 Que:F68 1:5 Que:F68 1:9 Que:F68 1:12 Que:F68:HPMC E5 1:6:1 Que:F68:HPMC E5 1:5:2 Que:F68:HPMC E5 1:4:3 | | PVPVA64 is 130°C, soluplus 70 °C and PEG 6000 57°C | | increases dissolution | |
| 41 | 2018 | Ovalbumin (OVA) | Glycerol tristearate (D118) and hydrogenated palm oil (DP60) | - | Tg D118 70°C Tg DP60 50,02°C | Tm OVA 84.5 °C | Lipid based implant | Release from D118-based implants faster than the DP60implants | [47] |
| 42 | 2019 | Etravirine (ETR) | PEG , PVP , PVPVA,SLP , HPMCAS , HPMC | 1:3 | ETR 100,85°C PVP K12 90°C PVPVA 101 °C SLP 70°C HPMC 178°C HPMCAS–MG 130°C | Tm ETR 226°C | Ekstrudate | Drug release PEG > PVP > PVPVA > SLP > HPMCAS > HPMC | (48) |
| 43 | 2018 | Atovaquone for brain cancer | PVP K30+ Spontaneously Emulsifying Component (SEC) | API:polimer+SEC 20:70:5 | Tg PVP K30= 172,81°C | Tm ATO 220,75°C | Extrudate | Incorporate in the SEC accelerate dissolution path | [49] |
| 44 | 2017 | Naproxen | Povidone K25 | 30%:70% | Tg Nap 7.8 °C Tg PVP K25 155°C | - | Extrudate | NPX 30% with HME results in a stable solid dispersion | [3] |
| 45 | 2020 | Ibrutinib (IBR) | HPMCAS , PVPVA ,PEG ,SLP, PVP , HPMC , HPC , PVOH | SLP + 50% IBR + 10% PEG6000 SLP + 50% IBR + HPMCAS. PVPVA + 50% IBR + 15% PVP k-12 + 50% IBR + 10% PEG6000 | Tg IBR 79,1°C PVP K12 90 °C PVPVA 101 SLP 70°C HPMC 178°C HPMCAS - MG 130°C | Tm IB 152,2°C | Ekstrudate | Solubility HPMCAS > PVPVA > PEG > SLP > PVP > HPMC > HPC > PVOH | [50] |
| 46 | 2011 | Celexocib (CX) | Eudragit 4155F and polyvinylpyrrolidone (PVP) | drug/polymer ratios of 1:9, 3:7, 1:1 and 7:3 | Tg PVP 154,6°C Tg SD PVP 3:7 130,70°CTg SD PVP 1:1 14,37°C Tg SD PVP 88,4°C Tg (1:9) SD 51,30°C Tg(3:7) SD 52,70°C Tg (1:1) SD 55,10°C Tg (7:3) SD 59,20 °C | - | Ekstrudate | Eudragit 4155F significantly increases the solubility of CX | [51] |
| 47 | 2020 | Celexocib | Soluplus® With 120 mg SD, lactose 120 mg, micro-crystalline cellulose, 90 | 16,7:83,3 25:75 50:50 55:45 60:40 65:35 70:30 | - | Tm CX 158°C | Tablet | Process analytical technology (PAT) for real time API analysis. | [52] |

 

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| | | | mg, 30 mg of Kollidon VA 64, 32 mg sodium starch glycolate, and 8 mg magnesium | 75:25<br>83,3: 16,7 | | | | The F4-F9 has increased its success | |
| 48 | 2020 | Diclofenac sodium | polyethylene glycol 400 added zein | 12.5:10<br>12.5:20<br>18.75:20<br>25:20<br>37,5:20 | Tg zein 168,4 °C | Tm 287,55 °C | Controle d release | The extrudate with zein-based diclofenac sodium was successfull y produced | [53] |
| 49. | 2020 | Glycyrrhetin ic Acid (GA) | Kollidon® VA64 and L-arginine/me glumine as alkalizers | 1:1:8<br>1:2:7<br>1:3:6<br>2:3:5 | - | Tm GA 305°C, Tm LA 228°C, and Tm MG 129°C | Extru date | The addition of an alkalizer increases the dissolution of ionizable ones such as GA | [54] |
| 50 | 2019 | Aripiprazole (ARP) | Kollidon VA64; Soluplus | ARP/KVA 70 wt%, ARP/SOP 85 wt % | - | Tm ARP 395 K | Extru date | Kollidon VA64 as the best polymer for amorphous Aripirazole extraction | [55] |
| 51 | 2018 | Haloperidol | Kollidon® VA64+Affini sol™15 cP, Kollidon® VA64+HPM CAS, | drug-polymer-polymer (1:5:5 and 2:5:5) | Tg Affinisol™ 15 cP (98°C) and Kollidon® VA64 (108°C) | Tm 152°C | Tablet | 1: 1 from Kollidon® VA64 and Affinisol ™ 15 cP are polymers suitable for 3D printing and rapid drug release | [56] |
| 52 | 2012 | Bicalutamid e (BL) | poly(ethylen e oxide) (PEO) | 1:10, 2:10 and 3:10 | Tg BL 56,4◦C | Tm BL 196°C | Ekstru dat | The solubility of BL in PEO liquid is estimated to be 31% | [57] |
| 53 | 2015 | Bicalutamid e (BL) | Kollidon VA64 | 5% and 30% bicalutamide | - | - | Ekstru dat | Extrudate 30%, dissolution depends on the physical and chemical properties of BL | [58] |
| 54 | 2016 | Indomethaci n (IMC) | Kollidon VA64 | 5%, 15%, 30%,50%,70%,9 0% drug loading | - | - | Ekstruda te control release | At pH 6.8 phosphate buffer the drug release increases in the drug extrudate 15% or more, at pH 2 HCl the drug release buffer increases at 5% drug | [59] |

 

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| | | | | | | | | extrudate | |
| 55 | 2020 | Ibuprofen | cellaburate:colophony | CLB:CLP:Ibu 30:55:15 25:45:30 20:35:45 | Tg polimer 74,3◦C Tg Cellaburate 130◦C | Tm film 157,2◦C Tm Cellaburate 155–165 °C | Extrude film Control release | Ibuprofen is amorphous at 30% (w / w) in 35:65 colophony: cellaburate films. | [60] |
| 56 | 2020 | Indomethacin | Kollidon VA64 | 1:1 | Tg Kollidon VA64= 105 °C | Tm 160 °C | Extru date | Solid dispersions contain residual crystallinity which affects the seed properties, polymeric crystal growth inhibition effectiveness, and supersaturation conditions. | [61] |
| 57 | 2016 | Piperine | Eudragit EPO,Kollidon VA 64, Soluplus | 10:90 20:80 40:60 | - | Tm piperine 135°C | Ekstru date | 10% w / w piperine / Soluplus significantly increases solubility and dissolution | [62] |
| 58 | 2020 | Meloxicam | Soluplus®+ Poloxamer | API:SOL:POL 2.5%:2,3:1 | - | - | Ekstru date | HME results have increased bioavailability compared to the innovator Mobic® | [63] |

## Discussion

### Polymers in the Hot Melt Extrusion Method

The use of polymers in HME must meet the requirements, namely, thermoplastic has a glass temperature between 50-1800C, has high-temperature stability, is not toxic, has low hygroscopicity to prevent crystallization [64]. Some of the polymers that are often used for HME are as follows:

### Eudragit®

Is the brand name of polymethacrylate-based copolymers. Eudragite is an amorphous polymer having a transition temperature between 9 and more than 150 0C. This polymer is non-biodegradable, non-toxic and non-absorbable [65]. Eudragite EPO with the active substance osthole has a solubility parameter of 20.55 MPa1 / 2, Δδ (the ratio of drug to polymer solubility) 2.76 and is classified as a miscible.

The comparison of osthole drugs with EPO 1: 6 and 1: 9 was successful in increasing dissolution and decreasing the crystallinity of the active substance and colloid dispersed in the carrier [12]. Eudragite is used as a polymer in the manufacture of mefenamic acid disintegration tablets for taste masking using the HME method [31].

### Kollidon VA 64® / Copovidone

Is the brand name of vinylpyrrolidone-vinyl acetate copolymer which is soluble in water and alcohol. Kollidon VA64 glass temperature is 105 ° C and melting point 160 ° C, complex viscosity 10,000 to 1000 Pa.s. The extrusion temperature is chosen in the itraconazole experiment with a ratio of 1: 4: 1 w / w ITZ-glutaric acid-Kollidon® VA 64 was 95 ◦C [13].

### Soluplus®

Is the brand name of polyethyleneglycol-polyvinyl caprolactam-polyvinyl acetate

 

grafted copolymer. With a ratio of PEG 6000: Vinilcaprolactam: vinyl acetate 13:57:30. It has a molecular weight of 118,000 g / mol [64]. The glass transition temperature is 70$^{o}$C. The low Tg makes Soluplus® good in the extraction process of Carbamazepine which is relatively low in temperature because Soluplus® is fast, low hygroscopic and will help maintain stability during storage[42].

Soluplus® provides the best solubility 160 fold increase in water solubility at a ratio of 1: 9, namely with the active substance 10% w/w piperine / Soluplus extrudates and the dissolution reaches 95% [66]. The solid dispersion lacidipine with soluplus® polymer is more physically stable than the VA 64® kollidon polymer [23].

**Poloxamer (PLX)**

Poloxamers are polyoxyethylene, polyoxypropylene block polymers [67]. Poloxamer is commonly used as solubilizing agents. However, in research conducted by Hwee Jing Ong and Rodolfo Pinal in 2018 the PLX 338 functions as a wetting agent, not a solubilizer. PLX 338 shows that the 20% (w/w) concentration of PLX is suitable for extrusion by taking only 5 minutes out of the extruder [41]. Other studies suggest that the combination of soluplus and poloxamer (2,3: 1) increases the dissolution of meloxicam and aids stability [63].

**Poly (*Ethylene Oxide*) (PEO)**

Having a low melting point of 62 $^{0}$C-69 $^{0}$C, the molecular weight of PEO decreases significantly after going through the HME process. PEO is degraded between temperatures of 330 $^{0}$C – 450 $^{0}$C so it is suitable for use as HME polymers that use high energy. Comparison of the drug Bicalutamide with polymeric polymer 1:10 had significant drug release over the 60 min period. During the extrusion process, PEO forms a gel layer with changes in thickness, composition and structure so that it is well hydrated and dissolved [57].

HPMC (*Hydroxypropyl Methylcellulose*)

In the preparation of griseofulvin drug extrudates 10% and 20% with 90% and 20% HPMC, the extrudate results are transparent and have a degradation temperature above 200$^{0}$C. HPMC has several grades including E5, E15, and E50. HPMC grade E5 has a Tg of 170-180 $^{0}$C, with a molecular weight of 28,700 g / mol; HPMC grade E 15 has Tg 170-180 $^{0}$C, with a molecular weight of 60,300 g / mol; HPMC grade E 50 has a Tg of 170-180 $^{0}$C, with a molecular weight of 86,700 g / mol. The hydrogen bonding of the polymer to the drug allows molecular stabilization and prevents stabilization [68].

**PEG (*Polyethylene Glycol*)**

The PEG used by HME was various, namely PEG 400, PEG 4000, PEG 6000. PEG 400 with a concentration of 10-20% was successful in making control release preparations on diclofenac sodium using the HME method [53]. The melting point of PEG 6000 is 57$^{0}$C, a combination of the active substance quercetin and polymer PEG 6000 with the HME method that has been done, namely the ratio of 1: 7 [46].

**Plasdone S-630**

Plasdone® S-630 is a copolymer of vinylpyrrolidone and vinyl acetate copovidone with a ratio of 60/40, having an average molecular weight of 24,000 to 30,000. This polymer was developed as a filler in the manufacture of tablets by direct compression and yields better dissolution tests than other binders [69]. The DSC results illustrated the absence of crystalline peaks in plasdone S-630 polymer with a ratio of 10% and 90% bifendate drug Plasdone ® S-630 [5].

**PVP K30**

The use of PVP 30 was reported in the study of atovaquone 20% with PVP K30 70%. PVP K30 was chosen because it has good miscibility with atovaquone, with Tg PVP K30 = 172.81 °C [49]. PVP K30 can also be used as a gelling agent in the manufacture of enteric coatings [70].

**Partially Hydrolyzed Polyvinyl Alcohol (PVOH)**

PVOP has the brand name Parteck® MXP, with Tg 60.8 ° C, Tm PVOH 150-200 ° C. The solubility parameter was 32.52 MPa1 / 2, Δδ (ratio of drug and polymer solubility) 8, 90. The miscibility between Ibrutinib (IBR) and each polymer is HPMCAS> PVPVA> PEG> Soluplus> PVP> HPMC> HPC> PVOH., PVOH has a low solubility capacity in dissolving IBR and producing solid solutions [50].

 

**Kollidon®12 PF (PVP / *polyvinyl pyrrolidone*)**

This polymer is used in the preparation of solid dispersion (Aripiprazole) with the addition of succinic acid as an acidifier [27], and as a polymer in the manufacture of lansoprazole enteric-coated tablets [71]. Tadalafil solid dispersion with Kollidon® 12 PF polymer shows a faster dissolution rate than Kollidon® VA 64 dissolution. Tadalafil has separated from Kollidon® 12 PF solid preparations due to a combination of erosion and diffusion mechanisms [72]. Each polymer has individual results that vary depending on the interaction of the active substance and the polymer.

The mechanism of solid dispersion using the HME method

The mechanism of the solid dispersion method with HME is in principle the same as for other solid dispersions. Polymers that are hydrophilic and some even have amphiphilic properties, such as soluplus in liquid media will form micelles that can trap hydrophobic drugs into the hydrophobic nucleus to increase solubility [73]. This HME is used to disperse the insoluble drug into the hydrophilic matrix at the molecular level including changes in the drug in the amorphous, crystalline, or between amorphous and crystalline form [74]. The following is illustrated using Figure 1, namely the process that occurs in the TSE tool.

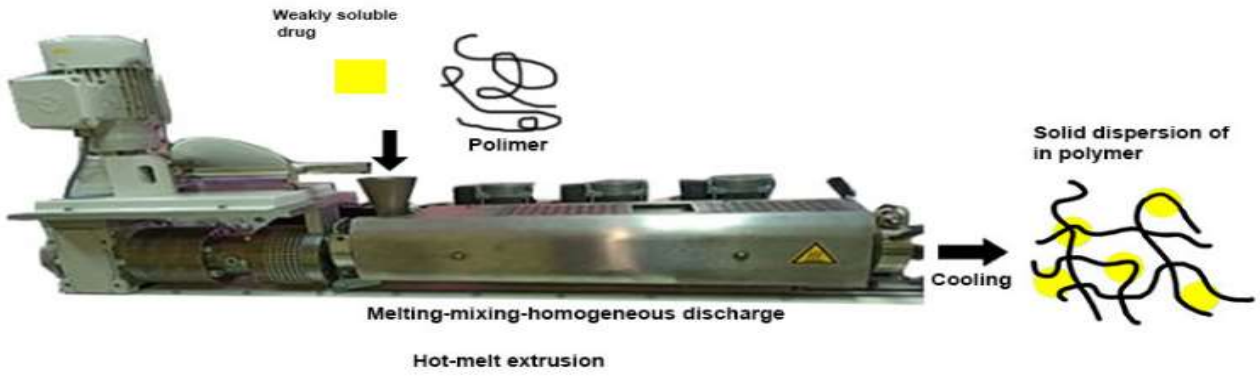


**Fig 1: Illustration of HME on the Twin Screw Extruder(12)**

**Steps to Prepare Solid Dispersion by HME Method**

Active substances that are usually processed through HME are those that have poor solubility in water because the advantages of this HME are that they can increase the solubility, dissolution rate, and bioavailability of active substances which have limitations [75]. Solubility is always a major problem in product manufacturing, solubility is closely related to the melting point and partition coefficient. Solubility is related to the crystallinity and interactions between the solute and the solvent. General equity Equation (GSE) proposed Yalkowsky [76]:

$$\text{Log Sw= 0, 5- 0, 01 (MP-25)-log } K_{ow}$$

Sw = Solubility in water (molar)
MP = melting point
Kow = the octanol–water partition coefficient of the solute.

If the marine substance has a melting point below 25 $^0$C, if it is liquid then the MP-5 temperature is set to zero. In this review, the steps for preparing solid dispersions will be explained, namely: We mix the active substance with a hydrophilic carrier with the desired ratio (drug: polymer, w/w) to obtain a physical mixture (PM) then put it in a powder mixer for about 20 minutes so that it is homogeneous before being put into the extruder machine. The final step is to enter API, polymer if necessary; you can add plasticizers, surfactants or others without adding solvents. By itself, we will get the results in the form of pellets according to the die that we set or want [28] [34].

 

This solid dispersion is usually unstable during storage; with this HME process will increase the stability of the active substance. If the preparation is unstable, the dissolution rate and bioavailability will decrease due to the separation phase, in which the separation phase is a direct factor of instability towards crystallinity [23].

**Determinants of Successful Solid Dispersion with HME**

The HME method will be successful, of course, with good preparation that must be met or also called a critical factor. The following will discuss the stages of the solid dispersion approach with HME:

**Pshychochemical Evaluation [48]**

We must know the characteristics of the material to be processed, namely the API and the polymer, ranging from polymers (Tg, Tm, Td, solubility in solvents, including donors or double bond recipients), and drugs (Tg, Tm, solubility in solvents, including donors or double bond recipient, log P, chemical stability).

**Thermodynamic Assessment [48]**

In this thermodynamic assessment, theoretically, we must know the solubility parameter δ, the prediction of Tg, and the interaction parameter (χ). Meanwhile, for the experiment, we can try to find the Tg of amorphous dispersion using the DSC method.

The process when making the extrudate

The tool used in HME is a screw extruder; it can use a single screw extruder (SSE), or a twin-screw extruder (TSE). TSE is commonly used and produces excellent mixing rates. We have to optimize the temperature, screw rotation, torque, die temperature, shear-stress time, residence time. Extraction temperature concerning Tg in both the polymer and the active substance. To obtain the desired product from both maximum mixing and flowability, the extraction temperature is usually set to 30-60 ° C above the Tg or Tm of the polymer [77,78].

**Statistical Testing [48]**

By looking at the correlation between chemical physics and thermodynamics.

**Test HME [48]**

3 things related to testing HME, namely:

- Solid dispersion characterization includes FTIR, SEM, XRD, DSC, TGA.
- Chemical interaction analysis (Raman spectroscopy)
- Pharmaceutical characterization (dissolution test, process evaluation)

Characterization of HME Solid Dispersion

To evaluate the results of the solid dispersion of HME applications, an examination can be done in the form of:

- Differential scanning calorimetry (DSC), DSC analysis is used as a first step to detect phase changes in the active substance and polymer used, as well as the phase transformations of the solid dispersion results. The results of this DSC examination, we get data on melting, miscibility, glass temperature, recrystallization from the solid dispersion results, and also to identify the presence of amorphous structures [79, 80].
- PXRD (Power X-ray diffraction), is used to see the crystallinity of preparation, in this case, the solid dispersion result [80]. If no crystalline peaks appear on the diffractogram, it indicates that the solid HME dispersion is amorphous and the amorphous form has high solubility compared to the crystalline form.
- TGA (Thermogravimetric analysis) to determine the degradation profile of drugs [81] and to see the thermal stability of single active substances or with polymers [28]. The TGA test gives us information that at what temperature the drug is degraded, thus assuring us that the temperature used during the melting process using the HME method does not damage the active substance of the preparation. It is hoped that the active substance can still show its action as a treatment because it is not degraded. The extrusion temperature greatly affects drug degradation, so selecting a low temperature on the TSE device is a prerequisite for obtaining high dissolution results [5].
- FT-IR (Fourier-Transform Infra-Red), this analysis is to see the bond between the active substance and the polymer. After HME treatment, did the peak position shift

 

or did a loss or even a new transmitted peak appears. HME is successful if no new transmittance peaks are found, but only a shift in the spectrum that can be explained by the amorphous nature of the HME results [73].

- SEM (Scanning Electron Microscopy), to see the crystalline properties of HME, see the morphology and particle size of HME results [82]. The success of HME is if the crystalline form of the active substance is no longer visible, but the API has already been dispersed into the polymer.

## Conclusion

HME is a promising method and has been successful with a variety of drug delivery systems such as tablets, control releases, nano lipids, transdermals, nanoemulsions and others. The purpose of various HME can be to increase the solubility, dissolution rate and bioavailability of API (Active Pharmaceutical Ingredient) which has poor solubility in water, as well as taste masking. The selection of polymer and API is the key to the success of this method; we must study the physical and chemical properties of the active substance and its polymer. HME extraction temperature is usually 30-60 $^0$C above the polymer glass transition temperature. The choice of API must be resistant to heating because this HME uses a high energy melting method. The mechanism in HME is by amorphizing the active substance so that the API will be dispersed in the polymer matrix and will increase the solubility of the API.

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