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Preparation of Oxcarbazepine Solid Dispersion by Hot Melt Extrusio for Enhanced Dissolution: Downstream Processing to tablets

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ABSTRACT

Solid dispersion of Oxcarbazepine (OXC) was prepared by hot melt extrusion of OXC with hydrophilic polymer. The main objective was to explore the potential of Hot Melt Extrusion technique (HME) as an industrial scalable green technique for the preparation of solid dispersion and therefore enhancement of dissolution of poorly soluble drug. Polymer for extrusion was selected on the basis of solubility parameters and glass transition (T_g). OXC solid dispersion was prepared using Kollidon VA 64 and Soluplus as hydrophilic carrier. OXC and polymer was mixed in different ratio and extrudates were evaluated for appearance, DSC, PXRD, flow property and dissolution characteristics. DSC and PXRD studies revealed the significant reduction in crystallinity of OXC. OXC-kollidon VA 64 extrudates have good flow property having angle of repose 29° and carr's index 11.2 and good compressibility with hardness 5-6 kg/cm^2. Particle size of extrudates exhibited significant effect on disintegration time and dissolution. OXC release was found to be complete within 45 min from tablets of OXC hot melt extrudates while plain OXC showed just 39 % release. Solid dispersion of OXC was successfully developed using HME technology followed by formulating it into directly compressible tablets.

Keywords: Hot melt extrusion, Oxacarbazepine, Solid dispersion, Solubility enhancement, Glass transition temperature, Solubility parameter

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INTRODUCTION

Poor aqueous solubility of existing and emerging drugs can limits the therapeutic potential to various capacities. Even though, years of research and series of solubilization techniques, till date there is no universal excipient or technique which can be versatile enough to solubilize wide spectrum of drug molecules. Solubility issues intensify the problems at drug development stage, where many potential candidates may be eliminated because of their poor solubility[1,2]. Beginning with polymorphic changes[3] and salt formation of an ionizable drug[4], co-solvency[5], solid dispersion[6], inclusion complex[7,8], micronization[9], self emulsifying delivery system[10], nanonization[11] etc. are widely explored techniques for solubility enhancement. Selection of solubilization method varies according to physicochemical property of drug and scale up feasibility of an individual technique.

Oxacarbazepine (OXC), a widely used antiepileptic drug, having poor water solubility. OXC has low log P (1.5) but high melting point suggesting, its high crystal lattice energy, which is responsible for its poor solubility. OXC must absorb energy to overcome the crystal lattice energy during its dissolution. Solid dispersion, inclusion complex, nanonization etc. are expected to turn it into none or less crystalline form where the low lattice energy promotes higher dissolution[12,13].

Hot melt extrusion (HME) has been emerged as an excellent technique for preparation of solid dispersion with considerable edge over other techniques. Industrial feasibility, continuous process, organic solvent free technology, very high drug loading, less numbers of unit operation, anhydrous processing of moisture sensitive drugs etc. are some of the salient features of HME technology[14,15]. In solid dispersion prepared by hot melt extrusion, drug exists as the molecule state having largest total surface area with no lattice energy which is needed for solubilization. Drug extrudates with hydrophilic carriers; which facilitate the solubility of drug in multiple ways. Hydrophilic carrier improves solubility and wettability of drug also prevents its precipitation[13]. Selection of polymer is crucial step in hot melt extrusion. Various polymers including HPMC, ethyl cellulose (EC), Soluplus, Eudragit E, Eudragit RS PO, Kollidon VA 64 and Kollidon K 30 have been explored for modulating the drug release. Hydrophobic polymers like EC and Eudragit RS PO are used to sustain the release of drug while hydrophilic polymers are used to enhance the dissolution or taste masking[16,17,18,19]. Glass transition temperature (T_g), degradation temperature, solubilization parameters, miscibility with drug etc are the key parameters for selecting the polymer for an individual drug[16,17]. Further, flow property and

compressibility of extrudates are essential parameters for downstream processing to convert them in unit dosage form. Wet granulation after hot melt extrusion may be tedious process hence hot melt extrudates should have enough compressibility for direct compression.

The main objective of this research work was to develop solid dispersion of a poorly soluble drug by Hot Melt Extrusion technique (HME) for enhanced dissolution. Another objective is to investigate the flow property, compressibility and disintegration time of hot melt extrudates to convert it into unit dosage form. OXC was chosen as poorly soluble candidate to improve dissolution.

MATERIALS AND METHODS

Materials

Oxcarbazepine was procured from Bajaj Healthcare Ltd., India. Kollidon VA 64, Soluplus, Kollidon CL, Kollidon CL M, Lutrol F 68 were procured from BASF India Ltd, India. Sodium starch glycolate, crosscarmellose sodium and magnesium stearate were purchased from Signet chemicals, India. Aerosil 200 was procured from Evonik industries, India. All the other reagents were analytical grade used without further purification.

Analytical method

A stability indicating RP-HPLC assay method was developed for the analysis of OXC. The HPLC system consisted of JascoPU-2080 Intelligent HPLC pump (Jasco, Tokyo, Japan) equipped with Jasco MD 2015 plus PDA detector (Jasco, Tokyo, Japan) and RP-8 (250 x 4.6 mm, 5 µ) column. Phosphate buffer pH 6.5: Acetonitrile (60:40) was used as mobile phase with the flow rate of 1.5 ml/min and detection wavelength at 215 nm. Retention time of OXC was 6 min.

Selection of polymer

Polymer was selected on the basis of their solubility parameters. It has been reported that closer the solubility parameters of drug and polymer, resultant system is more miscible system on melt extrusion[18]. Such types of systems are more stable over the period of time. Solubility parameter of OXC was assumed on the basis of its solubility in organic solvent. The polymer having solubility parameter closer to the solvent in which OXC having maximum solubility was chosen for further studies.

Preparation of the solid dispersion by hot-melt extrusion

OXC and different polymers – Kollidon VA 64 and Soluplus (Chemical structure shown in Figure 1) were accurately weighed and mixed by in a polyethylene bag for 10 min to obtain a

homogeneous physical mixture. Further, batches were also carried out by addition of plasticizer. Various blends with different ratio of OXC:polymer:platicizer have been extruded using Thermo Fisher Pharma HME 16 twin-screw extruder (Table 1). The extruder consisted of a hopper, barrel, die, kneading screw, and heaters distributed over the entire length of the barrel. Materials introduced into the hopper were carried forward by the feed screw, kneaded under high pressure by the kneading screw and then extruded from the die. The temperatures of the extruder barrel zones and die were set using external temperature controllers. The extrudate was collected and allowed to cool at room temperature, and then milled using a laboratory cutting mill. After milling, extrudates were sieved and used for further investigation.

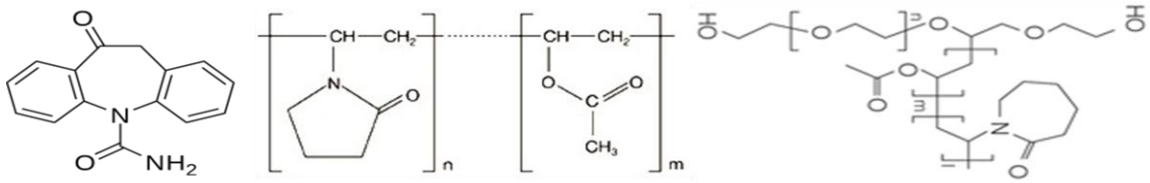


Figure 1: Structure of OXC, kollidon VA 64 and soluplus

Table 1: Batches for hot melt extrusion

Drug: Polymer: plasticizer	Ratios	Temperature (°C)
OXC: Kollidon VA64: Lutrol F68	45:45:10	120°C
OXC: Kollidon VA64: Lutrol F68	45:45:10	150°C
OXC: Kollidon VA64: PEG 6000	45:45:10	120°C
OXC: Kollidon VA64: PEG 6000	45:45:10	150°C
OXC: Soluplus	50:50	120°C
OXC: Soluplus	1:10	120°C
OXC: Kollidon VA64: PEG 6000	1:10:1	120°C
OXC: Kollidon VA64: PEG 6000	1:10:1	150°C

Characterization

Differential Scanning Calorimetry (DSC)

DSC was used to characterize the thermal properties of the polymer, drug, Physical mixture (PM), and hot-melt extrudates. DSC was performed with Pyris 6 DSC (Perkin Elmer, USA) instrument, under a pure nitrogen flux and with a heating rate of 10°C/min in the temperature range from 40°C to 300°C. Each sample was accurately weighted (1–2 mg) in an aluminum pan; crimped, sealed and blank aluminum pan was used as reference.

Powder X-Ray Diffraction (PXRD)

PXRD studies of OXC melt extrudates were carried out to understand the state of drug embedded within polymeric matrix. PXRD diffractograms were recorded on X'pert PRO MRD (PAN analytical BV, Almelo, Netherlands) equipped with a Cu Kα line as the source of

radiation. Standard runs using a 40 kV voltage, 30 mA current and a scanning rate of 0.02°/min over a 2θ range of 2-40° were used.

Scanning Electron Microscopy (SEM)

SEM was used to study the surface morphology of the extrudates and to examine the precipitation of drug from surface. Samples were mounted onto aluminum discs using double-sided adhesive copper mounting tape and placed in a dry atmosphere under vacuum overnight, prior to coating and analysis. Samples were subsequently coated with a thin film of gold (15 nm) using an Agar® Auto Gold Sputter Coater. SEM was performed using a JEOL 6500F (JEOL Ltd., Tokyo, Japan) field emission microscope operating at an accelerating voltage of either 2 or 5 kV with a 4 mA beam current emission. Images were captured using Jeol® software.

Flow property

Angle of repose, bulk density, tapped density, carr's index and hausner ratio were determined for OXC melt extrudates to evaluate the flow characteristics and compressibility. Further to these parameters will suggest the fillers to be added in order to formulate final blend in appropriate range for direct compression.

Preparation of tablet

Tablets were prepared by direct compression using 16 station single rotary tablet compression machine (Cadmach, India) using 19.00mm X 9.00mm capsule shaped standard concave punch with plain surface. After assessing the flow property suitable excipients were added to achieve suitable flow for direct compression and minimize the sticking during compression. Various superdisintegrants like sodium starch glycolate, crosscarmellos sodium, Kollidon grades etc were added in different ratio to investigate the effect of type and concentration of superdisintegrant on Disintegration Time (DT) of hot melt extrudates. Effect of particle size of melt extrudates on DT and dissolution was also evaluated to optimize the milling and sieving process for final formulation. Effect of filler like MCC, lactose and mannitol on DT was also evaluated.

***In vitro* drug disintegration test**

Disintegration time (DT) of tablets prepared from OXC hot melt extrudes was carried out to optimize extrudates particle size and concentration of superdisintegrant to achieve rapid disintegration of tablet. The milled extrudates were passed from different sieve (ASTM) 20, 30, 40, 60 (#) mesh sieve and material retained on each sieve was collected for further investigation. Extrudates of different particle size retained on sieve were mixed with Kollidon CL SF (4 %) and magnesium stearate (1 %). The blends were mixed thoroughly, followed by tablet compression. Further, Kollidon CL SF was replaced with crosscarmellose sodium, Kollidon CL M, sodium

starch glycolate to observe the effect of different superdisintegrants on DT. Tablet hardness was kept constant (4-5 kg/cm^3) for all the tablet formulations. *In vitro* drug disintegration test was carried out using a tablet disintegration test apparatus (Electrolab, India). For this 800 ml of water was taken in a glass beaker and subjected to warming. The temperature of the water was achieved to 37.0 ºC ± 0.5ºC. Then the tablets were evaluated for disintegration time.

***In-vitro* dissolution test**

In vitro dissolution was performed in 900 ml of 0.6 % w/v SLS in water in USP II apparatus (60 rpm). Dissolution study of plain OXC, tablets containing extrudates of various size and optimized formulation was carried out to understand effect of hot melt extrusion and particle size on dissolution characteristics. 5 mL of sample was withdrawn at 10, 20, 30, 45, 60 and 90 minutes and OXC release was calculated by developed analytical method.

RESULTS AND DISCUSSION

Selection of polymer

OXC was found to be easily soluble in Dichloromethane (DCM) and chloroform, with very poor solubility in polar solvents e.g. ethanol and methanol. Solubility behavior of OXC has suggested that it is more soluble in non polar solvent. Greenhalgh has classified compounds according to their difference in solubility parameters. Compounds with a $\Delta\delta < 7$ MPa$^{0.5}$ were likely to be miscible, but likely to be immiscible with a $\Delta\delta > 10$ MPa$^{0.5}$ [20]. Solubility parameter of DCM and chloroform is near to 19 while that of ethanol is 26[21]. Considering the literature on selection of polymer on the basis of solubility parameters, we have selected the polymer having δ near to 19. There are few polymers reported with δ value near to 19 having good extrudability. Soluplus (δ=19.4), Kollidon VA 64 (δ=19.7) and Eudragit E (δ=17.8) were found to be promising polymer for the melt extrusion with OXC[22]. However, Eudragit E has low T_g (43.7°C) compare to According to Hancock et al., the T_g of final system should be 50°C higher from its storage temperature[23] It is explained by Kauzmann temperature (T_k) - the critical temperature at which molecular motions in the materials become infinitely slow, which is generally at about 50 soluplus (70°C) and Kollidon VA 64 (102°C). Polymers with low T_g allowed high molecular mobility of drug within system. High molecular mobility of drug in polymer may result in crystallization out of drug which adversely affects the dissolution profile. °C below the glass transition T_g[24].

Characterization of OXC hot melt extrudates

OXC was extrudated with Kollidon VA 64 and Soluplus in various ratios (Table 1). The

compositions in which drug:polymer are 1:8 or higher showed clear solid solution while 1:1 showed solid dispersion characteristics. Hot melt extrudates of Kollidon VA 64 was very hard to breakdown easily and hence difficult to process. On addition of plasticizer (Lutrol F 68, PEG 6000) extrudates were easy to process. This is because, addition of plasticizer lower down the T_g. The extrudates prepared with Kollidon VA 64 using PEG as plasticizer was found to be superior in terms of extruadability and downstream processing to tablets compare to other batches. Moreover, processing temperature has no effect in disintegration and dissolution characteristic of OXC- Kollidon VA 64 hot melt extrudates (Table 1)

Differential Scanning Calorimetery (DSC)

DSC thermogram of OXC, showed sharp endothermic melting point at 215°C (Figure 2). Thermograms of OXC and polymers in physical mixture and at 1:1 ratio showed a small, slightly broad endotherm at 200 °C, indicated the reduced crystallinity of OXC. In physical mixture, small endotherm instead of sharp melting point was observed. This might be because of interaction of OXC and polymer in DSC pan during heating ramp. On heating polymer gets melted far before drug's melting point so drug starts interacting with rubbery polymer. When temperature rises to melting point of drug, drug has already been solubilized into molten polymer and hence exhibits broad melting endotherm. Suppression of sharp endotherm in physical mixture indicates the favorable interaction between drug and polymer. Kollidon VA 64 and Soluplus have their T_g, 70°C and 103°C, respectively. So we can expect during heating polymer get rubbery earlier, and interact with drug before temperature reaches to melting point of OXC. There is almost 100°C difference between OXC and polymer. PXRD can give better idea of crystallization in such cases. Hot-melt extrudates of OXC, showed no endothermic transition at the ratio OXC:polymer is > 1:8, indicating the formation of solid dispersion. Further, DSC thermograms suggested that type of plasticizer (PEG 6000 and Lutrol F68 in this case) have no effect on crystallinity of OXC. Drug to polymer miscibility and ratio play dominating role in amorphization of drug.

Powder X – Ray Diffraction (PXRD)

The X-ray diffraction patterns of OXC, polymers (Kollidon VA 64, Soluplus), hot melt extrudates are presented in Figures 3. Results of PXRD are in very well agreement with DSC study. As can be seen from figure 3, diffractogram of pure OXC showed distinct peaks at 11.9, 13.7, 15.9, 16.8, 17.7, 18.6, 20.2, 20.6, 22.5, 24.4, 24.6, 25.2, and 26.1. The same peaks with reduced intensity were observed in hot melt extrudates of OXC:polymer at 1:1 ratio. OXC remains in crystalline form at 1:1 ratio, however 50 % reduction in OXC crystallinity was

observed at this ratio. The crystallinity of OXC was found to be similar in Soluplus and Kollidon VA 64. At higher OXC:polymer ratio, OXC is molecularly disperse into amorphous polymeric matrix, showing no crystalline peaks of OXC.

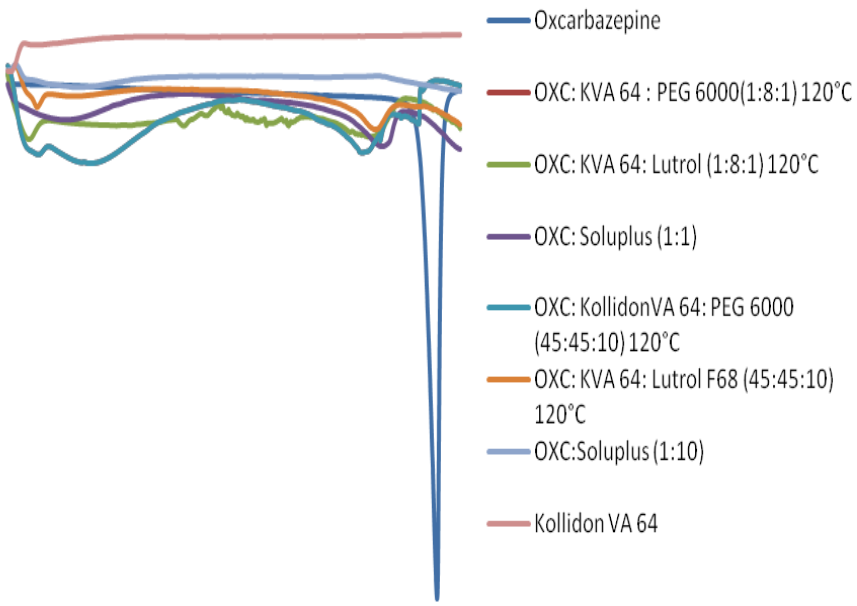


Figure 2: DSC thermograms of OXC, polymers and their hot melt extrudates

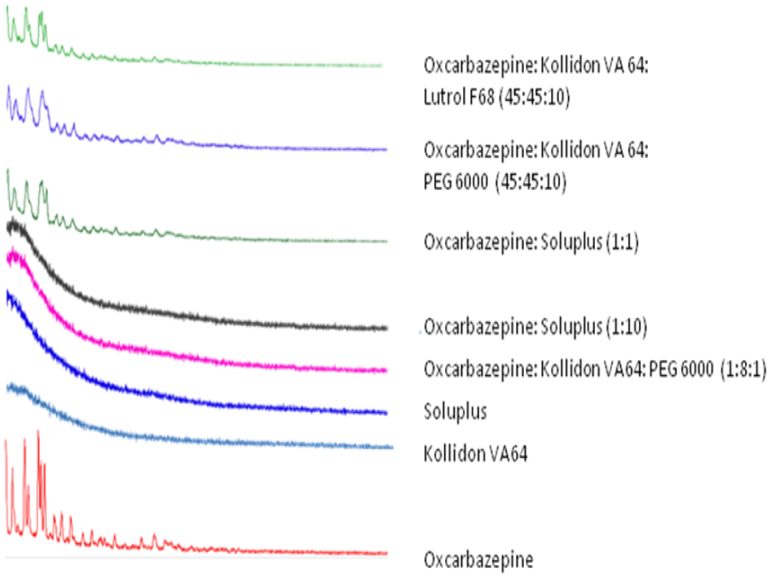
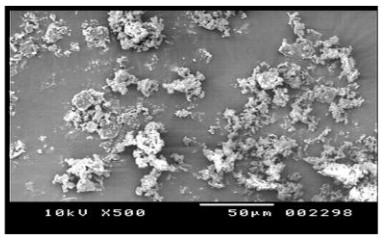


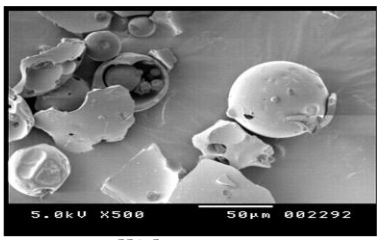
Figure 3: XRD pattern of OXC, polymers and their hot melt extrudates

SEM

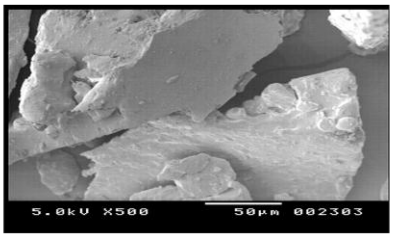
Surface morphology of the pure OXC and its extrudates were observed with SEM (Figure 4). The uniform surface of extrudates indicates the miscibility of OXC and polymer. Moreover, no drug crystals were observed on the surface of the extrudates.



OXC



Kollidon VA 64



OXC – Kollidon VA 64 extrudates

Figure 4: SEM images of OXC, polymer and extrudates

Flow property

Flow property was analyzed after milling and sieving of extrudates from ASTM 40 # sieve. Both OXC:Kollidon VA 64 and OXC:Soluplus, melt extrudates showed the angle of repose near to 30°, carr's compressibility index near to 11 and hausner's ratio near to 1.13 indicated the good flow property of hot melt extrudates. However, compressibility was major issues for Soluplus. Soluplus is an amphiphilic surfactant having mixed surface property of hydrophilic and lipophilic part, so during compression fusion welding is interfered due to hydrophobic surface of Soluplus, which allows compression but consolidation was absent. Moreover, relatively low moisture content of Soluplus hindered its consolidation.

Disintegration test

Effect of particle size of extrudes on disintegration time of the tablets was analyzed to optimize the particle size for further studies. It was observed that particles size of OXC extrudates exhibited significant effect on disintegration time and dissolution of tablet. Finer extrudates resulted in high disintegration time and slow drug release compare to coarser extrudates (Figure 5). No major difference observed between DT of all the disintregrants. However, Kollidon CL SF was found to be superior to others. Type of superdisintegrant (SD) has marginal effect on DT of both Kollidon VA 64 and Soluplus hot melt Extrudates, but addition of > 3 % SD result in significant reduction in hardness. Addition of 2 % MCC and 7 % Kollidon CL SF has significantly reduced the DT upto 22 min. Optimized formula of OXC tablet has been given in Table 2. MCC was found to be better than lactose and mannitol in this regard. Very low porosity of hot-melt extruded solid dispersion, on compression produce tablets with very low porosity. Even though DT of the tablets was high, drug release was complete (Figure 5) within an hour

indicating a rapid erosion of tablet. Drug release is guided only by dissolution from the tablet surface. Due to the low porosity and the stickiness when getting into contact with the dissolution medium, tablets produced from such melt extrudates do not disintegrate. Poor compressibility of soluplus extrudates can be address by addition of MCC.

Table 2: Optimized composition of OXC hot melt extrudates tablet

Ingredient	Weight (mg)
Oxcarbazepine: Polymer extrudes	666.67
Avicel PH 101	15.83
Kollidon CL SF	52.50
Aerosil	7.50
Magnesium Stearate	7.50
Total	**750.00**

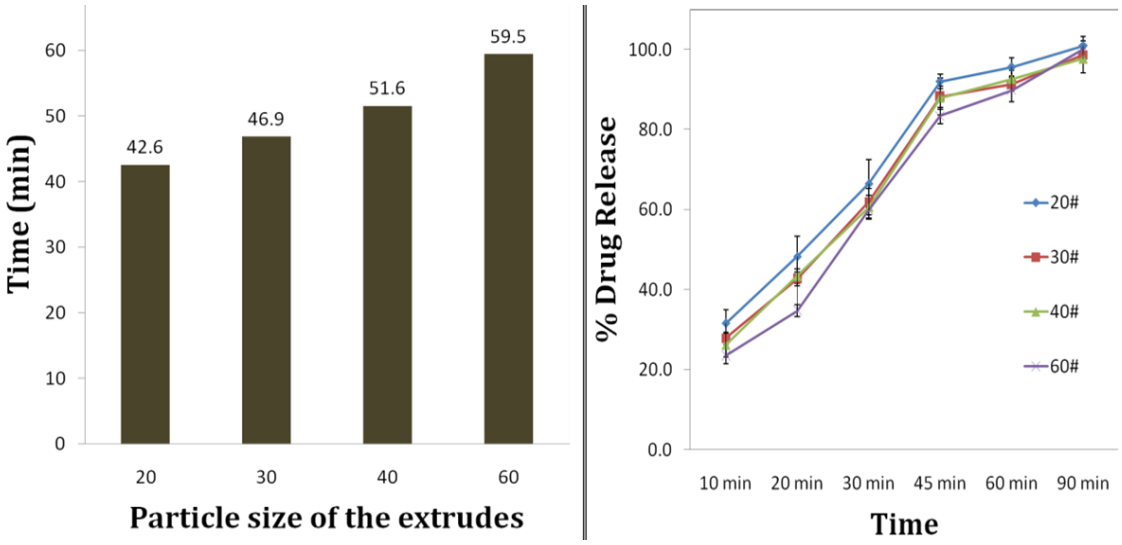


Figure 5: Effect of particle size of melt extrudate on DT and dissolution

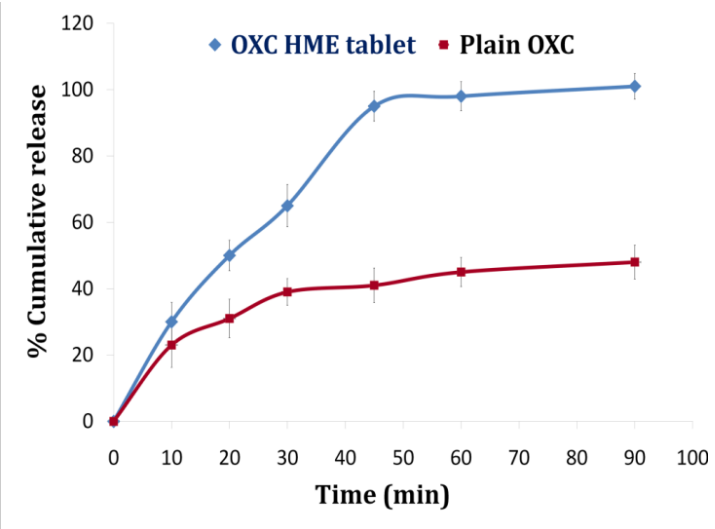


Figure 6: Dissolution profile of plain OXC and tablet of OXC hot melt extrudates

Dissolution study

Plain OXC showed 40 % release within 45 min, but thereafter dissolution is much slower yielding 49 % drug release at the end of 90 min (Figure 6). According to FDA dissolution method database, official dissolution media for OXC contains 0.6 % w/v SLS to maintain sink condition during dissolution[25]. Concentration of surfactant in dissolution media is decided on the basis of saturation solubility of OXC for maintaining sink condition. Saturation solubility of a drug in dissolution media is same, but dissolution profile can be varying according to particle size, solid state, dosage form and excipients in formulation. OXC hot melt extrudes tablet showed significantly higher dissolution - more than 90 % release in 45 min. Enhancement in dissolution is due to reduction in crystallization (50 %) of OXC in hot melt extrudates. Further hydrophilic carrier - Kollidon VA 64 (co polymer of PVP and vinyl acetate) promote the dissolution of OXC by enhancing its wettability. However, still it takes more time than 45 min to complete the OXC release because of slower surface erosion of Kollidon VA 64 tablet.

CONCLUSION

Hot melt extrusion is very versatile technique for enhancement in dissolution of poorly soluble drug. Preliminary studies of solubility and miscibility of drug and polymer is prerequisite for further processing of hot melt extrusion. DSC and PXRD study confirms the reduced crystallinity OXC in solid dispersion with Kollidon VA 64. Transition of polymorphic state of drug from crystalline to amorphous form depends on type of polymer used and drug to polymer ratio. Increase in amount of polymer reduces the crystallinity of drug because of higher chance of formation of molecular dispersion rather than solid dispersion. Addition of fillers and superdisintegrants is very much essential for achieving direct compression and rapid disintegration and dissolution of hot melt extrudates. Still, rapid dissolution of polymer extruded after tablet compression requires further attention and research in this field.

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