PTB Reports, 2016; 2(3): 47-51
A Multifaceted Peer Reviewed Journal in the field of Pharmacology, Toxicology and Biomedical Reports
www.ptbreports.org | www.phcog.net

Review Article

Hot-melt extrusion (HME)and its application for pharmacokinetic improvement of poorly water soluble drugs.

Devendra Ridhurkar*[1], Attila Vajdai[1] and Zsolt Zsigmond[1]

[1]Pharmaceutical Development Division, Egis Pharmaceuticals limited, Budapest, Hungary.

ABSTRACT

For orally administered drugs solubility is one of the rate-limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Poor solubility and poor permeability is responsible for 40 to 70% incidence of delay or failure for new chemical entities during the developmental process. Due to this, formulation scientist faces a major challenge to develope a formulation with good bioavailability.By adopting various technological approaches during the pharmaceutical product development which include physical and chemical approaches such as micronization, pH adjustment, solid dispersion, complexation, co-solvent, salt formation, nanotechnology, use of surfactant, hydrotophy and polymorphs that can be overcome. At present due to its wide applications, simple process and low costs, solid dispersion prepared by hot melt extrusion (HME) has gained popularity in the pharmaceutical industry as a means of improving the bioavailability of drugs. Hot-melt extrusion (HME) is an efficient technology for producing solid molecular dispersions with considerable advantages including the absence of solvents, few processing steps, continuous operation over solvent-based processes such as spray drying and co-precipitation and HME is one of the recommonded process by FDA to encourage move from batch-to-continuous manufacturing.

Key words: Hot melt extrusion, Solid dispersion, Solubility, Bioavailability, Poorly soluble drugs, Absorption.

Correspondence:
Dr. Devendra Ridhurkar, Pharmaceutical Development Division, Egis Pharmaceuticals limited, Budapest, Hungary.

Phone no: +36205950840
Email: devendra@egis.hu
DOI: 10.5530/PTB.2016.2.7

INTRODUCTION

Oral bioavailability of a drug depends on its solubility and/or dissolution rate and dissolution may be the rate-determining step for the onset of therapeutic activity.Therefore, BCS class II and IV compounds are usually characterized by a low bioavailability due to less absorption,which is a major concern of formulation scientist worldwide.[1] Bioavailability of BCS class II and IV compounds can be improved with solid dispersions by different approaches. Among the approaches of solid dispersion, hot melt extrusion (HME) has gained popularity in the pharmaceutical industry as a means of improving the bioavailability of drugs due to its wide applications, simple process and low costs. HME also offers an excellent alternative to other conventionally available techniques such as roll spinning and spray drying as no solvents are required thereby reducing the number of processing steps and eliminating time-consuming drying steps. In addition to being a proven manufacturing process, HME meets the goal of the US Food and Drug Administration's (FDA) process analytical technology (PAT) scheme for designing, analyzing and controlling the manufacturing process via quality control measurements during active extrusion process.[2] The purpose of this review article is to describe novel formulation design by using hot melt extrusion processing technologies for improvement of pharmacokinetic of BCS class II and IV compounds by enhancing solubility.

OVERVIEW OF THE LITERATURE

In literature it was found that number of *in-vitro* as well as *in-vivo* human clinical studies were performed with solid dispersions.

Perissutti and co-workers applied hot-melt extrusion technology to improve dissolution of carbamazepine.[3] The aim of this research was to use a ram extruder to directly prepare a fast release dosage form with uniform shape and density, containing poorly water soluble model drug and polyethylene glycol 4000 (PEG 4000) as a hydrophilic carrier and low melting binder. The investigation revealed that the extruded mixtures of an equivalent composition exhibited more rapid release than simple physical mixtures.

Hülsmann and co-workers worked on hot melt extrusion to improve solubility and dissolution of 17-Estradiol hemihydrate, a poorly water soluble drug.[4] Different compositions of excipients such as PEG 6000, polyvinylpyrrolidone or a vinylpyrrolidonevinylacetate-copolymer were used as polymers and Sucroester® WE 15 or Gelucire® 44/14 as additives. It was observed that the solid dispersions shows a significant increase in dissolution rate when compared to the pure drug or to the physical mixture. A 30-fold increase in dissolution rate was obtained for a formulation containing 10% drug, 15% PVP and 40% Gelucire™ tablets which clearly indicates enhancement of solubility due to hot melt extrusion process.

Loviride is an antiviral drug manufactured by Janssen which is active against HIV by competing with non-nucleoside reverse transcriptase inhibitor (NNRTI).When Loviride was melt extruded to a solid molecular dispersion in HPMC showed remarkable, lower food effect compared to capsules.[5]

Antifungal compositions of intraconazole were prepared as solid dispersions using the melt extrusion process. In a limited number of volunteers these tablets gave an area under the curve (AUC) in the fasted state that was 2.3 times more than the AUC of the marketed reference capsules.[6]

Ritonavir, a HIV protease inhibitor is an important drug to treat HIV infections, but due to its water insoluble nature it shows diminished bioavailability. In order to improve bioavailability of ritonavir by increasing solubility, nano/micro-dispersions of ritonavir were formed upon dispersion of melt extrudate in aqueous medium. The melt extrudate show improved dissolution rate and drug release properties of ritonavir compared to the crystalline raw material and thereby also enhance the bioavailability of ritonavir.[7]

More recently Douroumis and coworkers used HME technique to effectively enhance the solubility of ibuprofen, indomethacin, and famotidine.[8,9]

HOT MELT EXTRUSION PROCESS AND EQUIPMENT

Hot melt extrusion (HME) technology has proven to be a robust method of producing numerous drug delivery systems including improvements in bioavailability and therefore it has been gaining significant attention in the pharmaceutical industry. In short we can say that the melt extrusion process has evolved as an efficient manufacturing technique, to disperse or dissolves the drug in molten polymer, forming a solid dispersion or solid solution.

Extrusion is the process of pumping raw materials at elevated controlled temperature and pressure through a heated barrel of melt extruder into a product of uniform shape and density. The melt extruder comprises of an heating barrels, auxiliary equipment for the extruder, downstream processing equipment and other monitoring tools used for performance and product quality evaluation.[10] The auxiliary equipment for the extruder mainly consists of a heating/cooling device for the barrels, a conveyer belt to cool down the product and a solvent delivery pump. Scale-up models of an extruder with an output of 5-20 kg/hr is available for commercial production.In general, the extruder is composed of a feeding hopper, barrels, single or twin screws and the die and screw–driving unit as shown in Figure 1. The monitoring devices on the equipment include temperature gauges, a screw-speed controller, an extrusion torque monitor and pressure gauges. Though single screw extruder is the most widely used extrusion system, twin-screw extrusion(TSE) is the most common in the pharmaceutical industry because it offers better mixing capability, more stable melting process, shorter residence times and greater output. The screws in the extruder have a shaft onto which elements are placed at different angles viz 0°, 30°, 45°,60°, 90°. They are driven through a splitter/reducer gearbox and rotate together with the same direction of rotation(co-rotating) or in the opposite direction (counter rotating) and are often fully intermeshing. The extrusion barrel with an extruder can be divided into following zones;

Feeding zone: The objective of this zone is to convey material from hopper to barrel.

Melting Zone: The purpose of this zone is to heat/melt the material and reduce its viscosity.

Mixing Zone: In this zone, the material moves in a helical path by means of transverse flow, drag flow,pressure flow and leakage.

Metering Zone: It helps to reduce the pulsating flow of molten mass so that consistent product comes out.

Venting Zone: Remove any of the volatile materials and gases generated during processing.

Shaping Zone: The die can be round, ribbon shaped, film shaped or extrusion can also be carried out without die (in certain cases like controlled release applications).

The depth and/or pitch of the screw flights differ within each zone generating variable pressure along the screwlength (zone dependent). The types of elements used in the different zones constitute the screw configuration that is considered as the heart of the extruder.

CRITICAL PROCESS PARAMETERS

As the extruder has a number of zones[10,11] the barrel of a zone can be heated to a desired temperature depending upon the temperature profile required for extrusion process.[12,13] The temperature profile of the extruder is dependent upon the types of pharmaceutical applications and excipients used. The following process parameters can be directly controlled or monitored to enable extrusion process.

Barrel temperatures: Extrusion temperature profile of various zones is dependent upon glass transition or melting temperature of polymer used and degradation temperature of the drug or the type of application.

Feed rate and screw speed: The constant feeding rate and screw speed throughout the process is important as the combination of these two factors establishes the level of fill in the extruder. Due to constant feed rate and screw speed, there will be a constant amount of material in the extruder and thus the shear stress and residence time applied to material remains constant.

Melt viscosity: Melt viscosity is dependent upon the barrel temperature and molecular weight of the polymer used.

Melt pressure: Melt pressure and melt temperature are the most important parameters as these are the best indicator of extruder function. Process problems become obvious from their values. However, it cannot be controlled directly as it is affected in a complex manner by changing other process parameters such as screw rotation speed and temperature profile.

Melt temperature: Melt temperature is a actual temperature at which blend start melting. It is a function of melt pressure, barrel temperature and viscous heat dissipation.

Die temperature: Die temperature indirectly determines the viscosity and pressure that are necessary to overcome the resistance of the die leading to output.

Vacuum level for venting: During extrusion various gases can be generated due to high heat which may be entrapped in the final product and may impact the quality of product.Hence vacuums are used for the removal of gases effectively that helps to improve the quality of the extrudes.

Die design: The design of the die decides the shape of the extrudes.

MATERIALS USED IN HME FOR SOLUBILITY ENHANCEMENT

Polymers and carriers: HME has been used to improve the bioavailability of drug substances especially those having low water solubility by forming a molecular dispersions by melting the polymers and dispersing or dissolving the drug in molted polymer. Different kind of polymers are available for the application of solubility enhancement which are summurized in Table 1. The selection of polymer for solubility enhancement mainly depends on drug–polymer miscibility, polymer stability and function of final dosage form.

Plasticisers: Plasticisers are typically low molecular weight compounds capable of softening polymers in order to make them more flexible. Plasticisers decrease the glass transition tempearture (T_g) thereby reducing the processing temperature and ultimately improving the stability of the polymer and the drug. Plasticisers decrease the glass transition temperature (T_g) and the melt viscosity of a polymer by increasing the free volume between polymer chains. A reduction in polymer T_g depends upon the plasticiser type and its content. They improve the physico-mechanical properties of the final product.Different kind of plasticisers are available which are summurized in Table 2.

Other Processing Aids: The excessive temperatures needed to process unplasticized or under plasticized polymers,which may lead to polymer degradation. The stability of polymers that are susceptible to degradation can be improved by the addition of antioxidants (butylatedhydroxyanisole, butylatedhydroxytoluene and vitamin E), acid receptors and or light absorbers during extrusion.[14] Chelating agents such as edetate disodium (EDTA) and citric acid are another type of preventive antioxidant. Reducing agents such as ascorbic acid can also be used as antioxidant. Vitamin E TPGS has been reported as to plasticise polymers and enhance drug absorption.[15,16]

PREFORMULATIONS STUDIES FOR SCREENING OF

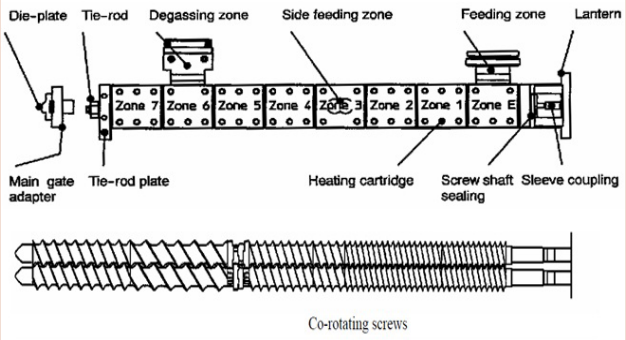
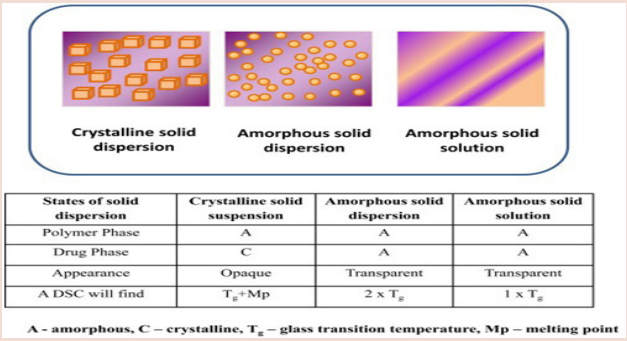


Figure 1: Schematic diagram of an Extruder.



States of solid dispersion	Crystalline solid suspension	Amorphous solid dispersion	Amorphous solid solution
Polymer Phase	A	A	A
Drug Phase	C	A	A
Appearance	Opaque	Transparent	Transparent
A DSC will find	T_g+Mp	2 x T_g	1 x T_g

A - amorphous, C – crystalline, T_g – glass transition temperature, Mp – melting point

Figure 2: Types of solid dispersion.

Table 1: Pharmaceutical grade polymer for solubility enhancement by HME

Chemical name	Tradename	Glasstransition temperature T_g (°C)	T_m (°C)
Polyethylene glycol	Carbowax®	-20	35-65
Hydroxypropyl cellulose	Klucel®	0	180-210
Hydroxypropylmethyl cellulose	Methocel®	160-170	190-200
Polyvinylpyrrolidone-co-vinyl acetate	Kollidon® VA64	101	-
Poly (vinyl pyrrolidone)	Kollidon® 12 PF	90	-
	Kollidon® 17 PF	138	-
	Kollidon®K30	149	-
	Kollidon®K90	156	-
polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol	Soluplus®	70	-
copolymers of ethylene oxide and propylene oxide	lutrol F-127	-	57
	lutrol F-68	-	55

Table 2:Common plasticizers used in pharmaceutical dosage forms

Type	Examples
Citrate esters	Triethyl citrate, tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate
Fatty acid esters	Butyl stearate, glycerol monostearate,stearyl alcohol
Glycol derivatives	Polyethylene glycol, propylene glycol
Phthalate esters	Diethyl phthalate, dibutyl phthalate,dioctyl phosphate
Sebacate esters	Dibutyl sebacate
Vitamin E TPGS	D-α-tocopheryl polyethylene glycol 1000 succinate
Others	triacetin, mineral oil, castor oil

POLYMER

The first and the foremost requirement to carry out the extrusion is extrusion temperature. Generally, extrusion is carried out 20-40°C above glass transition temperature(T_g) of polymer and 20°C below degradation temperature of drug/polymer.[15,17-21]For solubility enhancement the drug should have high solubility/miscibility with the selected polymer. The drug polymer miscibility/solubility can be determined by using the following qualitative techniques;

Solubility parameter: The Hansen solubility parameters of the drug and the polymers can be calculated from their chemical structure to check the miscibility of drug with polymer by using Hoftyzer and Van krevelen method. Materials with similar solubility parameters (δ) values are expected to be miscible. When the difference in solubility parameters of materials is less than five then the drug and polymer are considered to be miscible.

Differential scanning calorimetry (DSC): Modulated DSC is one of the best technique to understand the melting point and glass transition temperature (T_g) of the drug and polymer. If the drug is molecularly dispersed with polymer then single T_g is obtained as shown in Figure 2. Thus, DSC can predict the miscibility of drug with polymer in case of solubility enhancement.

Film casting: In this method drug and polymer are dissolved in a common solvent and a film is casted on glass. The dried polymer film formed may be transparent or API may crystallise. This method can also be used to evaluate tentative amount of drug loading that is miscible with polymer.

Degradation temperature: The degradation temperature of API, polymer and other excipients can be determined using thermogravimetric-analysis (TGA). The temperature at which significant loss in weight is observed can be considered as degradation temperature.

Melt viscosity: A rheoscope can be used to evaluate rheological properties and mixing characteristics of materials. Rheoscope comprises of an optical microscope, digital video camera and temperature control unit used in conjunction with rheometer platform. Rheological phenomena viz shear thinning, dilatancy, thixotropy, gelification, disaggregation, flocculation, homogeneity, orientation melting behavior, mixing etc. can be observed.

EVALUATION OF HME FORMULATIONS

The extrudes obtained from the extruder can be evaluated by using a numbers of techniques.[15] These methods are also useful to differentiate between solid solutions (molecularly dispersed drugs) and solid dispersions (physical mixtures of drug and carrier).

Differential scanning calorimetry (DSC): It can be used for the quantitative detection of transistions like T_g and T_m in which energy is required or liberated. It is also used for the study of drug excipient incompatibility and to identify amorphous and crystalline forms in extrudes.

Thermo gravimetric analysis (TGA): TGA can be used as a screening tool for the thermal stability of materials used in HME. TGA is limited

to studies involving either a weight gain or loss and is commonly used to study desolvation and decomposition.TGA is a measure of thermally induced weight loss of a material as a function of applied temperature.

X-Ray diffraction pattern (XRD): XRD is also used to characterize the crystalline properties of hot-melt extruded dosage forms.Crystallinity is reflected by a characteristic fingerprint region in the diffraction pattern. However, the sensitivity of the XRD technique is limited and can not generally detect crystallinity of less than 10%.

Infrared spectroscopy (IR): Infrared spectroscopy can be used to differentiate between peaks that are sensitive to changes in crystallinity.

Nuclear Magnetic Resonance (NMR): Solid state nuclear magnetic resonance (NMR) has been used to probe the crystallinity of materials and to detect changes in bonding between functional group.

Microscopy: Microscopy is one of the best methods to study the crystalline properties of hot-melt extrudates. Both optical and electron methods are suitable to examine the surface morphology of samples to probe for the presence of crystalline particles or amorphous domains. It is also possible to obtain reliable particle size information using these techniques.

***In- vitro* dissolution testing:** Determination of release profile to surrogate *in-vivo* performance.

Mechanical analysis: Tensile strength and elongation has to be checked to know the plasticity and brittleness of extrudes.

ADVANTAGES AND DISADVANTAGES OF HME

HME offers several advantages over conventionally available pharmaceutical processing techniques including (a) increased solubility and bioavailability of water insoluble compounds; (b) environment friendly and economical as no solvents are required; (c) no residual solvent in final product; (d) avoids the degradation problems thereby resulting in improved stability; (e) economical process with reduced production time, fewer processing steps and a continuous operation with efficient scale-up from laboratory to large scale production; (f) uniform dispersion of fine particles; (g) better content uniformity in extrudates; (h) no requirements for the compressibility of active ingredients; (i) good stability at changing pH and moisture levels and safe application in humans; (j) a range of screw geometries.[15,22-24]

However, HME has some disadvantages as well. The main drawbacks of HME include thermal process (drug/polymer stability) and high energy input, use of a limited number of polymers, high flow properties of polymers and excipients required and not suitable for relatively high heat sensitive molecules such as microbial species and proteins.[15,24]

MARKETED HME FORMULATIONS

Due to extensive work done on HME, every year several HME-related patents have been issued for pharmaceutical industries and have steadily increased since the early 1980s. So far, USA and Germany hold approximately more than half (56%) of all issued patents for HME in the market.[25] Despite this extensive work done, only a few commercialized HME pharmaceutical products are currently marketed with bioavalability enhancement.

Several companies have been recognized to specialize in the use of HME as a drug delivery technology, such as Soliqs® (Abbott), MeltDose® (Veloxis Pharmaceuticals), OptiMelt®(Catalant) and PharmaForm® (Formex). Soliqs® has developed a proprietary formulation which is known as Meltrex® (Amorphous dispersion) and redeveloped a protease-inhibitor combination product, Kaletra® (Ritonavir/Lopinavir). Kaletra® is mainly used for the treatment of human immunodeficiency virus (HIV) infections. The formulated, melt-extruded product was shown to have a significant enhancement in the bioavailability of active substances.[26] Furthermore, melt extruded Kaletra® tablets were shown to have significant advantages for patient compliance (i.e., reduced dosing frequency and improved stability) compared to the previous soft-gel capsule formulation as recognized by the FDA decision to fast-track approval. Norvir® (Ritonavir) which is also used for the treatment of human immunodeficiency virus (HIV) infections was developed by using Meltrex® technology. Additionally, Nurofen (Meltlets lemon) is available on the market as a fast dissolving tablet prepared by similar melting based technique.[9] Ibuprofen has been used as active substance in the Meltlets tablets. Moreover, Soliqs® has also developed a fast-onset ibuprofen system through a HME-related technology called "Calendaring" that was the first directly shaped HME product on the market.

Janssen Cilag recieved the approval from USFDA for etravirine tablets (Intelence®) indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. The formulation was developed by dispersing the drug in hypromellose using hot melt extrusion technology to enhance the bioavailability.

Santarus, developed fenofibrate tablets (Fenoglide™) indicated for the treatment of dyslipidemia. The formulation was developed by using hot melt extrusion process by dispersing the drug in the blend of polyethylene glycol 6000 and Poloxamer 188 in order to enhance oral bioavailability of fenofibrate.

Griseofulvin tablets (Gris-PEG®) based on HME process are available in market developed by Warner pharmaceuticals. Gris-PEG® shows improved bioavailability because of solubility enhancement of griseofulvin due to formation of solid dispersion with polyethyleneglycol.

Lilly developed nabilone capsules (Cesamet®)using polyvinylpyrrolidone as a melt extrusion polymer to make a solid dispersion for improving the bioavailability.[27]

CONFLICT OF INTERESTS

The authors report no conflict of interests.

ACKNOWLEDGEMNT

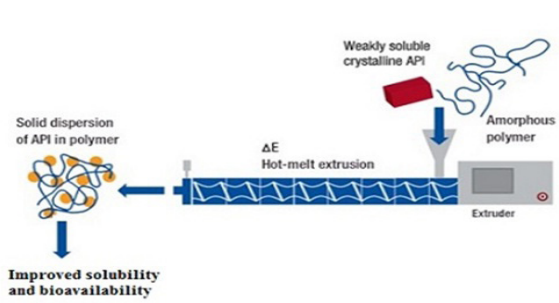
Authors convey thanks to Dr. Adam Orban, for his special guidance and moral support.

REFERENCES

1. Hasnain MS, Nayak AK. Solubility and dissolution enhancement of ibuprofen by solid dispersion technique using PEG 6000-PVP K 30 combination carrier. Bulgarian J Sci Ed. 2012;21:118-32.
2. Charlie M. Continuous mixing of solid dosage forms via hotmelt extrusion. Pharmaceutical Technology. 2008;32(10):76-86.
3. Perissutti B, Newton M, Podczeck F, Rubessa F. Preparation of extruded carbamazepine and PEG 4000 as a potential rapid release dosage form. Eur J Pharm Biopharm. 2002;53(1):125-32.
4. Hülsmann S, Backensfeld S, Keitel S, Bodmeier R. Melt extrusion- an alternative method for enhancing the dissolution rate of 17-estradiol hemihydrate. Eur J Pharm Biopharm. 2000;49(3):237-42.
5. Baert L, Elvire C, Verreck G. Antiretroviral compositions with improved bioavailability. Eur Pat.1997;0872233.
6. Vandecruys R, Gerebern P. Pharmaceutical compositions comprising cyclodextrins. Eur Pat.1997;0998304.
7. Tho I, Liepold B, Rosenberg J, Maegerlein M, Brandl M,Fricker G, *et al.* Eur J Pharm Sci. 2010;40:25-32.
8. Maniruzzaman M, Rana M, Boateng JS, Douroumis D. Dissolution enhancement of poorly water-soluble APIs processed by hot-melt extrusion using hydrophilic polymers. Drug Dev Ind Pharm. 2013;39(2):218-27.
9. Gryczke A, Schminke S, Maniruzzaman M, Beck J, Douroumis D. Development and evaluation of orally disintegrating tablets (ODTs) containing ibuprofen granules prepared by hot melt extrusion. Colloids and surfaces B. 2011;86(2):275-84.
10. Ghebre SI, Martin C. A book on pharmaceutical extrusion technology. Marcel Dekker Inc; NewYork.
11. Klein CE, Acquir J. Immune Defic. Syndr. 2007;44(4):401-10.
12. Martin C. Guidelines for operation of leistritz twin screw extruder. American leistritz corporation, Somerville. 2001;21-5.

13. Breitenbach J. Melt extrusion: From process to drug delivery technology. Eur J Pharm Biopharm. 2002;54(2):107-17.
14. Crowley MM, Zhang F, Repka MA, Thumma S, Upadhye SB, Battu SK, *et al*. Pharmaceutical applications of hot-melt extrusion: Part I. Drug Dev Ind Pharm. 2007;33(9):909-26.
15. Singhal S, Lohar VK, Arora V. Hot-melt extrusion technique. Webmed Central Pharmaceutical Sciences. 2011;2(1):1-20.
16. Khatry S, Abbulu K. Melt extrusion-an overview, International Journal of Pharmacy and Technology. 2011;3:685-03.
17. Andrews GP, Osama AD, Jones DS. Physicochemical characterization of hot melt extruded bicalutamide–polyvinylpyrrolidone solid dispersions. J Pharm Sci. 2010;99(3):1322-35.
18. Prodduturi S, Manek VR, Kolling MW, Stodghill SP, Repka MA. Solid-state stability and characterization of hot-melt extruded poly (ethylene oxide) films. J Pharm Sci. 2005;94(10):2232-45.
19. Saerens L, Dierickx L, Lenain B, Vervaet C, Remon JP, Beer TD, *et al*. Raman spectroscopy for the in-line polymer–drug quantification and solid state characterization during a pharmaceutical hot-melt extrusion process. Eur J Pharm Biopharm. 2011;77(1):158-3.
20. Troup GM, Mckelvey CA, Schenck L, Lowinger M, Rudeen B, Sinha A, *et al*. Process analytical technology for improved process understanding and control of a hot melt extrusion process Merck & Co., Inc., West Point, PA.
21. Sathigari SK, Radhakrishnan VK, Davis VA, Parsons DL, Babu RJ. Amorphous-state characterization of efavirenz-polymer hot-melt extrusion systems for dissolution enhancement. J Pharm Sci. 2012;101(9):3456-60.
22. McGnity JW, Koleng JJ. Preparation and evaluation of rapid release granules using novel melt extrusion technique. American Association of Pharmaceutical Scientists. 2004;153-4.
23. Jones DS. Engineering drug delivery using polymer extrusion/ injection moulding technologies. School of Pharmacy. 2008;4-9:18-7.
24. Grunhagen HH, Muller O. Melt extrusion technology. Pharmaceutical Manufacturing International. 1995;1:167-70.
25. Wilson M, Williams MA, Jones DS, Andrews GP. Hot-melt extrusion technology and pharmaceutical application.Ther Deliv. 2012;3(6):787-7.
26. Klein CE, Chiu YL, Awni W. The tablet formulation of lopinavir/ritonavir provides similar bioavailability to the soft-gelatin capsule formulation with less pharmacokinetic variability and diminished food effect. J Acquir Immune Defic Syndro. 2007;44(4):401–10.
27. Kissel T, Li Y, Unger F. ABA triblock copolymers from biodegradable polyester A-blocks and hydrophilic poly (ethylene oxide) B-blocks as a candidate for in situ forming hydrogel delivery system for proteins. Adv Drug Delivery Rev. 2002;54(1):99-34.

PICTORIAL ABSTRACT



SUMMARY

- The review article is about Hot-melt extrusion, a process used to disperse or dissolve a poorly soluble drug in a molten polymer to enhance its solubility and bioavailability. HME has become increasingly important in pharmaceuticals due to various reasons. Among them the most important are 1) the possibility of dissolving poorly soluble drugs in a solid solution. 2) Continuity of different process steps like mixing, melting, homogenizing and shaping using a single machine and also can be scaled up easily to improve efficiency and decrease operating costs.
- Work in this field is increasing and the literature published reveals many novel and interesting aspects of this technology such as *in-situ* salt formation, fast dispersing systems with foam like structures, complex formation in the melt and nanoparticles. Hence it is real value added technique in pharmaceutical research specially for poorly soluble APIs.

ABOUT AUTHOR

Dr.Devendra Ridhurkar presently working as a Sr.Scientist in Formulation development (Special Formulations) at Egis Pharmaceuticals, Budapest, Hungary. He is working on various formulation technologies to develop the formulation for global market. Prior to this he was associated with platform technology development group at Dr. Reddy's Laboratory, Hyderabad, India. He was involved in development of complex generics using HME, nanotechnology and cyclodextrin complexation techniques etc.

Dr. Devendra Ridhurkar is Ph.D. in Pharmaceutics from I.I.T.BHU., Varanasi. He has over 11 years of formulation development experience in industry. He has worked on new product development for 505 (b) (2), ANDAs for regulatory markets. He successfully developed and filed several products for regulatory market. He has more than 8 international publications and 5 patents to his credit. Also he attended and published several abstracts in national and international conferences.