RESEARCH ARTICLE

Solubility Enhancement of Poorly Soluble Drug by Hot Melt Extrusion Technology

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ABSTRACT

Improving solubility is a major hurdle for the pharmaceutical sector. Boosting solubility andd bioavailability of barely water-soluble medications is essential for efficient drug delivery. Solid dispersion, has gained popularity due to its capability of enhancing solubility and its adaptability in industrial processes. Other techniques like nanonization, micronization, complexation, lipid-based systems, and co-crystals also play vital roles in this area. Each method has its own advantages and constraints, and selection time and again relies on the particular characteristics of the medication and the intended result. It's captivating to observe how these advancements are influencing the future of pharmaceutical development. Its utilization is rising relative to traditional methods due to its process efficiency, solvent-free characteristics, and cost-effectiveness. The current study primarily addresses the process of categorization, preparation methods of solid dispersions, and their application to improve solubility of poorly soluble medications.

Objective of current research work was to enhance solubility of weakly soluble medications employing hot melt extrusion technology (HME) and describes its utilization on solubility besides dissolution enhancement. By boosting solubility enhancement of weakly soluble medications, it leads to increase oral bioavailability and minimizing local as well as systemic side effects and it also increasing patient compliance.

By using this technology prepared extrudes in optimized ratio of API: Polymer and compare solubility study of weakly soluble API against the extrudes prepared using solid solid dispersion technology.

Keywords: Weakly water-soluble medications, Solid dispersion, Solubility enhancement, Minimizing local as well as systemic side effects and Hot melt extrusion technology.

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INTRODUCTION

Hot melt extrusion technology has numerous advantages compared to traditional solid dosage form unit operations[8]. While this technology has long been utilized in the rubber and plastic industries, its application in pharmaceutical product development is rather recent.[1-3] Recently, significant efforts have been made to enhance this technology.[4-8] More than 100 articles have been published in scientific journal, and the quantity of Hot melt extrusion patents has consistently risen[9]. This technique undoubtedly promises to be the future's technology, with extensive applications in the creation of diverse dosage forms. Originally utilized solely for the manufacture of tablets and films, it is now being investigated for the creation of capsules, sustained-release medicines, and implantable devices. HME has proven to be an effective technique for improving various pharmaceutical dosage forms and drug delivery systems[10]. This new technology has numerous benefits as compared to conventional processing, comprising lack of solvents, rapid processing, straightforward and continuous operation, a high level of automation, and the capability to convert poorly compactable materials into tablet form. This approach involves the fundamental stages of combining and liquefying an active pharmaceutical ingredient, polymer, other excipients in hot melt extruder and extrusion through dies using one or more spinning screws to achieve the intended result[11]. The materials employed in hot melt extruded goods must exhibit a certain level of thermal stability alongside satisfactory physical and chemical stability. The interest in HME as a pharmaceutical method is expanding, and recent successes of this technique render it a viable option for drug delivery solutions.

MATERIALS AND METHODS

Component of Hot Melt Extruder

The primary components of an extruder include a feeding hopper, a screw driving mechanism, a revolving single screw extruder comprises one screw, while a twin-screw machine contains two screws[12]. The dimensions and diameter of these screws significantly influence the extrusion process. The length-to-diameter ratio may range from 20:1 to 40:1. This parameter is determined by the product type and the quantity of product to be produced by extruder.

Hot melt-extrusion process

HME incorporates traditional techniques of extrusion, venting, kneading, mixing, and melting[13]. This procedure can be categorized into distinct phases:

a) Feeding extruder

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Table 1: Qualitative and quantitative formulation of Spironolactone extrudes

Sr. No.	Ingredients	Specifications	Actual Qty./ batch (gm) 1:1 ratio	Qty.% w/w	Actual Qty./ batch (gm) 1:3 ratio	Qty.% w/w	Actual Qty./ batch (gm) 1:5 ratio	Qty. % w/w
1.	Spironolactone	USP	150.000	49.75	75.000	24.88	50.000	16.58
2.	Kollidone VA64	NF/PH.EUR	150.000	49.75	225.000	74.62	250.000	82.92
3.	Colloidal silicon dioxide [Aerosil 200 Pharma]	NF	1.500	0.50	1.500	0.50	1.500	0.50
	Total weight		301.500	100.0	301.500	100.0	301.500	100.0

b) Mixing and reducing size
c) Passing melt through die
d) Down stream processing

The drug, polymer, and drug release modifiers are combined, and the resulting physical mixture is introduced into the apparatus via a hopper[14]. Thereafter, the temperature within the barrel escalates. The melt is adequately blended by the internal screw to achieve a homogeneous mass, which is subsequently extruded through the die. The tablets or pellets can be acquired by sectioning the extruded product into the desired shape[15]. The product may be ground to obtain granules, which, when mixed with excipients, can be crushed to form tablets. Screws in extruder possess a shaft onto which components are positioned at various angles: 0°, 30°, 45°, 60°, and 90°. They are powered by a reducer/splitter gearbox and rotate either in the in opposite directions (counter-rotating) or same direction (co-rotating), and are frequently totally intermeshing[16]. Extrusion barrel of an extruder can be categorized in below mentioned zones[17].

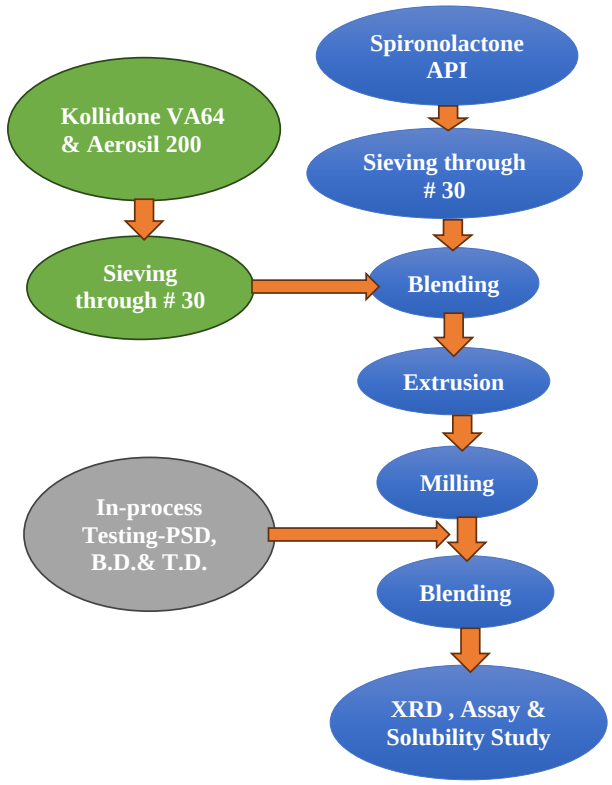

Figure 1: Process flow Diagram

Table 2: Extrusion In- Process Parameters of Spironolactone extrudes

Sr. No.	Feed rate (g / min)	Screw speed (RPM)	Screw Torque (%)
1.	8.00- 15.0	74	95.9
2.	8.00- 15.0	100	42.6
3.	8.00- 15.0	150	49.0

Feeding zone: Purpose of this section is to transfer materials to the barrel from the hopper.
Melting Zone: Viscosity of material is reduced by heating or melting in this zone.
Mixing Zone: A helical course is followed by the material as it travels through this zone, and it does so through the use of transverse flow.
Meter Zone: It helps to minimize pulsing flow of molten material, which results in a product that is consistent throughout the process.
Venting Zone: It is necessary to eliminate any volatile compounds and gases that are produced throughout the processing.
Shaping Zone: In certain circumstances, such as controlled release applications, extrusion can be done without a die[18], and the die can be spherical, film-shaped, or ribbon-shaped. Spironolactone were provided by Tianjin Tianyao Pharmaceuticals Co., Ltd, China, Kollidone VA64 were provided by BASF India Limited, Colloidal Silicon Di-oxide (Aerosil 200 Pharma) were provided by Evonik India Private Limited, India. Spironolactone API and Kollidone VA64 were individually sieved through a mesh #40 or a sieve aperture of 425 µm to achieve homogeneous particle size. Spironolactone API and Kollidone VA64 were amalgamated in a cone blender for 15 minutes at 16 rpm, followed by a 3-minute blending with colloidal silicon dioxide at the same speed. The amalgamation of Spironolactone API was conducted with Kollidone VA64 polymer in various proportions and batch size of each trial were same with 301.5 grams. The experiments utilized the twin-screw Pharma Lab 16 mm from Thermo Fisher Scientific. Spironolactone active pharmaceutical ingredient and Kollidone VA64 polymer blend were introduced into the gravimetric feeder, with the feed rate established between 6.0 and 12 grams/minute. The drug-polymer blend was fed into the extruder to produce a solid dispersion.
The die had a 2 mm aperture. The screw velocity was set at 100 rpm for the co-rotating twin screw. Mixing zones were designated in zones 3 and 6. Configuration of mixing zones

Table 3: In- Process Zone Temperature of Spironolactone extrudes

Sr. No.	Zone	Set Temp. ^{0}C 1:1Ratio	Actual Temp. ^{0}C	Set Temp. ^{0}C 1:3 Ratio 1:3	Actual Temp. ^{0}C	Set Temp. ^{0}C 1:5 Ratio	Actual Temp. ^{0}C
1.	Zone 1	25.0	25.9	25.0	27.2	25.0	28.3
2.	Zone 2	60.0	60.2	60.0	60.1	60.0	60.4
3.	Zone 3	100.0	100.9	100.0	118.2	100.0	99.3
4.	Zone 4	140.0	142.2	160.0	160.7	160.0	160.0
5.	Zone 5	160.0	163.0	160.0	160.7	160.0	159.7
6.	Zone 6	160.0	162.7	160.0	167.9	160.0	159.5
7.	Zone 7	160.0	162.5	160.0	161.1	160.0	159.3
8.	Zone 8	160.0	161.7	160.0	166.2	160.0	159.6
9.	Die	160.0	160.7	160.0	179.9	160.0	160.1

Table 4: Particle Size Analysis of Milled Extrude

Sr. No.	Sive Size	Tare Weight (gms)	Gross Weight (gms)	Net. Weight (gms)	% Retained
1.	20	258.4	258.3	0.1	0.20
2.	40	268.1	267.8	0.3	0.60
3.	60	245.5	238.6	6.9	13.80
4.	80	255.9	243.8	12.1	24.20
5.	100	289.6	280.3	9.3	18.60
6.	Pan	312.1	290.8	21.3	42.60
Total sample weight tested in (g)				50.0	100.00

Table 5: Bulk Density and Tapped Density of Milled Extrudate

Parameters	Batch. No. FT006
Hausner's Ratio	1.27
Tap Density (gms/ml)	0.67
Bulk Density (gms/ml)	0.53
Compressibility Index	21.22 (Passable)

consisted of two 30° elements, one 60° element, and the remainder included 90° components. The collected extrudates were subsequently processed using a hammer mill and filtered through a #40 mesh sieve. Before being used again, the solid dispersion powder was kept in air tight container with a desiccant.

RESULTS AND DISCUSSIONS

Characterization of Solid Dispersions

XRPD (X-Ray powder diffractometer)

X-Ray powder diffractometer analysis was conducted using a D\Max-2400 X-Ray powder diffractometer (Rigaku, Japan). Monochromatic Cu-Kα radiation (λ = 1.5406 Å) was employed throughout a 2θ angle of 2.000° - 40.005° range with an increment of 0.03°. XRPD was utilizsed to confirm crystal form of Spironolactone API and amorphous form in Spironolactone - Kollidone VA64 extrudes in different ratio of API and polymer (1:1 ; 1:3 & 1:5)

The XRPD patterns of Spironolactone API, and Spironolactone - Kollidone VA64 HME extrudes were shown in Fig. 1, 2, 3 & 4. Pure Spironolactone API exhibited strong sharp peaks observed at 2Ɵ = 9.2, 11.5, 12.4, 16.0 , 16.6, 17.3, 18.5, 20.3 , 21.9 and 29.9 ° and Fig. No. 1, demonstrating crystalline state of medication. However, in the XRPD pattern of Spironolactone - Kollidone VA64 HME extrudes (Ration 1:1) in fig. 2, exhibited sharp peaks observed at 2Ɵ = 9.4, 12.3, 15.9, 17.2, 18.4, 19.0, 20.6, 22.8, 23.6 and 32.7 ° , indicating that the Spironolactone –extrudes (Ration 1:1) shows does not convert from crystalline state to an amorphous state, In XRPD pattern of Spironolactone - Kollidone VA64 HME extrudes (Ration 1:3) in fig. 3, exhibited sharp peaks observed at 2Ɵ = 9.1, 12.3, 15.9, 17.2, 20.1,20.3 and 24.6 ° , indicating that the Spironolactone –extrudes (Ration 1:3) shows some sharp peaks of crystalline form are still available in extrudes in 1:3 but in the XRPD pattern of Spironolactone - Kollidone VA64 HME extrudes (Ratio1: 5) , has no dissimilar diffraction peaks were detected in Fig. 4 , suggesting that medication was in amorphous state.

Table 6 : Solubility data of Spironolactone API and extrudes

Name of Solvents/Media	pH	Solubility of Spironolactone API in mg/250 ml	Solubility of Spironolactone Extrudes (Ratio 1:5) in mg/250 ml
Purified water	7	6.69	NA
0.1 N HCl	1.2	6.77	15.0
Acetate Buffer	4.5	8.25	NA
Phosphate Buffer	6.8	8.74	NA

Solubility studies of Spironolactone - Kollidone VA64 HME Extrudes

Spironolactone is virtually insoluble in H_2O. It lacks ionizable groups within 1-11 pH range hence, within that range, it shows no changes in solubility in aqueous buffers. It is practically insoluble in water, mildly soluble in fixed oils and methanol, soluble in alcohol as well as ethyl acetate, and readily soluble in chloroform as well as benzene. Spironolactone was sourced from Tianjin Tianyao Pharmaceuticals Co., Ltd, China and comparative solubility studies were carried out using Spironolactone API (Crystalline form) as well as Spironolactone - Kollidone VA64 extrudes (Ratio 1:5) and results obtained are depicted as follows:

Solubility in water was assessed utilizing the shake flask method. An excessive quantity of solid dispersion sample was introduced into 100 mL of distilled water in a conical flask. The suspension was subsequently agitated in a water bath maintained at a steady temperature of 37 ± 0.5 ◦C for 24 hours. The suspension was passed through Whatman filter paper (no. 40). The solubility of Spironolactone API

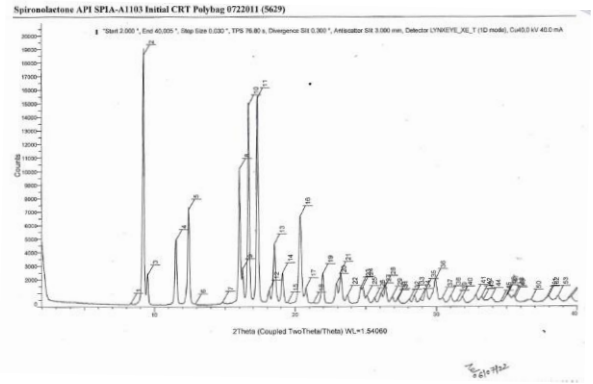

Figure 2 : XRPD Patterns of Spironolactone API (Crystalline form)

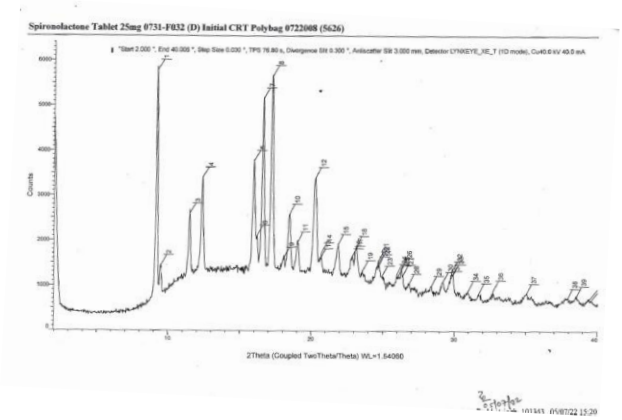

Figure 3 : XRPD Patterns of Spironolactone Extrude (Ratio 1:1)

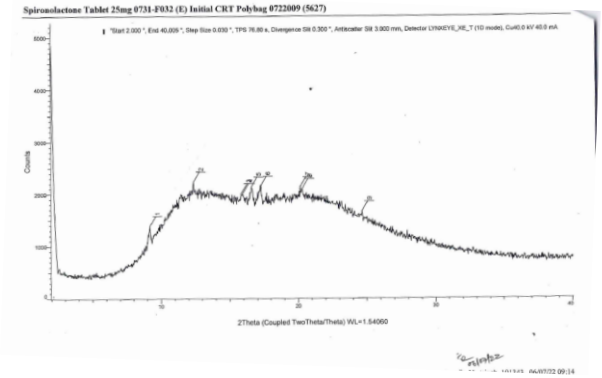

Figure 4 : XRPD Patterns of Spironolactone Extrude (Ratio 1:3)

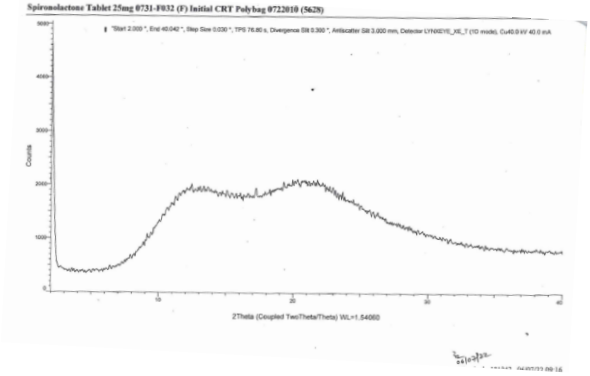

Figure 5 : XRPD Patterns of Spironolactone Extrude Amorphous (Ratio 1:5)

was carried out in different physiological pH 1.0 to 7.0 and solubility shown minimum in all different physiological pH . So based on that solubility of Spironolactone extrudes (Ratio 1:5) was conducted in pH 1.2, 0.1 N HCL and results found enhancement of solubility via solid solid dispersion i.e. HME technology Spironolactone extrudes (Ratio 1:5) as compared to the plain Spironolactone API.

CONCLUSION

Present research focuses on improving solubility of weekly soluble medications utilizing holt melt extrusions technology and the current studies concluded that enhanced solubility of weekly soluble medications. In these studies hot melt extrudes formed using solid solid dispersion method by utilizing hot melt extrusion technology.

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