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PASTILLATION WITH AMORPHOUS SYNTHETIC POLYMERS: A KEY TO SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUGS

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ABSTRACT

Solubility has always been a challenge for the pharmaceutical fraternity owing to the dependency of bioavailability on the same. The objective of the current work was to improve the aqueous solubility of a BCS class II anti-retroviral drug, ritonavir, by using melt technology via the Pastillation technique. EUDRAGIT® EPO was chosen as representative of amorphous high molecular weight synthetic functional polymers. Ritonavir with EUDRAGIT® EPO and other plasticization aid was processed using the melt technique to fabricate ritonavir-loaded pastilles by using an in-house Pastillation device. The ratio of the ingredients was studied using the DOE approach where the quantities of drug, polymer, and plasticizer were studied as independent variables, and dissolution time and processability were studied as responses. The optimized pastilles were further subjected to physicochemical analysis, morphological characterization, in-vitro drug release, and in-vivo pharmacokinetic studies in Wistar rats. It was observed that the optimized pastilles had excellent processability, good physical properties, and an improved dissolution rate compared to the marketed tablets. The improved dissolution was supported by the DSC and XRD data which showed the amorphous conversion of the drug, thus improving solubility in the aqueous medium. In-vivo pharmacokinetic evaluation in rats resulted in an improved bioavailability of the drug from the pastilles compared to the marketed tablets. It is believed that a simple and economic technique such as Pastillation can be efficiently used with high molecular weight synthetic functional polymers to improve the drug solubility thereby improving the bioavailability of the drug, which is a major problem in the pharmaceutical industry.

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Introduction

Solubility in recent years has been one of the important challenges to the research fraternity owing to the hydrophobicity of almost 40% of the drugs in practice [1-4]. Also, a majority of the drug in the developmental pipeline suffer poor solubility thereby low bioavailability, which is a major concern for their clinical use [5]. Around 70 % of the new molecules resulting from the drug development process face rejections due to the high throughput techniques such as in-silico screening owing to the solubility and lipophilicity issues. Nearly 60% of these new chemical entities belong to the Class II of the Biopharmaceutical Classification System (BCS) and have low solubility and high permeability. Despite high permeability, these entities are a solubility/dissolution rate limited and exhibit low bioavailability owing to slow drug release [6]. Traditionally, many techniques such as the use of surfactants, co-surfactants, micronization, solid dispersion, co-processing, etc. have been used to improve solubility. However, each of these methods has its disadvantage [7].

Melt technology in the pharmaceutical industry generally refers to a technological operation that now a days has been explored in excess to produce novel products efficiently and economically. Melt technology is an economic and green technology, which allows dust and solvent-free processes to fabricate final dosage forms involving concerning materials such as elastic materials [8]. The melt technique can result in an amorphous transformation of the action thus improving the dissolution rates and bioavailability thereafter [8]. With the help of a fusion method and by applying temperature, a solid mixture of drugs and various excipients can be melted into drops thereby forming pastilles which is a single step melting process to produce a final dosage form [9]. Pastillation technology has been widely utilized in the food and chemical industry over several years for

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solidification and improved handling of powdered chemicals. Pharmaceutical researchers utilized the combination of Pastillation and melt technology to prepare unit dosage forms for immediate release utilizing various additives [10-12]. During the Pastillation process, certain metastable auxiliary agents such as polyethylene glycols, pyrrolidones, sugar alcohols, etc. are applied. These auxiliary agents despite improving the Pastillation process help synergistically to improve the dissolution rates of the active medicament in the formulation [13]. The process of Pastillation in industries is carried out using an advanced setup known as "Rotoform".

Ritonavir belongs to the HIV-1 specific, protease inhibitor class of drugs falling in the BCS class II category exhibiting extremely low solubility and hence low oral bioavailability [6]. EUDRAGIT® EPO on the other hand is a cationic polymer containing dimethyl amino ethyl methacrylate and neutral methacrylic ester units. EUDRAGIT® EPO is amorphous in nature and soluble in acidic pH and has been widely used in the solubility enhancement of poorly water-soluble drugs [14]. Due to the absence of melting point but shear thinning properties above the glass transition temperature, EUDRAGIT® EPO has been successfully used in melt extrusion processes. Since the pastillation process does not offer any shear, understandably, such polymers have not been used by any researcher yet. The presented work utilizes the melt and the Pastillation technology to fabricate pastilles of ritonavir and EUDRAGIT® EPO. The aim of the study was to convert the drug to its amorphous version by using melt technology in presence of an acid soluble polymer, which would increase the immediate release of the drug in the stomach contents thereby improving the bioavailability.

Materials and Methods

Materials

Ritonavir drug (RIT) and EUDRAGIT® EPO (EPO) were kind gifts from Evonik India PVT. LTD. Polyethylene glycol 6000 (PEG) and stearic acid (SA) were procured from SD Fine chemicals. All other chemicals were procured from local sources.

Methods

Formulation of Pastilles Using Melt Technology [10, 15]

Based on the literature survey, a BCS class II drug was chosen to demonstrate the solubility and bioavailability enhancement. Similarly, EUDRAGIT® EPO was chosen as a solubility-enhancing agent from a class of amorphous high molecular weight synthetic functional polymers. PEG and SA were chosen as plasticizers to aid processibility. The experiments were designed using the one-factor-at-a-time approach wherein the ratio of EPO was kept constant and the ratios of drug and plasticizers were changed strategically in a range between 14.16%-45.45% and 9%-31% respectively **(Figure 1)**. For the formulation of pastilles the drug, EPO and Plasticizer mixtures were heated to a temperature of 70^0 C and the molten mass was dropped on a stainless steel surface maintained at a temperature of 5^0C from a fixed height of 1.5cm, further, the molten mass was allowed to set for a minute and scraped to form small pastille bead. An in-house fabricated pastillation device was used for the fabrication of the pastilles.

LOT	EPO	PEG	SA	RIT
PEG1	1	1		1
PEG2	1	1		0.5
PEG3	1	1		0.33
PEG4	1	0.6		1
PEG5	1	0.6		0.5
PEG6	1	0.6		0.33
PEG7	1	0.2		1
PEG8	1	0.2		0.5
PEG9	1	0.2		0.33
SA2	1		1	0.5
SA5	1		0.6	0.5
SA8	1		0.8	0.5
CON1	1			1
CON2				1

Figure 1. Summary of the experimental plan (Con: Control).

Friability Analysis of the Pastilles

A weighed amount of pastilles samples were placed in the drum of the Roche friabilator (Campbell Electronics, Mumbai, India) and rotated at 25 rpm for 4 min. Further, the pastilles were removed, de-dusted, and accurately weighed to calculate the losses [16]. Friability was calculated by using the following relationship:

$$\% F = (W0 - Wf / W0) \times 100 \quad (1)$$

Where W0 is the initial weight of pastilles and Wf is the weight after the friability test.

In-vitro Drug Release Studies
The release of the drug from pastilles was evaluated by studying dissolution studies in 0.1 N HCl upto 2 h using USP dissolution apparatus (Type II) at a temperature of 37 ± 2 °C and rotation speed of 50 rpm. The aliquots were withdrawn every 15min. The withdrawn aliquots were filtered using a 0.2-µm nylon filter upon which they were analyzed spectrophotometrically at 240 nm to determine the content of the drug.

Differential Scanning Calorimeter Analysis of the Pastilles [17]
The DSC thermogram for the drug and pastilles was recorded using a differential scanning calorimeter (DSC) (Hitachi, DSC 7020). Approximately 5 mg sample was heated in a sealed, pierced aluminum pan and was processed for a temperature range of 30°C to 300°C with a heating rate of 5°C/min under nitrogen stream (flow rate of 40ml/min).

X-ray Diffractometry (XRD) Studies of the Pastilles
X-ray diffraction (PW 3710, Philips Ltd.) studies were carried out using a Cu–Ka radiation source which was used with the scanning rate of 5° C per min at the rate of 2 h/min. X-ray diffraction measurements were carried out on optimized pastille formulation, ritonavir powder, EPO polymer, and PEG 6000.

Scanning Electron Microscopy (SEM) Analysis of the Pastilles
To study the surface morphology, the pastilles were subjected to SEM analysis. The samples were sputtered with platinum in an ion sputter for 300s and the images were collected at an acceleration voltage of 15kV using an electron detector of the scanning electron microscope (FEI Quantum 200E instrument).

In-vivo Pharmacokinetic Studies in Rats
The in-vivo pharmacokinetic studies were approved by the animal ethics committee of the AISSMS college of Pharmacy and all the norms were followed in the due course of the study. For the studies, male Wistar rats weighing about 300g were divided into 2 groups containing 6 animals each. The animals were kept fasted with free access to water for 12 h before dosing. One group was fed with grounded pastilles (0.33mg/kg) suspended in 0.5 % w/v methylcellulose aqueous solution while the other was fed with marketed ritonavir tablet (grounded and suspended in 0.5 % w/v methylcellulose aqueous solution). Post-dosing, blood samples (2 ml) were withdrawn at 0,1,2,3,4,5 and 6-hour intervals from the retro-orbital plexus of the rats and stored in EDTA-coated tubes. The blood samples were further centrifuged at 15,000 rpm for 10 minutes and the separated plasma was stored at -20^0 C for further analysis. The drug content in the plasma samples was analyzed using the bioanalytical HPLC method [18] (Jasco Model PU 2080 Plus pump, Tokyo, Japan).

Results and Discussion

Formulation of Pastilles using Melt Technology
The quantities of the drug, polymer, and plasticizer were optimized with the experimentations as described in the methods. It was observed that with very less or no plasticizer, it was not possible to form good pastilles and tend to tail/ for threads while leaving the pastillation nozzle. With a very high quantity of plasticizer, the pastilles tend to lose their sphericity and flatten out before solidification. The optimized formulation contained 23.07% PEG 6000, 38.16% EUDRAGIT® EPO and 38.16% drug. Most pharmaceutical polymers exhibit pseudoplastic behavior and since the viscosity decreased upon application of shear, these prove an ideal candidate for the hot melt extrusion type of process. However, since the pastillation process is devoid of shear application, difficulty in processing was observed as described above, when the plasticizers were not used or used in suboptimal quantities. With an optimal combination of polymer and plasticizer, it was possible to process such low Tg, amorphous but highly functional polymers, like EUDRAGIT® EPO in pastillation. This finding opens the door for use of more such polymers for various applications in the pastillation process [19].

Friability Analysis of the Pastilles
It was observed that with the increased PEG concentration the friability of the pastilles was seen to increase, the same can be attributed to the brittle nature of the PEG. Similarly, with low quantity of PEG threading was observed which can be attributed to the nature of EPO polymer. The optimized batch was reported to have a friability of 0.75%.

In-vitro Drug Release Studies
From the In-vitro release studies, it was visible that the drug dissolution upon pastillation was improved considerably when compared to the dissolution study of the alone drug. The same can be attributed to the conversion of the active drug into an amorphous form in the due course of pastillation. Also, the amorphous nature and the solubility of EPO in acidic pH provide a synergistic effect in improving the drug solubility and thus dissolution. The release of the drug from pastilles was found to be around 80% at the end of 2hr compared to 35% of bulk ritonavir **(Figure 2)**.

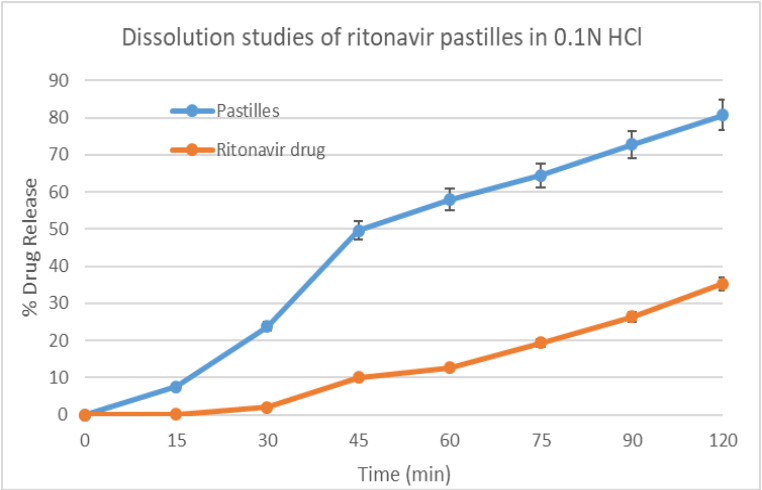

Figure 2. Dissolution studies of the ritonavir pastilles.

Differential Scanning Calorimeter Analysis of the Pastilles

DSC studies conducted on pastilles indicate complete amorphization of the drug and uniform mixing of the ingredients into pastilles. DSC thermogram **(Figure 3)** shows the absence of any thermal event near the melting point of the drug. Also, a significant reduction in the glass transition temperature (Tg) of the polymer was observed in the pastilles containing stearic acid which indicated the interaction between the polymer and plasticizer to form a single system. In the case of pastilles containing PEG as a plasticizer, no such Tg reduction was observed. Distinct endotherm pertaining to the presence of free PEG was also observed in such pastilles. No effect of the presence of PEG on Tg of polymer indicates retention of polymer properties in pastilles and thus possibly better storage stability as an added advantage.

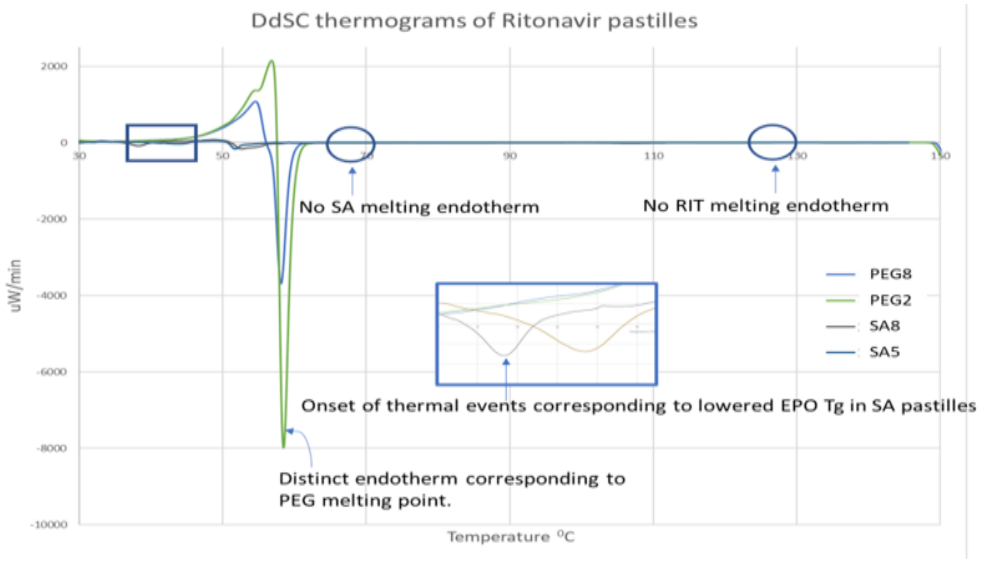

Figure 3. DSC studies of the ritonavir pastilles.

X-ray Diffractometry (XRD) Studies of the Pastilles

X-ray diffractograms of the ritonavir drug exhibited sharp peaks, indicating the crystalline form of the drug. However, in the pastille X-ray diffractogram, it was observed that the ritonavir peak was absent. It is evident that owing to the melt processing the drug was converted to the amorphous form which led to increased solubility. Also, the intensity of the peaks of PEG and polymer was seen to decrease in the formulation X-ray diffractogram indicating uniform and complete mixing of the polymer, drug, and PEG phases **(Figure 4)**.

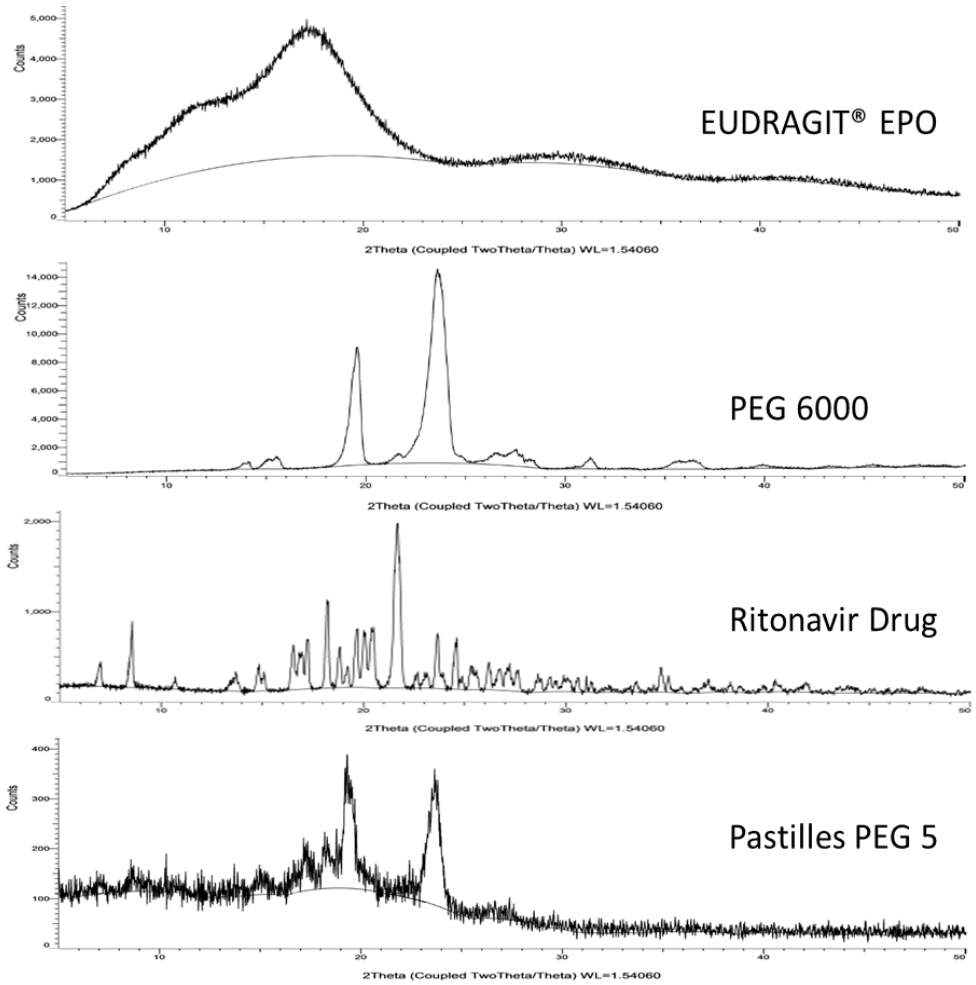

Figure 4. X-ray Diffractograms of EUDRAGIT® EPO, PEG 6000, Ritonavir Drug, and Pastille formulation

Scanning Electron Microscopy (SEM) Analysis of the Pastilles

The surfaces of the pastilles were found to be plain and smooth **(Figure 5)**, Also the drug was completely incorporated into the pastilles as no distinct phases were seen on the surface. The average diameter of the pastilles was found to be 2.9mm.

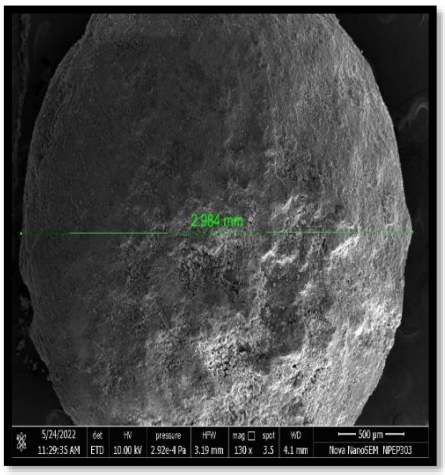

Figure 5. SEM image of ritonavir pastilles.

In-vivo Pharmacokinetic Studies in Rats

It is evident from **Figure 6** that ritonavir pastilles had an improved bioavailability marked by the significant increase in Cmax as compared to the ritonavir-marketed tablets. The same can be attributed to the improved dissolution of the drug from the pastilles leading to improved absorption and thus improved bioavailability. The melt technique used for the fabrication of

pastilles and amorphous polymer content synergistically improves the conversion of the drug to its amorphous form and thus improves solubility. The pharmacokinetic parameters of the in-vivo studies are given in the table below **(Table 1)**.

Table 1. Pharmacokinetic parameters of the in-vivo studies in Wistar rats

Parameter	Pure Drug	Pastilles
Ke	0.123	0.107
Cmax (ng/ml)	4.69	8.19
Tmax	2 hr	2hr
AUC t-t∞	11.707	24.953
AUC 0-t	55.480	82.473
AUC 0-∞	67.187	107.426

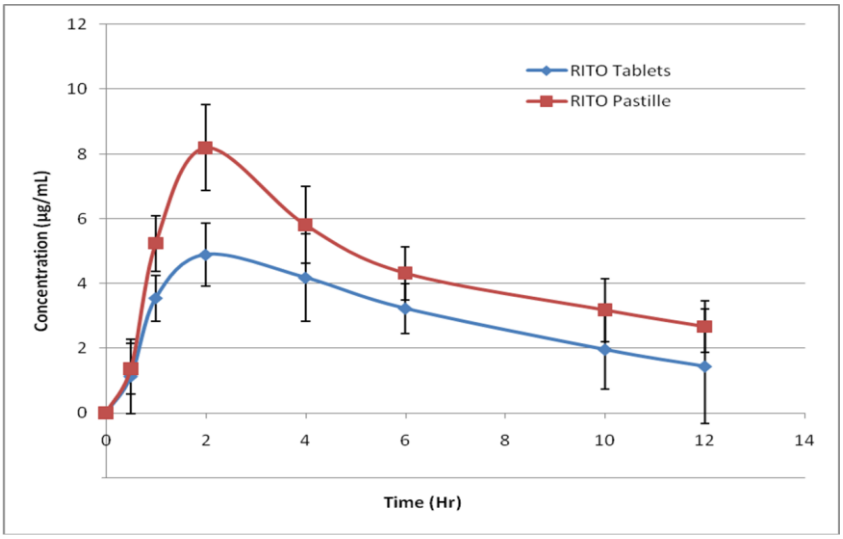

Figure 6. Plasma drug concentration-time profile of the drug and optimized batch pastilles in rats. (n=6)

Conclusion

The aqueous solubility of poorly soluble drugs is a prime issue in the pharmaceutical industry and requires utmost attention as the fate of the newly developed molecules depends on their aqueous solubility. Numerous solubility enhancement techniques have been tried by the research fraternity, however, the authors believe that a simple, economic and effective technique for solubility enhancement is the need of the hour. The authors, through the presented work, demonstrated that solubility enhancement could be well achieved by the use of high molecular weight non-melting synthetic amorphous polymers via the pastillation technology. By taking care of various formulation requirements, such as the right choice of plasticizers and overall composition, the authors were able to achieve the solubility and bioavailability enhancement along with associated desired properties of the pharmaceutical formulations such as acceptable hardness & friability values and shelf-life stability. The authors are of the view that a novel combination of high molecular weight non-melting synthetic amorphous polymers with pastillation technology can open the door to much unmet solubilization needs that the pharmaceutical industry is facing.

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Ethics statement: None

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