International Journal of Pharmaceutical research and Applications
Volume 8, Issue 4, Jul.-Aug. 2023, pp: 443-451 www.ijprajournal.com ISSN: 2456-4494

Sustained Release Spheroidal Pastilles Using Novel Low Density Bed Deposition Technology

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Date of Submission: 04-07-2023 Date of Acceptance: 16-07-2023

Abstract:
Spheroidal particles like pellets provide number of advantages over conventional tablets both from biopharmaceutical and pharmacokinetic perspective. Use of pastillation technique to fabricate highly functional dosage forms such as sustained release has not been fully explored. The aim of the presented work was to fabricate sustained release spheroidal pastilles using Novel single step pastillation technology. The objective was to fabricate sustained release spheroidal particlesof BCS class I antihypertensive drug, Metoprolol Succinate and a unique anionic methacrylate copolymer, EUDRAGIT® FS 100 using Low density bed deposition (LDBD) process. Aerosil® 200 was used as deposition bed for facilitating solidification and spheronization of pastilles. The ratio of the ingredients was studied using DOE approach where the quantities of drug, polymer, and plasticizer were studied as independent variables. Processability, extent of dissolution and aspect ratio of pastilles were studied as responses. It was observed that the optimized pastilles had good sphericity, processability, acceptable physical properties, and sustained release characteristics. DSC and XRD data showed the amorphous conversion of the drug, thus enhancing release characteristics from pastilles. In conclusion the study provided strong evidence that simple but effective modifications in commercially viable and economic production technologies such as Pastillation, can be advantageously used for producing spheroidal functional particles for pharmaceutical formulations in a single step production process.

Keywords: Pastillation, EUDRAGIT®, Sustained release, sphericity, Aerosil®, LDBD

I. Introduction:

In the recent years, multiparticulate dosage forms also known as microparticles have expanded in popularity for a varied number of motives such as sustained or controlled release of medicaments, zero order dissolution rate, less dosing frequency etc [1]. There has been considerable amount of research efforts which have been disbursed on sustained or oral controlled release multiparticulate systems for drug delivery owing to its advantages over the monolithic forms of dosage formulation [2].

Multiparticulate oral dosage forms are generally a collection of a multiple small isolated units which unveil certain distinct characteristics. Generally in the multiparticulate dosage forms the drug substances is plurally divided amongst the multiple subunits, thereby giving the dosage form its unique characteristics [3]. These multiparticulate unit can also be coated so as to achieve sustained release characteristic where the drug containing spheroidal particles act as reservoir. Fabrication of spherical particles in pharmaceutical arena is generally limited to a handful technologies such as wrusters process, extrusion-spheronization, tangential spray etc. These processes are generally time consuming and involve multiple steps making the overall process complex. Techniques like pastillation on the other hand provide a simple, single step formation of multiparticulates[4,5].

Patillation technology is a widely used process in the field of agro-chemical, petrochemical and chemicals for solidification of hazardous and dusty powders or chemicals into pastilles which are hemispherical solid units having uniform size. Pastillation, thus eases the handling of such hazardous moieties. The process of pastillation involves dropping of molten chemicals from a certain height onto a cooled metal surface for its

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rapid solidification and formation of uniform dimension pastilles. Depending on the viscosity of the melt, the dropping height and the surface, the pastilles flatten to a certain extent or form a semi-spherical unit [6]. The large scale pastillation is generally carried out using special equipment known as 'Rotoformer'

Geometry is an important parameter when it comes to multiparticulates in pharmaceutical industry. Spherical particles provide a varied number advantages ranging from improving functional characteristics to process improvement characteristics. Sphericity other than providing improved surface area, provides numerous handling advantages such as ease in coating, excellent flowability, uniform drug distribution, compaction to Multiple-Unit Pellet System etc [7,8]. Spherical microparticles are generally a choice for the sustained release delivery systems as they provide high flexibility in controlling the release. Sustained release delivery systems are designed to accomplish a prolonged and controlled therapeutic release of drugs which leads to a better management of chronic or acute conditions. Although, several attempts have been previously made by researchers to prepare spherical pastilles, the same consisted of multiple steps thereby making the process complex. In this article we have attempted a novel single step pastillation technique, LDBD, for fabrication of spherical sustained release pastilles.

II. Materials and Methods:

2.1. Materials:

Metoprolol Succinate drug, EUDRAGIT® FS 100 and Aerosil® 200 were kind gifts from Evonik India Pvt Ltd. Polyethylene glycol 6000(PEG) was procured from SD Fine chemicals. All other chemicals were procured from local sources.

2.2. Methods:

2.2.1. Formulation of spheroidal pastilles [1,5,9] coupled with LDBD process

Based on the literature survey, a BCS class I drug, Metoprolol Succinate was chosen to check the sustained release characteristics of the formulations. EUDRAGIT® FS 100 was chosen as a matrix forming agent from a class of amorphous high molecular weight synthetic functional polymers dissolving only above pH 7.2. PEG 6000 was chosen as a plasticizer to aid processibility. Aerosil® 200 was chosen as an agent to assist the LDBD process. The experiments were designed using full factorial approach wherein the amount of drug was kept constant and polymer and plasticizer concentration were strategically varied (Table 1). For the formulation of pastilles, the mixture of drug, FS 100 and PEG 6000 were heated to a temperature of 65^0 C ($\pm 5^0$ C) and the resultant molten mass was dropped from a fixed height of 1.5cm on a bed of Aerosil® 200 (about 2 inches thick filled in a flat container) at room temperature. After all the molten mass was processed, the contents of the flat container were sifted thru 20# ASTM sieve to separate out the pastilles. An in-house fabricated pastillation device fitted with 16-gauge stainless steel needle was used for the fabrication of the pastilles.

Table 1: Summary of the experimental plan

LOT	EUDRAGIT® FS 100	PEG 6000	API: Excipient ratio
PE1	1.13	1.13	1:2.25
PE2	1.13	0.75	1:1.86
PE3	0.75	1.50	1:2.25
PE4	1.50	1.50	1:3.00
PE5	1.13	1.50	1:2.63
PE6	0.75	0.75	1:1.5
PE7	0.75	1.13	1:1.86
PE8	1.50	1.13	1:2.63
PE9	1.50	0.75	1:2.25
CON1	1.50	--	1:1.5

2.2.2. Drug content analysis of the pastilles:

The drug content of the optimized pastilles was determined by using a UV spectrophotometry method. Briefly, a known amount pastilles were crushed and converted to powder, the powder was further sonicated with methanol to extract the drug. Drug content was analysed spectrophotometrically at 224 nm by plotting a calibration of the same in methanol using Jasco 550 UV visible double beam spectrophotometer

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2.2.3. Physical characterization of the pastilles:
2.2.3.1.Particle size determination:
The particle size of the pastilles was calculated using optical microscopy. Fifty random pastilles were selected and their maximum and minimum diameters (multiple view) were measured using optical micrometer and the average values were recorded.

2.2.3.2. Friability analysis of the pastilles:
For the friability analysis a weighed amount of pastilles formulation were engaged in the drum of the Roche friabilator (Campbell Electronics, Mumbai, India) which was further rotated at 25 rpm for 4 min. The pastilles were further removed, de-dusted, and weighed accurately to calculate the losses [10]. The friability was calculated using following equation:
% F = (W0 – Wf / W0) * 100
W0: initial weight of pastilles, Wf: weight after the friability test.

2.2.3.3. Aspect ratio measurements on spheroidal pastilles
Aspect ratio of the pastilles was calculated using optical microscopy [11,12]. Fifty random pellets were selected and their maximum and minimum diameters (multiple view) were measured using optical micrometer. The Aspect ratio (AR) for a particle was calculated using the following equation
AR= dmin/dmax
dmax: maximum diameter, dmin:minimum diameter
A mean of AR values along with standard deviation from measurements of all 50 pastilles, was calculated for each batch.

2.2.3.4. Scanning Electron Microscopy (SEM) analysis of the pastilles:
The surface morphology of the pastilles were carried out using SEM analysis (FEI Quantum 200E instrument).
The samples for the analysis were sputtered with platinum using an ion sputter for 300s and the images were recorded at an acceleration voltage of 15kV using an electron detector.
2.2.4. In-vitro drug release studies:
Pastilles equivalent to ~50mg of Metoprolol succinate were filled into size '0' empty hard gelatin capsules and were subjected to dissolution in pH 6.8 buffer upto 10h by using USP dissolution apparatus (Type II) at a temperature of 37 ± 2 °C and rotation speed of 50 rpm. Aliquot samples withdrawn every 15min were filtered using a 0.2-µm nylon filter and analysed spectrophotometrically at 224 nm to determine the drug content [13].

2.2.5. Differential Scanning Calorimeter analysis:
The DSC thermogram for metoprolol and pastilles were recorded using a Hitachi, DSC 7020 differential scanning calorimeter. For the analysis approximately 5 mg sample was sealed in an aluminium pan, pierced and subjected to 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).

2.2.6. X-ray Diffractometry (XRD) studies of the pastilles:
X-ray diffraction studies for the pastilles and drug were carried out using a PW 3710, Philips X-ray diffractometer employing a Cu–Ka radiation source. The scanning rate employed by the diffractometer was 5° per min. X-ray diffraction measurements were carried out on optimized pastille formulation, drug powder, bulk polymer, and PEG 6000

III. Results and Discussion:

3.1. Formulation of pastilles and measurement of aspect ratio
The quantities of the drug, polymer, and plasticizer were optimized with the experimentations as described by the full factorial design. It was observed that with less amount of plasticizer there was thread like formation as the molten mass left the pastillation nozzle. Similarly, high plasticizer concentration caused the pastilles to lose their sphericity and flatten out before solidification. The same was indicated from the below depicted equation generated from the Design of Experiments software.
Processability =1.00000 +0.000000 * FS100 +2.66667 * PEG6000+0.000000* FS 100 * PEG 6000
The optimized formulation contained 47.92% PEG 6000, 36.10% EUDRAGIT® FS 100 and 15.97% drug.
It was observed that the quantity of PEG and overall melting ingredients in the formulation had a clear impact on processability, with higher quantities of PEG favoring acceptable processability factor of > 4. Aspect ratio (AR) on the other hand, was apparently affected by presence of all the ingredient in optimal concentrations. While high PEG concentrations could impart

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fluidity to the molten mass and improve processability, very high concentrations with respect to FS 100 appeared to to distort the spheroidal shape during solidification process, as seen via low aspect ratio values. Presence of the drug as melting ingredient, also appeared to be contributing to improvement in AR values in optimal formulations. The fabricated pastilles were spherical and were found to have the AR close to 1, indicating sphericity of the formulations. Figure 1 displays processability factor recorded on the scale of 0 to 5 and aspect ratio on the scale of 0 to 1.

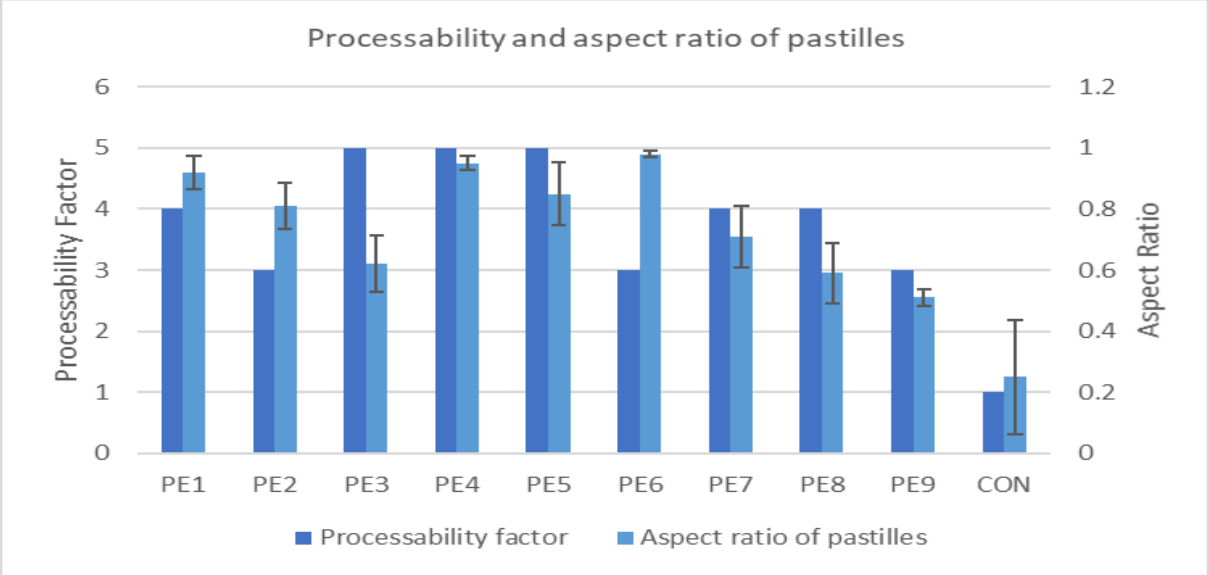

Fig 1: Processability and aspect ratio of the formulated pastilles; The processability was assigned a score on the scale of 1-5 where 1 meant least processable mix and 5 was the best

3.2. Drug content analysis of the pastilles:
The metroprolol content in the pastilles was determined and it was observed the drug content was found to be in the range of 99.5% to 101.4% of the theoretical content. The appropriate drug content established the uniform drug distribution potential of the fabrication technology used.

3.3. Physical characterization of the pastilles:
3.3.1. Particle size determination:
The average size of the pastilles were found to be around 1.93 (± 0.14) mm. The uniform size of the pellets was attributed to the smooth functioning of the fabricated in-house equipment as well as the cushioning effect provided by the silica bed used during the fabrication of pastilles.

3.3.2. Friability analysis of the pastilles:
Friability data (fig 2) shows acceptable performance by most formulations, with friability values bellow 1% w/w. 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. Conversely, higher amount of the methacrylate polymer provided strength to pastilles helping in reduction of friability.

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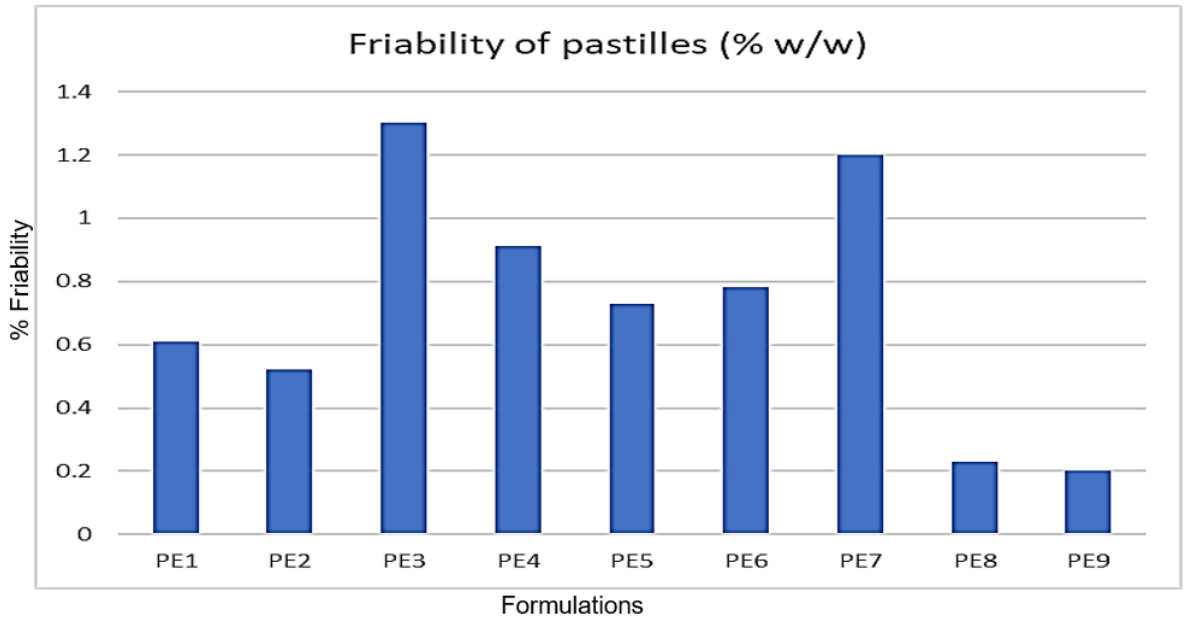

Fig 2: Friability of Metoprolol succinate SR pastilles.

3.3.3. Scanning Electron Microscopy (SEM) analysis of the pastilles:

The pastilles of optimized batch were were spherical in appearance (Fig 3a). Presence of colloidal silicon dioxide on surface of pastilles used for solidification process and spheronization, was seen (fig 3b and 3c). Additionally, presence of colloidal silico dioxide is also expected to change surface charactristics of the pastilles and help in managing possible stickiness and flow properties.

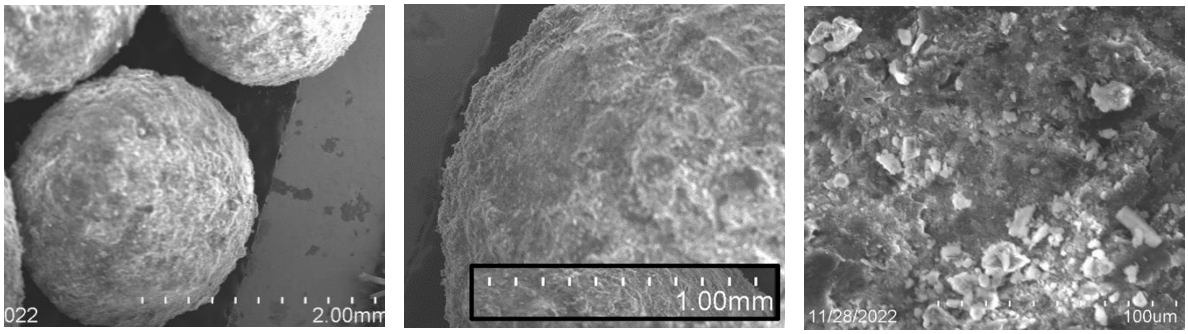

Fig 3: SEM image of Metoprolol pastilles.

3.4. In-vitro drug release studies:

From the dissolution profiles (figure 4), it was clearly evident that the drug release from pastilles could be sustained for significant period of time from all the formulations. While in most formulations, release profiles followed mixed order pattern, with flattening of curve towards end of studied time, formulations PE4 and PE5 indicated an uniform linear release depicting a zero order release. It appears that optimal ratio the polymer, EUDRAGIT® FS 100 and the plasticizer has significant role in ensuring end release of drug from pastilles.

Apparently, close to zero order release coupled with high end release achieved in this formulation is an effect of optimal ratio of release controlling excipient, plasticizer and its relative concentration with respect to the drug. Presence of amorphous form of active in pastilles is also believed to further ensure end release at appreciable rate. Role of PEG 6000 in formulation is dual as a plasticizer and a pore former. Presence of PEG in free crystalline

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form is believed to be helping in sufficient pore formation and complete release of API.

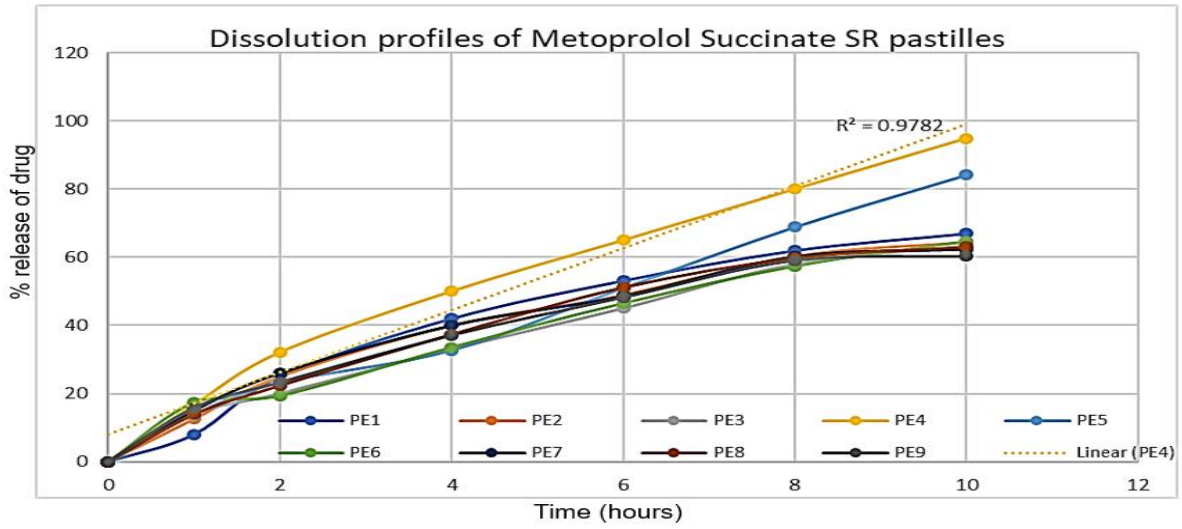

Fig 4: Dissolution profiles of Metoprolol succinate SR pastilles.

3.5. *Differential Scanning Calorimetry analysis of the pastilles:*

DSC studies conducted on pastilles indicate complete amorphization and solid solution of the drug and uniform mixing of the ingredients into pastilles. DSC thermogram (Fig. 5) shows the absence of any thermal event near the melting point of the drug, while such endotherm was clearly seen in case of Metoprolol succinate API and its physical mixture with PEG 6000 and EUDRAGIT® FS 100 [14]. Additionally, distinct endotherm pertaining to the presence of free PEG was also observed in such pastilles. Solid solution form of drug coupled with sustained release characteristics provided by the polymer, is expected to provide more reproducible dissolution performance and complete release of active from pastilles

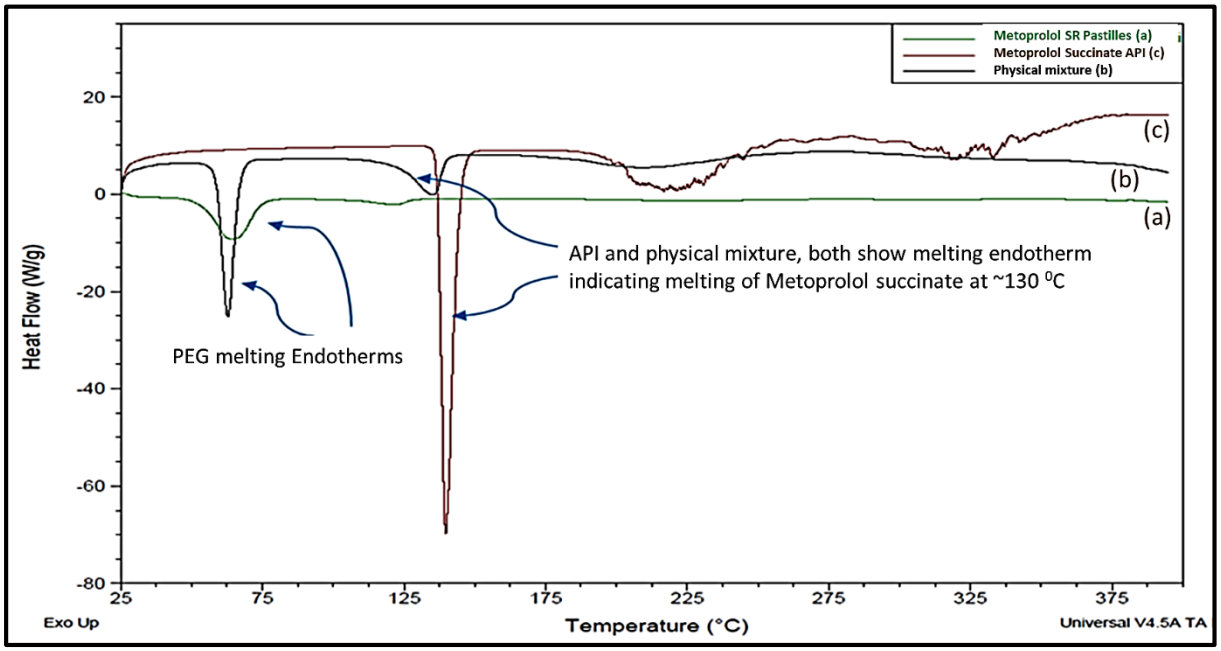

Fig 5: DSC studies of the Metoprolol pastilles.

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3.6. X-ray Diffractometry (XRD) studies of the pastilles:

EUDRAGIT® FS 100 displayed amorphous nature understandably, due to its high molecular weight methacrylate backbone. X-ray diffractograms of the Metoprolol Succinate drug exhibited sharp peaks, with marker peaks identified at 2 theta value of ~14 and 20. Sharp peaks were also noted for PEG 6000 at 2 theta values of ~19 and ~23. This indicated crystalline form of API and PEG, both. However, in the X-ray diffractogram of the pastilles, marker peaks of Metoprolol Succinate were missing. This indicated amorphization of API in pastilles evidently due to the melt process and further assistance provided by the methacrylate polymer backbone [15]. Also, In the diffractogram of pastilles, two peaks pertaining to presence of crystalline form of PEG were prominently seen. While no investigation related to quantification of PEG were done, decrease in peak intensity appeared proportionate to the amount present in the pastilles (fig. 6). The role of PEG in such form is believed to be contributing towards processability and sphericity of pastilles.

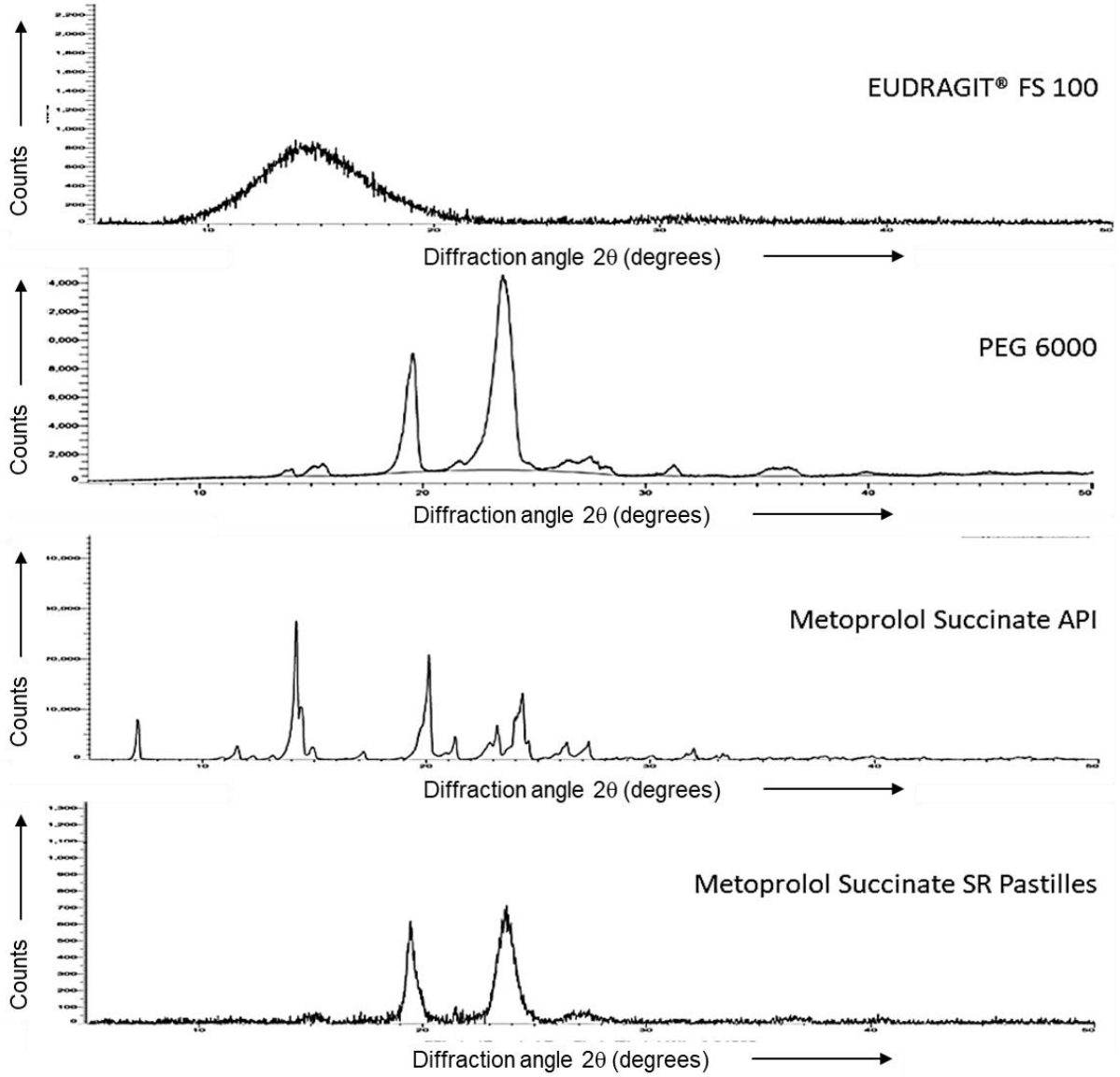

Fig 6: X-ray Diffractograms of EUDRAGIT® FS 100, PEG 6000, Metoprolol Succinate Drug, and the Pastille formulation

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IV. Conclusion:

Although well accepted and widely used, formulation and manufacturing of spherical modified release pellets conventionally requires use of multiple step, resource and time intensive technologies. Use of pastillation technology has been reported with few lipidic excipients to formulate hemispherical or flat pastilles, which can not replace the pellets due to the suboptimal shape and thus limited versatility it offers. Formulation of modified release, spheroidal, pellet like pastilles using amorphous, highly functional, non-melting but low Tg polymers has never been attempted before. The authors in this work fabricated spherical sustained release pastilles employing a single step LDBD process, which is economic and industrially feasible. The technique employed by the authors involving fewer variables works as a continuous process of manufacturing. The spherical pastilles thus produced not only eases the handling and processibility of the final formulation but also provides all the added advantage of the pellet system used in pharmaceutical industry. The fabrication technique used by the authors also causes amorphization of the drug which can be further used to prepare flexible release regimen of different BCS Class drugs as required. Further downstreaming processes such as functional coating or compression into MUPS tablets can be explored. The process used for cooling and spheronizing the pastilles at ambient temperature, uses significantly less energy in production and thus has a remarkable potential of reducing overall carbon footprint and enabling sustainable future.

Acknowledgement: The authors would like to thank the management of AISSMS College of Pharmacy for their support in the due course of this experimental work

Author Contributions:
Mr. Ashish Guha was involved in the conceptualization, resources, methodology, formal analysis, data curation, writing, review & editing of the manuscript. Prof. Mangesh Bhalekar was involved in conceptualization, supervision, data curation, investigation and validation of the work. Prof. Ashwini Madgulkar was involved in supervision, data curation & review of the work.

Conflict of Interest: The authors have no conflict of interest to declare

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