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Short Communication

COMPRITOL® 888 LIPID MATRIX VIA TWIN SCREW EXTRUDER

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ABSTRACT

Objective: The objective of this research was to explore the potential of Hot Melt Extrusion (HME) technique by using theophylline as the model drug to produce sustained release tablets utilizing Compritol®888 ATO as the retarding material and to study the influence of lipid: excipient ratio, excipient type as well as the processing conditions of the extruder on the release profile.

Methods: The tablets prepared using hot fusion method was compared to the ones concocted by the HME technology. During the HME process, a powder mixture of moisture-free drug, lipid, and other adjuncts was introduced into the extruder and liquefied inside the barrel of the extruder. The *in vitro* dissolution studies of the formulations were carried out in pH 7.2 buffer using USP Apparatus 2. The extrudates were characterized via differential scanning calorimetry.

Results: Comparing the two methods of processing, it was observed by the dissolution studies using phosphate buffer pH 7.2, that the tablets prepared by Hot Melt Extrusion method had a higher extent of release where all 3 formulations crossed 80% at the 8-hour mark, whereas the tablets prepared by hot fusion method did not show such consistency.

Conclusion: This study demonstrated the fact that Compritol®888 ATO is a suitable waxy material that can be used as a matrix-forming agent to control the release of theophylline using the Hot Melt Extrusion process.

Keywords: Theophylline, Hot-melt extrusion, Compritol®888 ATO, Sustained-release tablets, lipid matrix

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Theophylline (1,3 dimethylxanthine) is a naturally occurring alkaloid, closely affiliated to caffeine. Its primary use is in the treatment of reversible airway obstruction and an adjunct to the therapy of left ventricular failure [1]. Sustained release of drugs alleviates the patient's burden by reducing the dose frequency. Therefore, it is necessary to use dissolution methods during the development stage of oral SR tablets in order to allow pharmacokinetic screening, hence to predict the absorption rate and the bioavailability [2]. One of the main issues with the existing Theophylline sustained-release tablets is the difficulty to control the release rate of the drug. Moreover, the drug release rate is likely to differ between batches, and advanced technology is needed to ensure consistency among the tablets [3]. Drug absorption from a conventional matrix tablet is greatly affected by its transition rate in the gastrointestinal tract, and correspondingly, the bioavailability varies widely [4].

There are various methods to formulate sustained release tablets, such as Diffusion Sustained Release, Dissolution Sustained Release, pH-Dependent System, Altered Density System, Osmotic Pump System, Ion Exchange System [5]. The drug release from the undermentioned formulation might be attributed to the diffusion-controlled mechanism.

The choice of the matrix is essential because the matrix will regulate the drug release from the formulation and thereby sustain the therapeutic action over time [6]. Compritol®888 ATO which consists of glyceryl behenate, a fatty acid ester of glycerol with an HLB of unit value, with low fusion point, has been employed as retard material for sustained-release dosage forms [7]. Glyceryl behenate is a waxy material, originally applied as a lubricant for tablets and is now widely used as a sustained-release excipient.

Multiple methods have been employed to procure sustained-release dosage forms from glyceride-based formulations, i.e., thermoplastic or melt granulation [8], melt pelletization [9], hot-melt extrusion [10] and hot-melt coating [11]. In hot-melt extrusion technology process, polymer and excipients are conveyed by a rotating screw through a heated barrel of the extruder. The polymer melts at the high temperature, and the molten mass is incessantly pumped through the die connected at the end of the barrel. The molten polymer rapidly solidifies when the extrudate exits the machine through the die. When the shape of the die is changed, the final product may take the form of a film, pipe, tube, or granule [12].

Hot Melt Extrusion (HME) technology has numerous benefits which include the creation of unique dosage concepts, easily monitored which provide comprehensive documentation and simplifies quality control, continuous process with lower batch to batch variation, the potential for automation with reduction of capital investment and labor costs. Also, HME is an environmentally friendly process since the process does not require the use of solvents [13, 14]. Other than enhancing the bioavailability of a drug, the technique is useful to produce modified-release formulations with delayed drug delivery characteristics along with being capable of masking the taste, thus increasing the palatability [15].

The objective of the study was to formulate theophylline sustained-release lipid matrices using the HME process and compare it with the hot fusion method. Compritol®888 ATO was used as hydrophobic matrix base, and various distinct filters were incorporated to control the release rate. Six formulations were prepared by varying the composition and the technique (table 1).

Theophylline was purchased from Yarrow Chem Products (Mumbai, India). Compritol®888 ATO, was generously supplied by Gattefossé (SAS,France), Avicel was a gift sample from Signet Chemical Corporation Pvt Ltd (Mumbai, India), Fujicalin and Lactose were obtained from Gangwal Chemicals Pvt Ltd (Bhiwandi, India) and Sisco Research Laboratories Pvt Ltd (Mumbai, India) respectively, and were used as received.

The first 3 formulations were prepared using the hot fusion method.

For the preparation of formulations 1, 2 and 3 (table 1), Compritol®888 ATO was melted in a china dish at 70 °C using a water bath. While maintaining the temperature, theophylline was added and mixed until a homogeneous dispersion was obtained. The mixture was cooled and passed through a mesh size 60 sieve. The excipients including Avicel/Fujicalin/lactose combination mixtures

were subsequently added, thoroughly mixed as per the ratios mentioned in table 1, and then compressed using Rimek Mini Press-I Multipunch automated machine to obtain 500 mg circular tablets.

The latter 3 formulations were prepared using (HME).

For formulations 4,5 and 6 (table1); Compritol®888 ATO and Theophylline were blended with the Avicel/Fujicalin/lactose combination mixtures prior to the extrusion process via the twin screw extruder (STEER-Omicron 10P, India) and were then subjected to a barrel temperature of 60 °C, 70 °C and 80 °C and screw speed rpm of 100. The external to internal screw diameter (Do/Di) ratio of the HME apparatus was 1.71. The powder thus obtained was passed through mesh size 60 sieve, the excipients were added, and the resulting mixture was compressed using Rimek Mini Press-I Multipunch automated machine to produce 500 mg circular tablets.

Table1: Compositions for hot-fusion and HME process tablet formulations

Ingredients	Hot fusion processed tablets			Hot melt extrusion processed tablets		
	1	2	3	4	5	6
Theophylline (% w/w)	20	20	20	20	20	20
Compritol®l888 ATO (%w/w)	15	15	15	15	15	15
Avicel (%w/w)	-	-	32.25	-	32.25	-
Fujicalin (%w/w)	64.5	32.25	32.25	64.5	32.25	32.25
Lactose (%w/w)	-	32.25	-	-	-	32.25
Magnesium Stearate (%w/w)	0.5	0.5	0.5	0.5	0.5	0.5

The rationale for implementing different formulation processes was to evaluate the effect on the theophylline dissolution patternswith respect to each other as well as against the marketed sustained release tablet.

Characterization of formulation blends was performed, and the tapped density and bulk density was found to be in the range of 105 kgm^{-3} to 250 kgm^{-3} and 80 kgm^{-3} to 200 kgm^{-3}respectively. Compressibility index was ranging from 13.3% to 25.2% and the Hausner ratio varied from 1.15 to 1.34; thus the flow character was found to lie between fair to good. The hardness of tablets was evaluated using a hardness tester (Electrolab Tablet Hardness Tester (model EH 01) 500N). The hardness did not change much with respect to the diluents, and it ranged from 5 $kgcm^{-2}$to6 $kgcm^{-2}$for all the formulations. Thermal characteristics of extrudates were studied using differential scanning calorimetry (DSC) (DSC50, Shimadzu, Japan). The samples were heated from ambient temperature up to 300 °C under nitrogen atmosphere. As seen in fig. 1, the theophylline peak is observed at 282.36 °C indicating that the integrity of the base drug is not lost, along with revealing that it was found compatible with Compritol®888 ATO as well as the HME process. It can be deduced that neither of the components acted as an impurity towards the other indicated by the sharp endothermic peaks at around 70 °C and 280 °C due to Compritol®888 ATO and theophylline respectively. The integrity of the drug was thus shown to have been maintained. The absence of any peak at around 100 °C revealed the anhydrous nature of the blend since the HME technique is a solvent-free process.

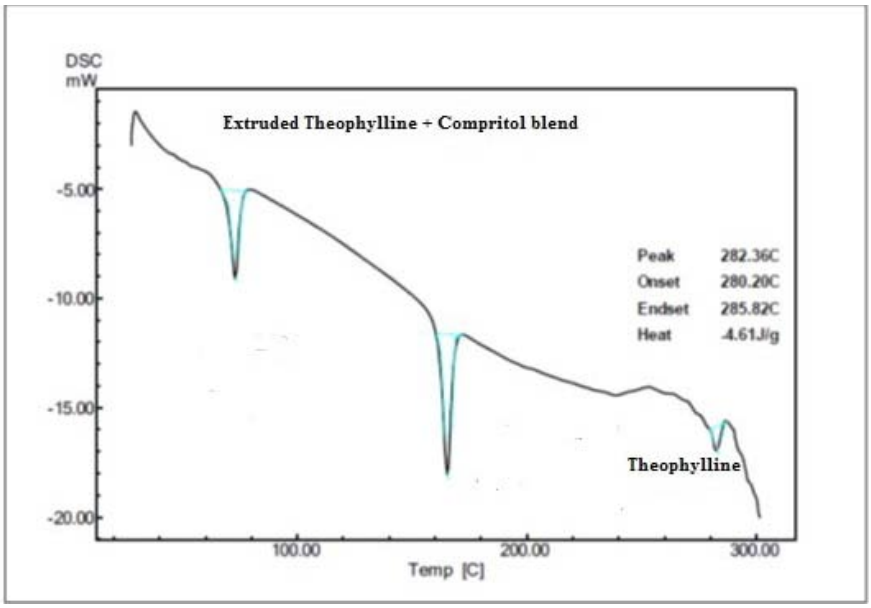

Fig. 1: DSC thermograms of theophylline with an extruded theophylline+compritol blend

The *in vitro* dissolution studies of the formulations was performed using a dissolution tester USP (Electrolab TDT-08L) The USP Apparatus 2was adopted and paddles rotated at a speed of 50rpm throughout the study. The medium used for the dissolution of the Theophylline tablets was phosphate buffer of pH 7.2. The temperature of the water bath was maintained at 37 °C.

Samples were withdrawn at predetermined time intervals and replaced with fresh buffer after each withdrawal. The dissolution was run for 8 h. The withdrawn samples were subjected to UV analysis at a wavelength of 273 nm (Shimadzu UV-1601PC UV-visible spectro-photometer) to determine the content of Theophylline.

The drug-release pattern with respect to time was studied between the tablets prepared by hot-fusion, by hot-melt extrusion and the marketed tablet of theophylline sustained release tablet. The results are depicted in fig. 2 and fig. 3. The marketed tablet of Theophylline showed an almost uniform release where the amount of

Theophylline released at the end of 8 h was seen to be less than 30%. Among hot-fusion processed tablets, Formulation 1 and 2 had a comparable uniform release pattern with around 35% of drug released by the end of 2 h; while by the end of 8 h, more than 70% of Theophylline was released for the formulations 1 and 2. Formulation 3 showed a high initial release of the drug reaching almost 70% by the end of 2 h. The release pattern leaned towards a ceiling effect after 6 h of dissolution reaching a peak release of 79% at 8 h.

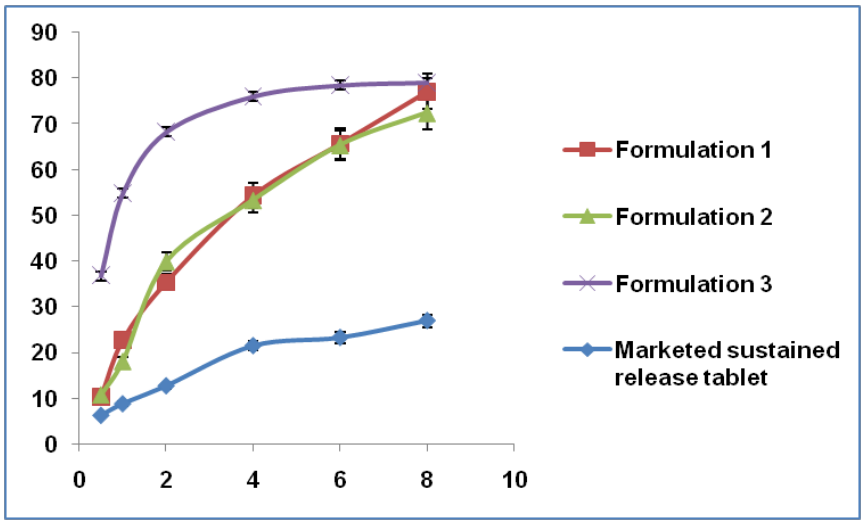

Fig. 2: Release pattern of tablets processed from hot-fusion method and the marketed sustained release tablet (Results are expressed as mean±SD, n=3)

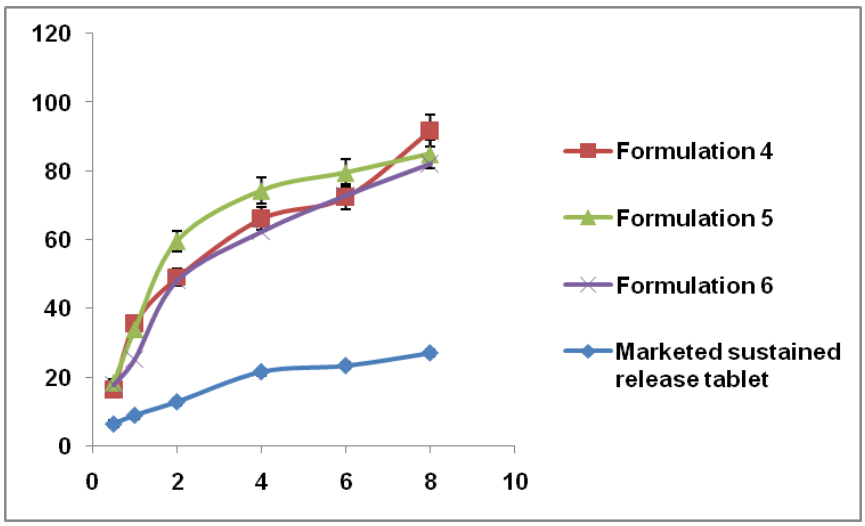

Fig. 3: Release pattern of tablets processed by HME method and the marketed sustained release tablet (results are expressed as mean±SD, n=3)

As seen in fig. 3, in the formulations processed by HME method, the dissolution studies of all three formulations showed a similar pattern. Formulation 5 had a slightly faster release rate compared to the formulations 4 and 6 while formulation 4 had the highest percentage released at the end of 8 h. Formulation 4 had a sudden peak release between the 6th and 8th hour of the study. As shown by the results of the dissolution studies, the formulation containing 64.25% of Fujicalin (formulation 4) showed the highest percentage of Theophylline released at the 8-hour mark, being the only formulation out of the 6to cross 90% of drug released. We can also deduce that formulation containing Avicel as excipient showed a faster release of the drug over the first 6 h compared to those devoid of that particular excipient.

Comparing the two methods of processing, it was observed by the dissolution studies using phosphate buffer pH 7.2, that the tablets prepared by HME method had a higher extent of release where all 3 formulations crossed 80% at the 8-hour mark.

Previous researchers have attempted to formulate theophylline sustained-release tablets using ethylcellulose [16] and hydroxypropylcellulose [17] by direct compression. There is also mention of Eudragit RSPO matrix [18] and studies comparing different grades of hydroxypropyl methylcellulose and effects of polymer concentration on drug release profile [19]. Unlike previous polymers, which swell in water, and where the matrix ultimately disintegrates, the Compritol®888 ATO based inert matrices might provide another solution for the controlled release of those freely water-soluble drugs that require formulation into sustained or controlled drug release systems. Although it is hard to compare the results of different studies from the literature directly, the amount of Compritol®888 ATO employed in the matrix tablets in our study

(15% w/w) proved to be a sufficient amount to sustain theophylline release for more than 8 h.

This study demonstrated the fact that Compritol®888 ATO is a suitable waxy material that can be used as a matrix-forming agent to control the release of theophylline. The HME technique showed to be a continuous and effective method for the preparation of sustained-release tablets. The drug, polymer, and other ingredients should be stable at the elevated processing temperature during the 2–3 min that the powder blend is processed through the equipment. The prepared>8hour sustained-release matrix tablets would provide an extended duration of therapeutic effect of theophylline.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

All authors have none to declare

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