# IN VITRO INVESTIGATION FOR EMBEDDING DEXTROMETHORPHAN IN LIPIDS USING SPRAY DRYING

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In the present investigation three lipids namely, compritol 888ATO, compritol E and precirol ATO5 were used for loading the hydrophilic drug dextromethorphane. The aim of this investigation was to find the possibility of the tested lipids to carry a hydrophilic drug and controlling its release. The spray drying technique was applied to produce the lipid loaded dextromethorphan in a microparticles. The results reveald the formation of nearly spherical microparticles with plausible yield and entrapment. DSC and FTIR showed the presence of interaction between dextromethorphan and the tested lipids. The release of drug from the prepared microparticles resulted in expulsion of dextromethorphan from the microparticles of compritol E and precirol ATO5 in a fast rate. However, compritol 888ATO microparticles released the drug mor slowly. It was concluded that compritol 888ATO appear as a promising lipid for sustaining the release of dextromethorphan.

## 1. Introduction

Since two decades biocompatible lipids were introduced in the field of drug delivery as micro- and nanoparticles that act by carrying drug to the biological system as alternative to polymers[1-4]. Lipid-based formulations can be applied to influence the absorption of active ingredients through different mechanisms to modify the release of active ingredients, improve drugs bioavailability, affecting the intestinal environment, stimulate the lymphatic transport of active ingredients, and interact with enterocyte based transport [5]. Solid lipid particles have the advantage of allowing hydrophilic and/or hydrophobic drugs to be incorporated [6,7]. The loading capacity of drug in the lipid particles is affected by the drug solubility and miscibility in lipid, the chemical and physical structure of lipid materials, as well as the polymorphic state of lipid[8]. The percent drug encapsulated in lipids can vary from 1- 5% for hydrophilic compounds[9,10] and up to 80% for lipophilic compounds.[6,11]. Solvent evaporation and melt dispersion methods were used for preparing solid microparticles[12].

Solid lipid microparticles have been extensively studied as oral, parenteral, topical formulations and as glycerol behenate-based solid lipid system for pulmonary delivery [13-16]. Behinates has been used as a lubricant in tablet production[17]. Compritol 888ATO has been used

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for coating oral sustained-release dosage forms [18,19]. Increasing the amount of compritol 888 ATO led to prolonged drug release profile [20]. Vitorino et al [21] investigated the role of different factors affecting the size of solid lipid nanoparticles prepared by the emulsification–solvent evaporation method using compritol and precirol.

Dextromethorphan [DXM] was first reported as an effective treatment of cough without the undesirable side effects of codeine [i.e. drowsiness, nausea, and constipation]. Since that time, DM has become the active ingredient in many over the counter [OTC] products for treatment of cough and cold due to upper respiratory tract infection [22]. DXM is readily absorbed into the bloodstream and crosses the blood brain barrier with a measurable cerebral spinal fluid/plasma ratio of 32.8 to 80% [23].

DXM has a plasma elimination half-life of about 1.4 to 2.6 hours [24]. As DXM has short duration of action, it is required to be administrated in frequency of three to four times a day [25]. The extent of absorption of DXM from the sustained release formulation was significantly higher than that for the marketed immediate release DXM tablet because of lower elimination rate and longer half-life [26] Wu et al. concluded that DM premedication offers preemptive analgesia and reduces postoperative pain and morphine requirement [27].

The preparation of DM in a sustained release formulation should improve the patient acceptability and it can also lead to the reduction of the number of doses administered; leading to better patient compliance, with less chance of overdose leading to coast reduction that associated with treating cough symptoms.

Fischer and Khanna[28] prepared a pharmaceutical sustained release preparation of DM comprising a polystyrene sulfonate resin which has been cross-linked with about 3% to about 10% divinyl benzene, having an average particle size of at least 48 μm and less than 100 μm onto which DXM has been loaded in a ratio of DXM hydrobromid to resin of about 1:3 to about 1:10. Many authors tried to sustain the release of DXM using different formulation techniques for example using matrices of Eudragit® RS-PM inert matrices. [29], and hydroxypropylmethyl cellulose (HPMC K100LV) and methacrylic acid copolymer (Eudragit L100-55) matrix[30]. Sustained release matrix tablets of DM hydrobromide were prepared by wet granulation using hydroxypropyl methyl cellulose as the hydrophilic rate controlling polymer [26]. On the other hand DXM resinate received attention for the same purpose using Amberlite® IRP69 and DowexR50W [31]. Complexes of ion-exchange resin and DXM, were prepared using different particle sizes of the resins, where, aqueous colloidal dispersions of ethylcellulose and poly[vinyl acetate (Kollicoat® SR30D) were used for fluid-bed coating [32]. The ion-exchange capacity, the degree of crosslinking, as well as resin particle size affect DXM release [33].

The aim of the present study is to investigate the preparation of solid lipid microparticles ([SLM) for DXM using glyceyl behinates and precirol and using spray drying technique. Studying the effect of SLM on the release behavior of DXM.

## 2. Experimental
### Materials
Dextromethorphan (DXM) Hydrobromide was kindly provided from Riyadh Pharma Pharmaceutical Company (Riyadh, Saudi Arabia). Gglyceryl behenates (Compritol® 888 ATO, Compritol® E) and glyceryl palmitostearate (Precirol® ATO 5) was purchased from Gattefossé (Saint Priest, France). Trisodium phosphate anhydrous was purchased (Barcelona, span). Sodium Lauryl Sulfate was purchased from Sigma (Saint. Louis, MO, USA). All other chemicals were of analytical grade.

### Preparation of Binary Mixtures
Physical mixtures were prepared by mixing DXM and individual carriers, Compritol® 888 ATO, Compritol® E or Precirol® ATO 5 in a mortar (the weight ratio of DXM to the lipid carriers used was 1:1).
### Preparation of the spray Dried SLM
Appropriate ratios [1:1, 1:3 and 1:5] of DXM and either one of the tested lipids were completely dissolved in dichloromethane. Each of the resultant solutions was spray dried in a

Buchi mini spray drier [Mini Spray Dryer B-290 advanced, BÜCHI Labortechnik AG, Flawil, Switzerland] with 0.5 mm nozzle. Solutions were fed into the spray drier under the following conditions: inlet temperature 53-60 °C, outlet temperature 35-39 °C, flow rate of the solution 16 ml/min, nitrogen flow rate 40-50 $m^3$/h and atomizing nitrogen pressure 4 pound per square inch. The dried products were collected in collection vessel and weighed.

### Microparticles Characterizations
### Entrapment Efficiency

The encapsulation efficiency of DXM that was entrapped in the lipid particle after the spray drying process was determined as the mass ratio of the entrapped drug to the theoretical amount of DXM used in the preparation. Spray dried particles equivalent to 5 mg of drug were accurately weighed and dissolved in a suitable quantity of dichloromethane. The drug content was determined spectrophotometerically at 278 nm [34].

### Morphological Analysis

The morphological characteristics of spray dried lipid particles were observed by scanning electron microscopy (SEM). The samples were sputter-coated with a thin gold palladium layer under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then scanned and photomicrographs were taken with an SEM (Jeol JSM-6360 LV, Tokyo, Japan).

### Differential Scanning Calorimetry (DSC)

Differential scanning calorimetery studies were performed for the free DXM and the encapsulated drug in lipid microparticles using a Shimadzu DSC-60 system [Shimadzu, Koyoto, Japan] under the following conditions: sample weight 3-5 mg, scanning speed $10^o$C/ min, in the 25-200 $^o$C temperature range. The samples were heated in hermetically sealed aluminum pans and Indium was used as standard.

### FTIR spectroscopy

Fourier transform infrared (FTIR) spectrum was recorded on Perkin Elmer FTIR instrument (Perkin Elmer FT-IR, USA). Samples were prepared as KBr pellet and scanned against a blank KBr pellet background at a wave number ranging from 4000– 650 $cm^{-1}$ with resolution of 1.0 $cm^{-1}$.

### Release study from the lipid microparticles

The release measurements were performed using USP dissolution apparatus I [35] at 50 rpm (Caleva Ltd., Model 85T, Philips, Maidstone, UK) using a continuous automated monitoring system, which consists of an IBM computer PK 8620 series and PU 8605/60 dissolution test software, Philips VIS/UV/NIR single beam eight cells spectrophotometer Model PU 8620, and Watson-Marlow peristaltic pump. In each flask, 450 ml 0.1N HCl [pH 2] for the first two hours after which 150 ml of 0.2 M trisodium phosphate with 1% sodium lauryl sulphate were added to give a final pH of 6.8, the temperature was maintained at 37± 0.5 $^o$C [36].

The drug-loaded lipid microparticles containing 50 mg of drug were dispersed on the release medium. The dissolved drug was determined spectrophotometerically at 278 nm. The release experiments were conducted in triplicate and the means of the percent of drug dissolved were calculated.

### RESULTS AND DISCUSSION

Solid lipid microparticles (SLM) by spray drying was developed as an alternative carrier system, to solid dispersion for embedding hydrophilic drugs into lipid for the aim of modifying hydrophilic or soluble drug release.  Based on lipids which are solid at room temperature, SLM are prepared by spray drying method. As a lipid carriers SLM should be tolerated, having high bioavailability, a nice targeting effect and are amenable to large scale production [37-40]

### Electron scanning microscope

Electron scanning microscope was conducted to study the shape and the morphology of the prepared microparticle of the drug using different polymer namely, Precirol ATO 5, Compritol E, Compritol ATO 888 using spray drying technique. Figure 1 shows the morphology of the DXM particles which have cubic crystalline shape.

As the boiling point of dichlorometane 39.6°C and the inlet temperature in the spray drying chamber is 53-60°C, so, the small droplets are going to evaporate leaving DXM precipitate and disperse in a nearly soft lipid particles that is solidify by entering the cyclone where the outlet temperature lies between 30 and 35°C. during the particle journey part of the lipid microparticles collide with the wall of the drying chamber and sticked causing a decrease in the yield. In figure1, The majority of particles appear as spherical shape as in case of 1:1 ratio where the surface of the particles seems smooth with minor irregularity. As the lipid ratio increase the irregularity become increasing and some of the particles appear as little collapsed sphere. These finding reflect that as the ratio of drug increase the inner volume of the sphere seems as impact solid of dispersed drug into lipid. The collapsing of the spheres appears clearly in the ratio of 1:3 and 1:5 compritol 888 ATO and 1:5 compritol E.

Decreasing the drug ratio resulted in hollow spheres of less density with elastic lipid shell containing the dispersed drug.
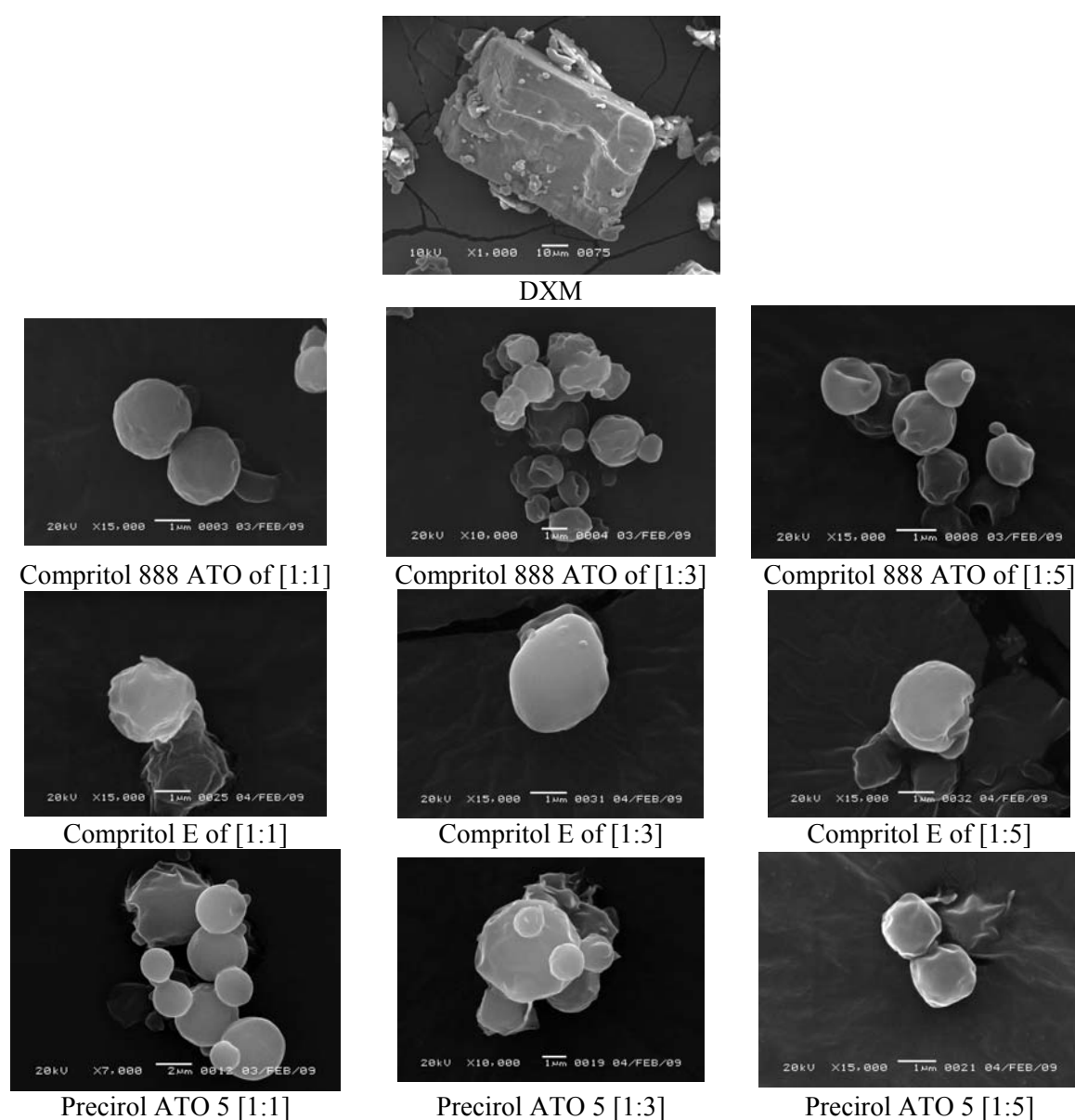


DXM

Compritol 888 ATO of [1:1]   Compritol 888 ATO of [1:3]   Compritol 888 ATO of [1:5]

Compritol E of [1:1]   Compritol E of [1:3]   Compritol E of [1:5]

Precirol ATO 5 [1:1]   Precirol ATO 5 [1:3]   Precirol ATO 5 [1:5]

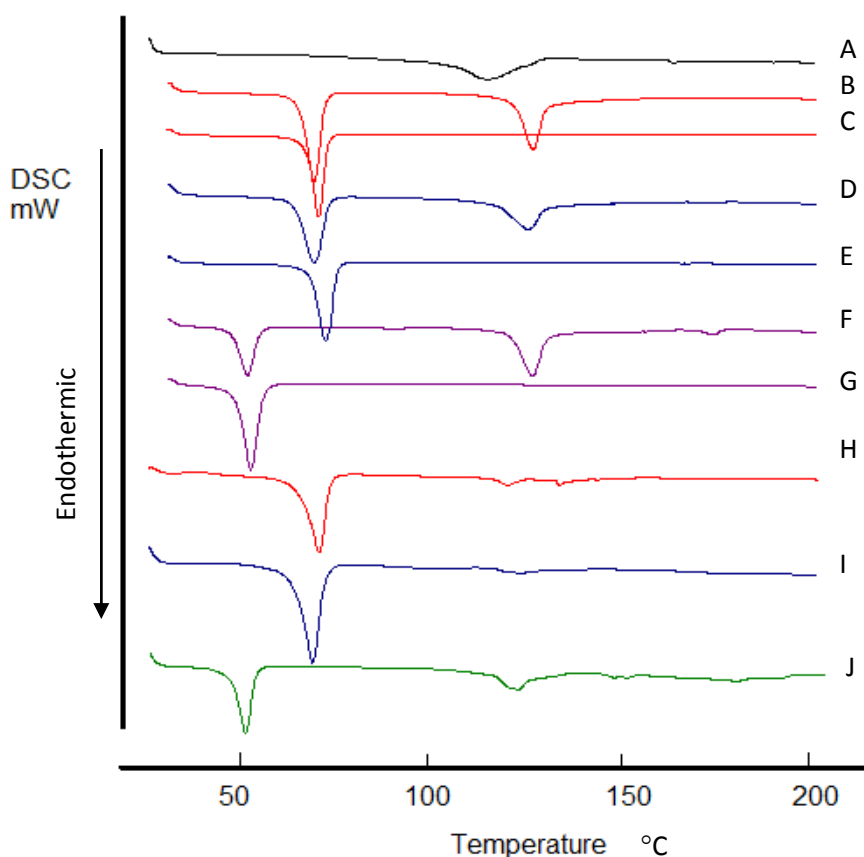*Fig. 1: SEM of the prepared DXM in solid lipid microparticles*

*Fig. 2. DSC of pure, physical mixtures [PM] and 1:3 spray dried solid lipid microparticles containing DXM. A,pure DXM; B, compritol 888ATO PM; C, pure compritol 888ATO; D, compritol E PM; C, E, pure compritol E; F, Precirol PM; G, pure precirol; H, compritol 888ATO 1:3 Spray dried ; I, compritol E 1:3, Spray dried ; J, precirol 1:3 Spray dried*

*Table 1 : DSC endothermic peaks temperature [ºC] and heat [J/g] for untreated DXM and different lipids, physical mixtures and spray dried microparticles.*

| Lipid type | Untreated | | Physical Mixtures | | Spray dried Solid lipid microparticles DXM: Lipid ratio | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1:1 | | 1:3 | | 1:5 | |
| Lipids | | | | | | | | | | |
| | Peak [ºC] | Heat [J/g] | Peak [ºC] | Heat [J/g] | Peak [ºC] | Heat [J/g] | Peak [ºC] | Heat [J/g] | Peak [ºC] | Heat [J/g] |
| Compritol® 888 ATO | 71.31 | -100.01 | 70.09 | -138.21 | 66.68 | -24.52 | 71.27 | -63.19 | 68.84 | -79.63 |
| Compritol® E | 73.23 | -124.39 | 70.13 | -115.14 | 66.3 | -38.31 | 69.48 | -77.85 | 69.6 | -92.72 |
| Precirol® ATO 5 | 53.50 | -138.65 | 52.67 | -138.65 | 50.75 | -11.40 | 51.84 | -38.76 | 52.25 | -68.11 |
| Dextromethorphane | | | | | | | | | | |
| Compritol® 888 ATO | 116.3 | -97.44 | 127.39 | -83.37 | 124.25 | -3.95 | 120.65 | -5.16 | == | == |
| Compritol® E | 116.3 | -97.44 | 125.89 | -53.05 | 118.28 | -2.426 | 114.07 | -3.47 | == | == |
| Precirol® ATO 5 | 116.3 | -97.44 | 127.2 | -77.06 | 123.49 | -1.412 | 123.45 | -13.61 | 126.25 | -5.56 |

## DSC Study

Fig. 2 shows the DSC thermogram of pure DXM, pure lipids, the prepared physical mixtures as well as the prepared microparticles using spray drying technique. Table 1 depicts the peak temperatures of the different endothermic peaks as well as the measured enthalpy.

In the DSC curves of DXM, physical mixture and solid lipid microparticles, an endothermic peak was observed at 116.3°C for pure drug, indicating the melting point of DXM. The endothermic peak of pure drug was also shown in case of the physical mixture at 127.39, 125.89 and 127.2°C for compritol 888ATO, compritol E and precirol respectively, which may reflect an interaction with lipid or perhaps a change in the crystal form. While, the pure lipids showed sharp endothermic peaks at 71.31, 73.23 and 53.5°C for compritol 888ATO, compritol E and precirol respectively, representing their melting points. However, in the physical mixture the endothermic peaks reading were 70.09, 70.13 and 52.67°C for compritol 888ATO, compritol E and precirol respectively. These results indicate the slight decrease in all the tested lipids melting points about one degree in case of compritol 888ATO and precirol, and about three degrees in case of compritol E.

The case of precirol (glyceryl palmitostearate) spray dried particles showed a sharp endothermic peaks at 50.75, 51.84 and 52.25°C for DXM: precirol ratios of 1:1,1:3 and 1:5 respectively. This means as the amount of drug increase the melting point exhibits further decrease. This effect may reflect an interaction between DXM and precirol.

On the other hand as compritol is glyceryl behinate, decreasing DXM ratio in the solid lipid microparticles to 1:5 lipid makes the endothermic peak of the drug to completely disappear. However, there were increasing in the peak temperature in case of 1:3 ratio followed by further increase in 1:5 ratio. The endothermic peaks of lipids showing another phenomenon, where, a marked decreasing in the peak when 1:1 ratio, slight decreasing when lipid increase up to 1:5 in case of compritol E. But the case of compritol 888ATO showed a slight increase in peak temperature in 1:3 ratio and marked decrease in 1:5 ratios. In all cases the measured enthalpy was lower than the pure lipid or the physical mixtures.

Due to glycerides polymorphism, they crystallize in different subcell arrangements-hexagonal, orthorhombic and triclinic[41]. Glycerides display polymorphism with three or more individual forms, including $\alpha$, $\beta'$ and $\beta$ modification, as a mixture of glycerides another intermediate form $\beta_i$ modification is also included[41]. As compritol composed of mono, di and tri behinates glycerides, the melting point will differ from brand to another according to the percentage of each ester. Compritol 888ATO showed melting point at 71.31°C, while compritol E showed melting point at 73.23°C. It was reported that, for pure tribehenate, the melting point of $\alpha$ modification is 69°C, that of $\beta'$ modification is 74.8°C and $\beta$ modification is 83°C, respectively[42]. In the spray drying procedure lipids was dissolved in dichloromethane and the small droplets from the nozzle suddenly facing a vaporizing temperature of solvent leading to super saturation and solidification of lipids and drug. These conditions will ,of course, affect lipid crystallization and melting points. The main modification of compritol was reported as $\beta'$ and $\beta_i$ [43,44]. As general $\beta$ modification exist mainly in pure triglycerides, but the existence of diglycerides usually leads to a large number of lattice imperfection and prevent the transformation to $\beta$ modification[45]. As DXM exist in the lipid matrix this will lead to the increase in the lattice defects of lipid. For the moment, the small particle size leads to a decrease in the crystallization point[43]. The shift to higher melting peak of DXM may be a result of changing in the lipid included DXM crystalline structure to be more stable. This may strengthen by the property of surface activity of glycerides that have HLB values 2 [46], as they will form a reverse micells in dichloromethane to occupy the hydrophilic DXM in their core.

Table 2 show the yield and entrapment efficiency of DXM in lipids. It is noticed the highest yield and entrapment was for the ratio 1:5 DXM to compritol 888ATO that may be attributed to the large number of micells and the smaller amout of drug to be included. The lowest yield of 1:1 ratios may be due to the higher drug percent and consequently the higher density particles that will fastly adhere to the wall of the instrument.

*Table 2:  Entrapment efficiency **and yield of** spray dried microparticles*

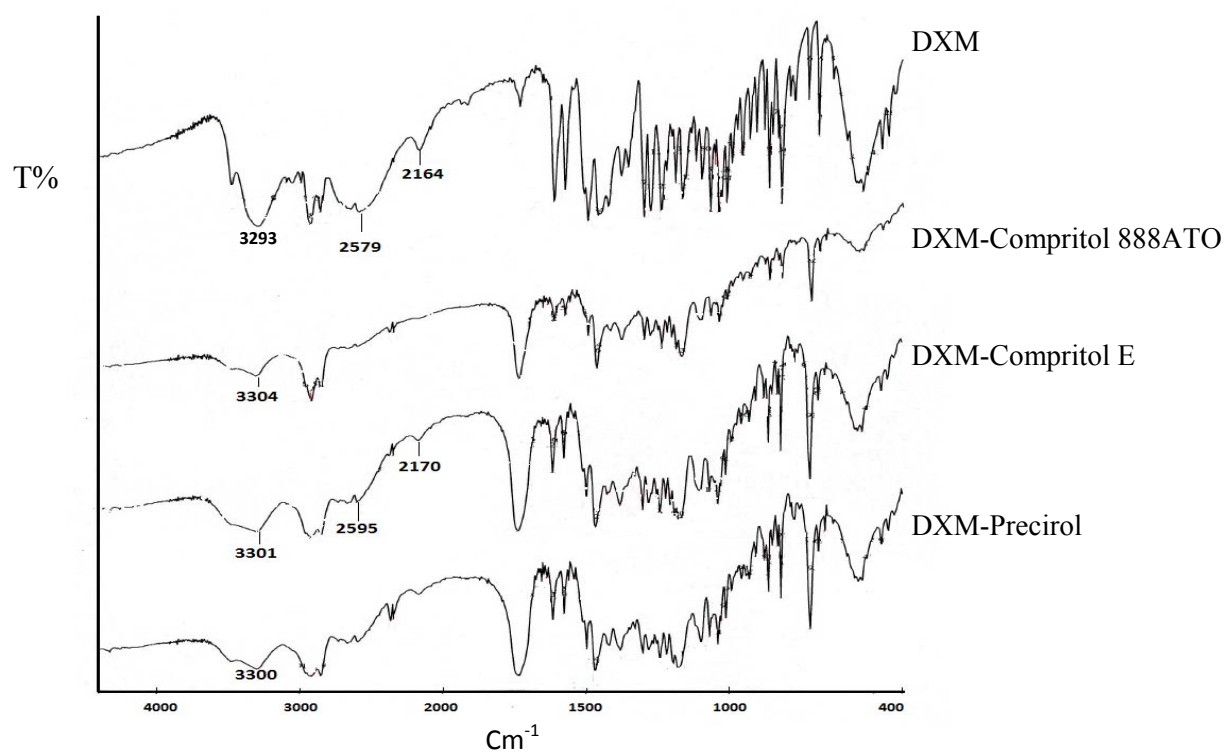| Lipid | DXM:Lipid ratio | Entrapment Efficiency [%] | Yield % |
|---|---|---|---|
| Compritol® 888 ATO | 1:1 | 73.7 | 53.4 |
|  | 1:3 | 75.0 | 58.6 |
|  | 1:5 | 85.8 | 62.6 |
| Compritol® E | 1:1 | 35.9 | 32.6 |
|  | 1:3 | 35.8 | 26.0 |
|  | 1:5 | 54.0 | 38.3 |
| Precirol® ATO 5 | 1:1 | 51.9 | 38.7 |
|  | 1:3 | 63.1 | 45.7 |
|  | 1:5 | 56.4 | 41.7 |

*Figure 3: FTIR spectrum of DXM and the formed solid lipid microparticles*

## FTIR Study

Fig. 3 shows the FTIR spectrum of pure DXM and the prepared solid lipid microparticles. DXM spectrum shows that prominent absorption bands at 2164 and 2579 cm$^{-1}$, corresponding to the NH+ stretching vibration in the tertiary amine group of the drug, disappeared [or shifted] in the solid lipid nanoparticles. In addition, new absorption bands emerged around 3300 cm in the solid lipid microparticles spectra. These spectra reveal the presence of a molecular interaction between the tertiary amine group  of DXM and free hydroxyl groups present in the mono and di glycerides. This kind of interaction assumed to be a weak ionic association as hydrogen bonding.

**Release study**

Figure 4 represent the release of the prepared solid lipid microparticles compairing the different lipids at the same ratios. While table 3 represent the relative release rate (RRR) of the prepared lipid microparticles to the control DXM. It was found that 96.5% of DXM (control) was dissolved at 25min.(figure 4c), and totally dissolved within 30min. In case of precirol the lowest RRR at 25 min. was 0.897 for 1:3 ratio that means the drug released in a fast fasion. The case of compritol E, it seems like precirol with little retardation in the release. However, solid micoparticles prepared using compritol 888ATO showed a decrease in the release rate reaching about 83% at 4 hours.
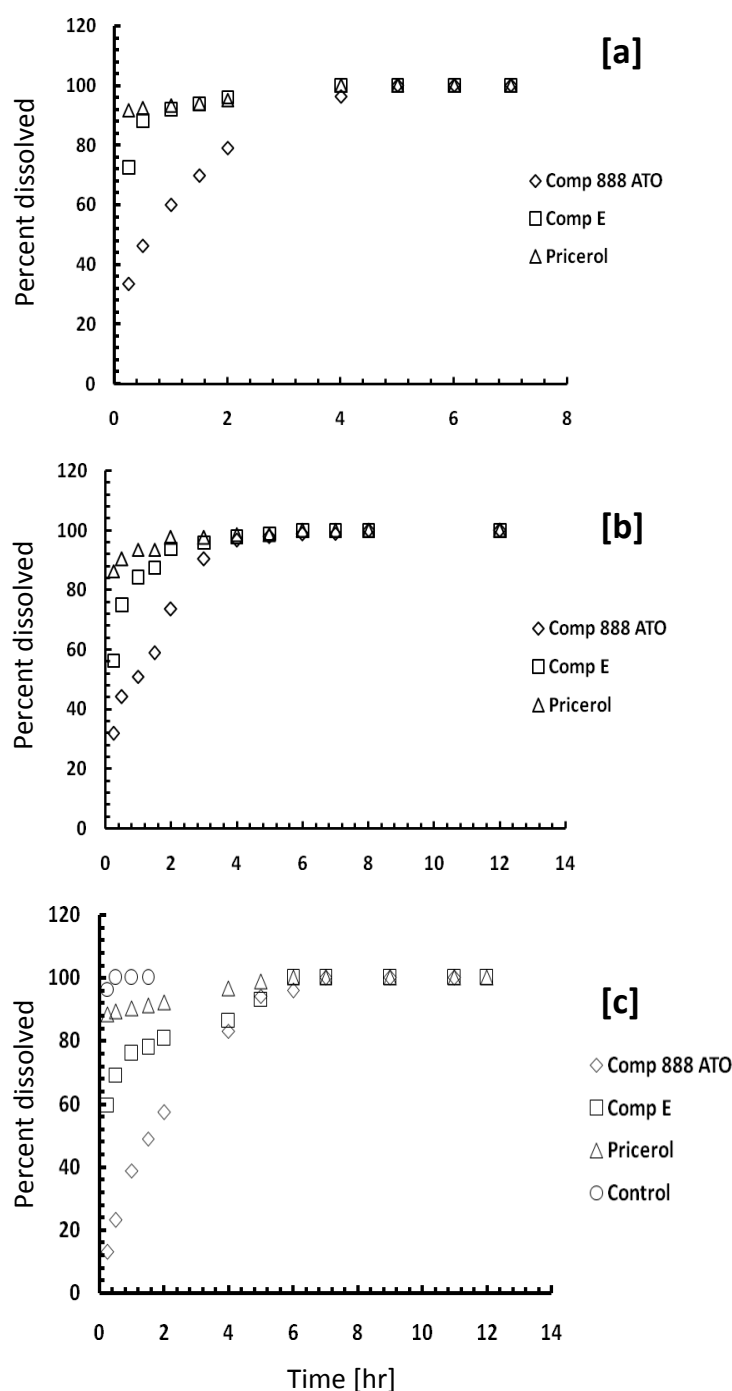


*Fig. 4 : Release of DXM from solid lipid microparticles using different drug lipid ratios*
*a,1:1; b, 1:3 and c, 1:5*

*Table 3 : Relative release rate (RRR) of DXM from different spray dried lipid microparticles*

| Time [hr] | DXM: lipid ratios of microparticles | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Compritol 888 ATO | | | Compritol E | | | Pricerol ATO 5 | | |
| | 1: 1 | 1: 3 | 1: 5 | 1: 1 | 1: 3 | 1: 5 | 1: 1 | 1: 3 | 1: 5 |
| 0.25 | 0.346 | 0.330 | 0.134 | 0.752 | 0.585 | 0.618 | 0.951 | 0.897 | 0.916 |
| 0.5 | 0.462 | 0.442 | 0.231 | 0.881 | 0.751 | 0.692 | 0.924 | 0.905 | 0.893 |
| 1 | 0.599 | 0.510 | 0.388 | 0.920 | 0.845 | 0.760 | 0.933 | 0.937 | 0.902 |
| 1.5 | 0.697 | 0.590 | 0.489 | 0.938 | 0.877 | 0.779 | 0.940 | 0.949 | 0.912 |
| 2 | 0.790 | 0.737 | 0.572 | 0.960 | 0.939 | 0.808 | 0.951 | 0.976 | 0.922 |
| 4 | 0.962 | 0.968 | 0.831 | 1 | 0.980 | 0.865 | 1 | 0.986 | 0.966 |
| 5 | 1 | 0.979 | 0.942 | 1 | 0.990 | 0.933 | 1 | 0.996 | 0.987 |
| 6 | 1 | 0.990 | 0.960 | 1 | 1 | 1 | 1 | 1 | 1 |
| 7 | 1 | 0.99 | 1 | | | | | | |
| 8 | 1 | 1 | 1 | | | | | | |

These results revealed a variability in the composition between compritol 888ATO and compritol E that is expected to increase the interaction between DXM and compritol 888ATO than that with compritol E. Freitas and Miiller[47] found that the crystal behavior of lipid modification has been determined for triglycerides as follows: α reveals a spherulic pattern, β' is of loosely packed spherulite and β shows large coagulated platelets. The drug loading capacity was determined by the microstructure of the subcell. A high drug loading is a characteristic for the less stable crystal modification. However, the less stable modification will transform to the more stable one during storage. The formation of a perfect crystal leads to drug expulsion from the matrix with no room for the guest molecule[48,49]. These results suggest the formation of lipoidal microcrystalline structure from lipids similar to micelle formation together with some molecular interaction between DXM and the tested lipids led to plausible entrapment of the hydrophilic DXM in the lipid. But this kind of loading drug was not able to keep the drug for longer period of time in the release medium, and the pH did not affect the drug release. In spite of these finding compritol 888ATO still having the promise to be a nucleus for sustained release dextromethorphan formulation.

## 3. Conclusions

The present investigation suggested the use of three lipids (compritol 888ATO , compritol E and precirol ATO 5) used mainly as lubricant for carrying DXM (hydrophilic drug) using the spray drying technique. The maximum yield obtained for compritol 888ATO in drug to lipid ratio 1:5. This ratio appears promising for preparing sustained release dextromethorphan in the future.

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