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Research Article

Management and Treatment Outcome of Sepsis: A Clinical Pharmacist Intervention

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ABSTRACT

Background: Sepsis is defined as a life threatening organ dysfunction caused by a dysregulated host response to an infection. When people suffer from sepsis, it results in widespread inflammation, swelling and blood clotting. This study targeted to assess the management and treatment outcome of sepsis.

Objectives: The purpose of the study was to identify the treatment patterns followed in various departments of hospital, to provide patient counseling to patients/bystanders, to give awareness to nursing professionals for early identification of sepsis.

Methodology: A prospective observational study was carried out for a period of one year in various departments of a tertiary care hospital. The vital parameters and routine laboratory tests were assessed. Patients and their caregivers were educated for special care on sepsis. An awareness session was provided to nursing professionals on early identification and care on sepsis.

Results and discussion: A total of 115 patients were recruited for the study that was screened for sepsis by Systemic Inflammatory Response Syndrome criteria. These patients were presented with an infection in a particular site in their body. The result of the study indicated that there is a higher prevalence of sepsis patients with pulmonary disorders. Majority (63%) of the patients were provided with cephalosporins to treat the infection. 85% of the patients had a past history of diseases. Patient counseling was provided during ward rounds to patients and bystanders. 95% of the patients have recovered from the disease condition.

Conclusion: This study mainly aimed at understanding the management of sepsis in various departments of a tertiary care hospital. The primary treatment provided, the details of the patients who were subjected to culture studies, treatment provided during discharge, patient counseling and educational programs to nurses were done during the study.

Keywords: Sepsis; SIRS; Treatment; Vital parameters; Early identification; Nurse education

INTRODUCTION

Sepsis is defined as a life threatening organ dysfunction caused by a deregulated host response to an infection [1]. The infections of the lung, urinary tract or abdominal organs results in sepsis finally leading to inflammation, swelling and blood clotting. A significant decrease in blood pressure that reduces blood supply to vital organs can be witnessed in sepsis. Multiple organ failure and death are a result of lack of prompt identification and treatment of sepsis. Septic patients are more observed with readmissions, mortality and length of hospital stay when compared to patients treated for other conditions. The cost of treating sepsis is remarkably high and it exceeds the cost of treating congestive heart failure and acute myocardial infarction.

The outcome of sepsis can be elevated by early identification and prompt management. A number of actions ("bundles") in the current professional proposals can be followed the moment after diagnosis of sepsis. If there is an evidence of either low blood

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pressure or inadequate blood supply to organs, septic patients should receive antibiotics and intravenous fluids within the first three hours. Blood cultures should be obtained within this time period. Close monitoring of blood pressure and blood supply to organs should be in place after six hours, and the lactate should be measured again if initially it was raised [2].

The hospital admissions are common due to the increased prevalence of sepsis. People are living longer and more medical and surgical interventions are performed which lead to such a trend in the current scenario. It is witnessed that some cases of sepsis are preventable, particularly in groups of people who are at greater risk. The vulnerability to sepsis are more among the very young, the very old and pregnant women. The lumber of sepsis in our healthcare system is significant with large digit of cases per year in India. The global efforts to recognize pathophysiology, improve early diagnosis, and standardize the management of sepsis resulted from the escalating incidence of sepsis and the unacceptably elevated mortality rates. It is important to understand the spectrum of disease for gauging severity, determining prognosis, and developing methods of standardization of care of sepsis.

As the body does not differentiate the initial inflammatory phases of sterile inflammation from that of bacterial inflammation, identifying sepsis can be a tackle. Medical providers more rapidly discover sepsis through proper education about its causes and symptoms to the patients and families. In the intensive care unit, patients and their families can support in preventing the progress of infections as early and effectively as possible. Time is of essence once sepsis is identified. The location and causes of the suspected infection should be established by the healthcare providers by ordering laboratory tests. The progress of the patient should be tracked and antibiotic therapy should be attuned accordingly.

The incidence of sepsis in hospitals can be lessened by proper patient counseling to the patients or the bystanders. Several points should be focused while counseling the patients. Awareness to the public and professionals concerning the prevention of infection can be achieved by good hand hygiene and hand washing techniques. Information regarding vaccinations like influenza (flu) in high risk patients will shrink the likelihood of septic condition. Community acquired sepsis and urinary tract infections are more likely observed in older patients. The incidence of sepsis can be dropped off by appropriate counseling to them [3].

A clinical pharmacist can pick up the knowledge of hospital staffs regarding the identification and treatment of sepsis. Clinical pharmacist should confirm that sepsis is identified promptly and appropriately. Recording vital signs (pulse, blood pressure, heart rate, and respiratory rate) enables the recognition of sepsis. Educating the healthcare workers especially the nurses regarding the identification of sepsis symptoms and prompt recording of the vital signs can alert the physicians to start the treatment of sepsis immediately.

MATERIALS AND METHODS

A Prospective observational study was conducted for a period of one year with an aim of assessing the management and treatment outcome of sepsis from General medicine, Nephrology, Pulmonology and ICU departments of a tertiary care referral hospital, KIMS AL SHIFA Super Specialty hospital, Perinthalmanna, Malappuram, Kerala. The patients were preferred from the departments by inclusion and exclusion criteria. This study was approved by the ethical committee of the institution and an official consent was also obtained for the purpose of performing the study. Adult patients presented with sepsis at the time of admission and sepsis developed inside the hospital during the hospital stay, patients more than 18 yrs of age, patients agreeable to involve in the study were recruited. Pediatric patients, patients with psychological disorders, patients who were readmitted to ICU during their hospital stay were excluded from the study.

An individually designed data collection form was used to record and collect patient data. All relevant data for the study were collected from case file, prescription, interviewing patient for medical history, relevant laboratory reports, medication chart, vital parameters, and medical diagnosis etc. The symptoms and laboratory parameters were also assessed. The site of infection was identified and antibiotics prescribed were also recorded. Patients and their caregivers were educated for unique care on sepsis and to prevent further occurrence of sepsis. An awareness session was conducted to nursing professionals on early identification and care on sepsis. Information concerning the care of sepsis was educated to them during the session.

Data was entered into Microsoft excel and the recorded data were statistically analyzed using statistical package for social sciences (SPSS) software version 23.0 for WINDOWS. Different tools were utilized to perform statistical analysis of data. Continuous data were summed up using mean and Standard Deviation (SD), categorical variables were summarized using frequency with percentage and analyzed using Paired t-Test. Repeated measure ANOVA was used to match upto the routine biomarkers of each patient.

RESULTS

The study regarding the management and treatment outcome of sepsis was conducted in a Super Specialty Hospital in Kerala according to a well-designed study protocol. Data were collected using an appropriate data collection form from various departments like General medicine, Pulmonology, Nephrology and ICU for a period of 12 months. Maximum data were collected during the study period to assess the disease. A total of 115 patients were selected for the study who were screened for sepsis by SIRS criteria. These patients presented with an infection in a particular site in their body. Among the 115 patients included in the study, majority of the patients [48% (n=55)] exhibited pulmonary infections followed by patients with urinary infections, [37% (n=43)] (Figure 1).

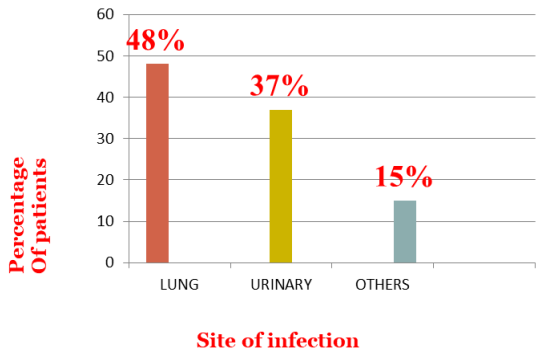

Figure 1: Graph on comparision of Site of infection and percentage of patient
A: Lung; B: Urinary; C: Others.

This was parallel to the study conducted by Dudhipala, et al. [4] in a tertiary care hospital in Kolkata. Wang, et al. [5] also concluded that the respiratory tract infections are more in patients with sepsis conditions. Improper practice of inhalational devices containing steroids might be the reason for sepsis in pulmonary patients. Lack of proper catheter procedures can be the basis for sepsis in urinary tract infected patients. The remaining 15% (n=17) of the patients had sepsis in the abdomen, arthritic areas etc. Majority of the patients admitted in the hospital were already acquired with the sepsis from the community [67% (n=77)] (Figure 2).

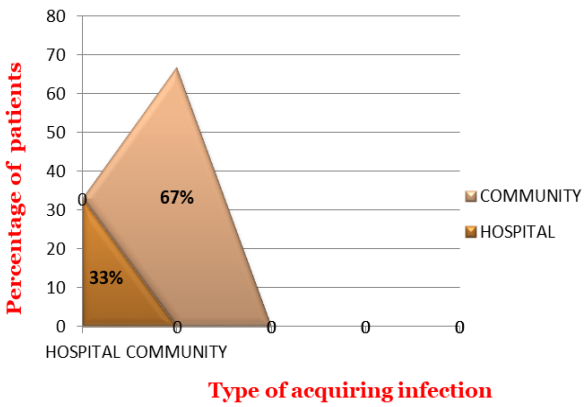

Figure 2: Type of acquiring infection with sepsis from the community and hospital.
A: Community, B: Hosptial

The remaining 33% (n=38) acquired sepsis after the admission to the hospital (hospital acquired). The study conducted by Dahan, et al. [6] also concluded a higher incidence of sepsis from the community. Lack of awareness of proper hygienic practices can be the source for higher rate of community acquired sepsis. The same was fulfilled by long term mortality study conducted by Paliwal, et al. [7]Culture studies in urine, blood, sputum or synovial fluid reflected that only 37% (n=43) of the patients were exposed to specific cultures related to their disease and in the remaining 63% (n=72), no culture studies were performed (Figure 3).

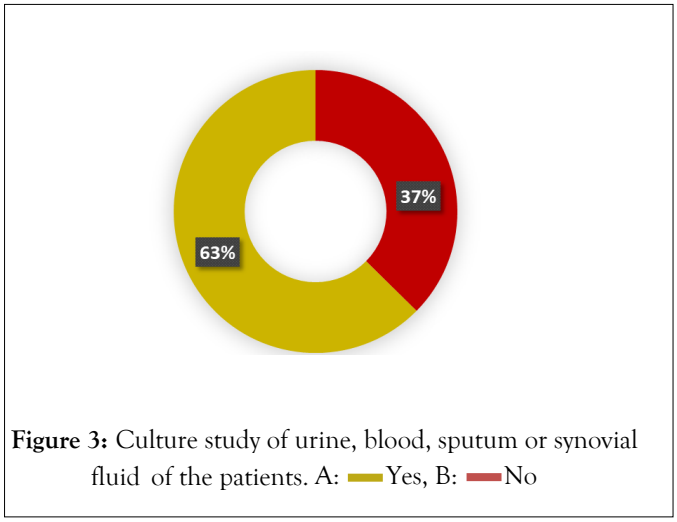

Figure 3: Culture study of urine, blood, sputum or synovial fluid of the patients. A: Yes, B: No

It might be due to lack of time for the doctors to stay for the culture results to initiate the treatment. Experienced doctors may locate any kind of infection in the patient. This might assist them to start the treatment as soon as possible. The importance of culture studies were successfully revealed in the study conducted by Peres, et al. [8] in neonatal patients. Another study by Chiu, et al. [9] also highlighted the importance of culture studies in sepsis patients. The importance of trends in vital parameters and routine biomarker studies was explained in the study handled by Leng, et al. [10]. Gram negative bacteria accounted for majority of diseases (65%), followed by Gram positive bacteria (23%) (Figure 4).

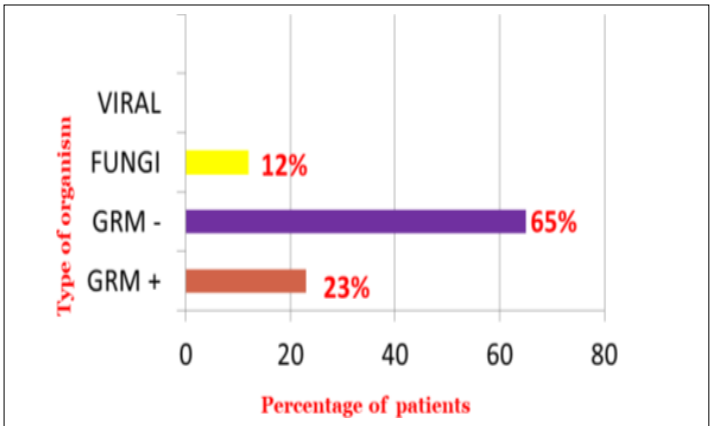

Figure 4: Comparison of type of organism and percentage of the patients. A: Gram positive, B: Gram negative, C: Fungi

The Study on patients concluded that a higher percentage of gram negative organisms were responsible for pulmonary infections in the human body. In the study performed by Dahan, et al. [6] gram negative infections were predominant when compared to gram positive infections. Study conducted in neonatal patients in a tertiary care hospital by Peres, et al. [8] reported that gram negative organisms were more prevalent compared to other causative organisms. Fungal infections accounted for about 12% and there were no viral infections in any patients. Among the total antibiotics used, Cephalosporin's accounted for about 63%. It was followed by a 10% use of carbapenems and 9% use of fluroquinolones. Other antibiotics like penicillin's were used for 10% of the patients. Another 10% of the patients were not prescribed with antibiotics (Figure 5).

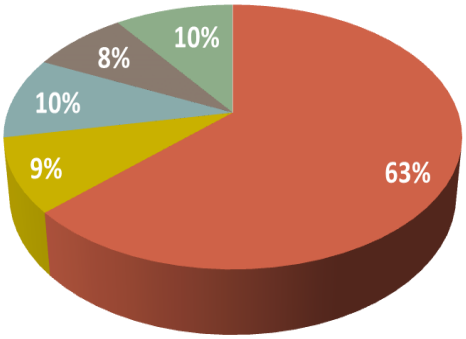

Figure 5: Antibiotics Prescribed to the sepsis patients. A: CEPH, B: FLRQ, C: CRBP, D: Other, E: No AB

Leung, et al. in their study observed that amoxicillin and clavulanate combinations were used to treat respiratory, urinary tract and intra-abdominal infections. In their study, intra-abdominal infections were paired with nitroimidazoles [10]. The study performed by Dahan, et al. [6] concluded that appropriate antibiotics are provided to the patients within 24 hours of presentation of sepsis. The study conducted and it is observed that broad spectrum antibiotics were broadly used to treat sepsis during their identification along with the fluids. About 51% (n=59) of the patients were provided with intravenous fluids throughout their stay in the hospital. The remaining 49% (n=56) were not under fluid treatment. Fluids like normal saline or lactated Ringer's solution are provided to survive the disease depending on the condition of the patient. Study conducted in Asian Intensive care units explained about fluids provided to patients with or without vasopressors. An alternative study performed by Dahan, et al. [6] in an Intensive Care unit in India justified about initial fluid administration based upon central venous pressure measurement, lactate clearance and urine output. Among the 115 patients treated for sepsis only 1% (n=1) was screened for sepsis condition with the q.SOFA scoring system (Figure 6).

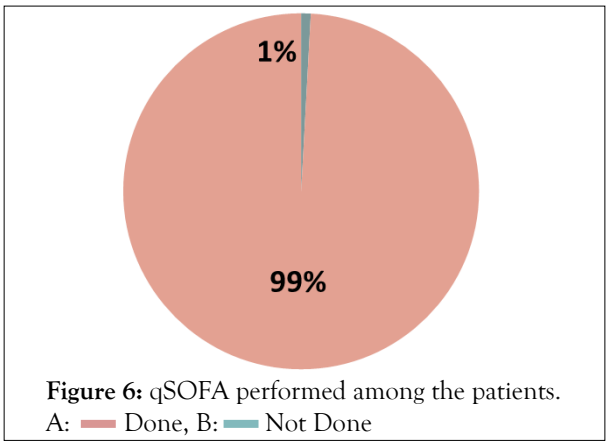

Figure 6: qSOFA performed among the patients. A: Done, B: Not Done

In the remaining 99% (n=114), q.SOFA was not performed. The q-SOFA or the Quick Sequential Organ Failure Assessment is the latest criteria or the scoring system to confirm the presence of sepsis in a patient which is based on 6 organ systems (cardiovascular, respiratory, renal, liver, neurological and hematological). This score can predict mortality risk of septic patients. SOFA scoring systems were employed in research study conducted by Leung, et al. [10]. They alerted the critical care physicians to promptly assess septic patients when quick SOFA score is 2 points or more. it also included SOFA scoring system for early prediction of severe sepsis study. The mortality risk of respiratory and pulmonary and intra-abdominal infections by quantifying SOFA scores and evaluated the requirement for organ support in the intensive care unit.

The laboratory tests done on patients at the time of admission and later during their hospital stay was observed. The parameters were analyzed using paired t-test in order to verify their significance in the study. In the 90 patients who were tested for ESR values, it was observed that there is a significant difference in the ESR with p-value <0.05. This illustrates that the intervention is successful. 68 patients out of 115 were tested for polymorphs value. The p-value (<0.05) obtained in the table, denotes that there is a significant difference in the values observed. This reveals that the intervention was successful. Lymphocytes were tested for 62 patients and it was observed that there is a significant difference in the p-value (<0.05) obtained which highlights successful intervention. In the 80 patients tested for hemoglobin, the p-value obtained (<0.05) denotes there is a significant difference in the tested values. This shows that the intervention was successful.

The vital signs like heart rate, respiratory rate, temperature and blood pressure were monitored 3 times a day and an average value was noted down continuously for four days during the hospital stay. The changes in the patient value were analyzed using Repeated Measure Anova. The p-value (>0.05) obtained after statistical analysis showed that there no significant difference in the above parameter. Therefore, heart rate value is not significant. The respiratory rate illustrated a p-value <0.05 which showed there is a significant difference in the values obtained.

The temperature showed a significant difference with a p-value <0.05. This focused on the statement that temperature is significant. Systolic Blood Pressure and Diastolic Blood Pressure were monitored. After analysis, the systolic BP showed a p-value <0.05 which explains about its significant difference. There is no significant difference in the diastolic BP and the p-value obtained here was >0.05.

The study was limited to few departments in the hospital excluding the gynecology and neurosurgery departments and the sepsis stages in patients were not identified. A post interventional study was not performed in patients to assess their improvement in their disease conditions. The importance of early identification of sepsis and monitoring the trends in vital signs and routine biomarkers were not discussed with the doctors treating sepsis conditions. The study can be continued in hospitals for proper identification and management of sepsis. Awareness to healthcare professionals regarding their role in sepsis management can be done as continuing educational programs. A proper guideline for early identification and management of sepsis can be introduced in the hospital.

DISCUSSION

In another study, Cefepime was used as a model drug to investigate the encapsulation efficiency and release profile from a hydrophilic drug delivery platform using chitosan microspheres.

The study showed possible entrapment, but no *in vivo* relevance, permeability, and potential scale up were discussed [1].Although prod rugs have been utilized to improve the lipophilicity of molecules, the covalent linking might result in a toxic or less effective form of the drug. Our alternative approach improves the drug lipophilicity without possible interference with the therapeutic efficiency [2].

In this study, SLNs were investigated as a potential carrier to enhance the intestinal uptake for CEF. An initial screening of the cefepime's and the lipids' physicochemical properties was performed as a first step in determining potential lipids, surfactants, drug concentration, and other excipients to achieve a successful formulation. Cefepime's is a crystalline hydrophilic molecule with poor lipid permeability. In the screening process, lipids with a mixture of short, medium, and long-chain fatty acids were favored in order to maximize CEF encapsulation through dispersion between the imperfect crystals of the lipids.

In determining the lipid formulation to be used, we have investigated different percentages of lipids and SLNs preparation techniques. The tested lipids concentration ranged from 2-10% total lipid mixtures. In addition, other surfactants at multiple ratios were studied. Using our optimization criteria of particle size, encapsulation efficiency and zeta potential we have narrowed down our optimized formulations to two formulas with unpaired CEF. Solid lipid nanoparticles have been widely considered to advance the biopharmaceutical properties and pharmacokinetics of drugs. It has been used to create a long acting injectable drug delivery platform for intramuscular and subcutaneous administration in addition to the successful delivery of mRNA [3,4].

When it comes to safety, lipids used in SLNs are thought to be well accepted *in vivo* since they are generally made of physiological compounds and, thus, digestion should cut the risk of severe and prolonged toxicity. However, formulators must take-care attention of the possible toxicity from surfactants. The toxicity profile of the developed SLNs was not assessed. However, the lipids used in all formulations are categorized as GRAS, and the surfactant used in all formulations did not exceed 2% of the total prepared volume. Exploring the possible chemical complexion by ion-pairing of CEF to further block the surface charges and better encapsulate CEF in SLN was our second step of enhancing encapsulation and improving permeability NaSA was the anion of choice. Sodium stearate dissociates in water to a negatively charged stearate, which can be used to block the positively charged quaternary nitrogen of CEF. Coupling of the NaSA and the CEF was achievable at both molar ratios of 1:3 and 1:1 CEF-NaSA. Maximizing the yield was not in the scope of this study. Therefore, it was decided to use the 1:3 molar ratios in the subsequent steps of loading the SLN formulation. The reason being that the 1:3 ion pair product was easier to handle than the 1:1 ion pair, which was sticky and carried a static charge.

The vibrational modes of the unpaired and ion paired CEF bonds were studied using IR and Raman. The molecule vibration is a function of many factors, among which are ionic and hydrogen bonding. The shift in the 1629 cm-1 Raman peak of the CEF (C=C peak), the appearance of a new peak at 1501 cm-1, and the change in the ionic functional carbonyl group of the β-lactam at 1775 cm-1 confirm CEF sodium stearate molecular interactions. In addition, the fingerprinting region of the IR spectra suggests changes around the vibration of the carbonyl groups of sodium stearate.Both IR and Raman complement each other and confirm the changes in the CEF bonds' vibrations due to changes in the environment around the CEF molecule before and after ion pairing. These changes could be attributed to ion-ion pairing or dipole-dipole molecular interaction.

The apparent permeability of the CEF formulations was performed across excised rat jejunum tissues using *ex vivo* side-by-side diffusion technique. The apparent permeability parameter is commonly used in such studies to indicate the passive transport of a molecule. The rat jejunal tissue has high similarity to human jejunal tissue structurally in tight junctions and mechanically where most drug absorption processes occur [4,5].

Ion pairing of the CEF with the NaSA improved both the permeability of the un-encapsulated CEF-NaSA and the encapsulation of CEF-NaSA into the SLN and thus improved the CEF permeability. The net effect of the two combined mechanisms was more than 40 folds improvement of the CEF permeability compared to the untreated CEF solution. The formation of different drug complexes and ion pairs have been utilized to improve drug bioavailability to facilitate drug penetration into specific tissues, for example, but not limited to the retina and inner ear [7-9]. A study showed an improved ocular bioavailability of Timolol by sorbic acid ion pairing [10].An increase in the negative zeta potential of the NaSA-CEF nanoparticles compared to the CEF nanoparticles was also observed. This could be attributed to the anionic fats (stearate) incorporation in the SLN, resulting in an increased surface negative charge.

The CEF-NaSA ion pair SLN negative zeta potential was significantly higher than the CEF-SLN formulas. The increased negative zeta potential of the SLN can provide physical stability of SLN through high repulsion. The particles' surface charge on the cellular uptake and permeability was studied and found to be significant yet small in the range of -2 to -16 mv. Yet, a considerable decrease was confirmed for higher charge levels [1]. One reasoning is that the intestinal mucus exhibits a net negative charge due to the silica and sulfonic acid structure; a slightly negative particle can allow particle movement within the mucus layer as long as the mucus is not dense and its structure is sufficiently broken. On the other hand, positively charged particles could be immobilized due to charge interaction with the negatively charged mucus [2].

In terms of the effect of SLN size, the average particle size of 110 nm favors the penetration of the particles through the intestinal membrane. This explains the difference in the net improved permeability of CEF from the 5% CEF-SLNs with an average size of 111 nm compared to the 7% CEF-SLNs with an average size of 283 nm, although the encapsulation of the drug in the latter was higher. Thus we concluded that the net effect depends on both the type and the magnitude of the charge on the

particles and the mucus structure, as confirmed by another study [3,4].

CONCLUSION

Currently the CEF is only available as an injectable form. Our efforts to prepare it in a oral formulation will maximize the therapeutic use of this antibiotic. The CEF ion pair formulation was successfully prepared and evaluated. The loaded SLN showed significant improvement of the CEF permeability and the ion pairing of the CEF with sodium stearate further enhanced the CEF encapsulation in SLN and its penetrability as well. The NaSA-CEF ion paired SLN is thus a promising oral formula for CEF and may present a strategy not only to formulate the CEF as oral dosage form but also to solve the oral impermeability of ionized drugs.

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