International Journal on Emerging Technologies 10(2): 376-383(2019)

ISSN No. (Print) : 0975-8364
ISSN No. (Online) : 2249-3255

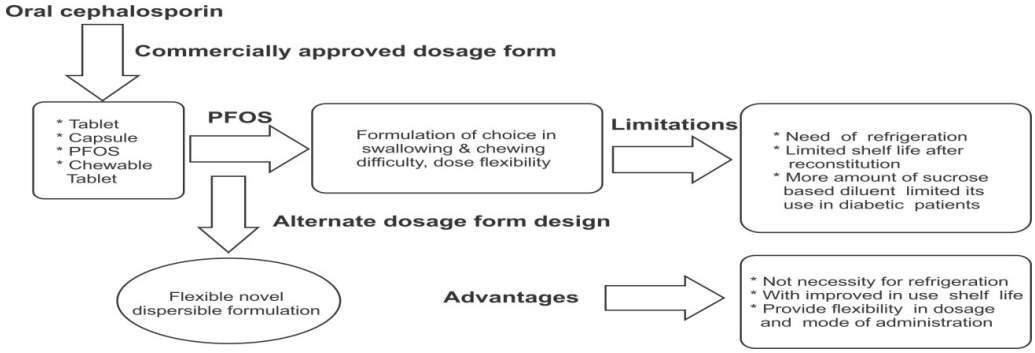
Refrigeration and the Shelf Life of Oral Cephalosporin Powder for Suspension Dosage Form: Review and Proposal

Saravana Perumal Govindan[1], Senthamarai, R.[2] and Anbarasu, K.[3]

[1]Research Scholar, Department of Biotechnology, PMIST, Vallam, Thanjavur (Tamil Nadu) - 613403, India.
[2]Principal, Periyar College of Pharmaceutical Sciences, Tiruchirappalli-620021, (Tamil Nadu)-620021, India.
[3]Assistant Professor, Department of Biotechnology, PMIST, Vallam, Thanjavur (Tamil Nadu) - 613403, India.

(Corresponding author: Saravana Perumal Govindan)
(Received 15 May 2019, Revised 30 July 2019 Accepted 15 August 2019)
(Published by Research Trend, Website: www.researchtrend.net)

ABSTRACT: The cephalosporin powder for oral suspension tends to have a flexible therapeutic application in the condition of bacterial infections across the age groups from pediatric to the geriatric population and also has the potential application in the condition of swallowing and chewing difficulty. Refrigeration of oral cephalosporin powder for suspension dosage form plays a vital role in maintaining the dosage form stability for particular days after reconstitution. The necessity of refrigeration and impact on overall product shelf life after reconstitution tends to reduce its potential application. The observed limitations stress the importance to design an alternate dosage form. This review aimed to look for an alternate dosage form design in place of commercially approved cephalosporin powder for oral suspension dosage form to avoid the necessity of refrigeration and intended to have the potential application in the condition of swallowing and chewing difficulty. Finally, this review highlights that solid dosage form in the form of dispersible formulation with flexible design along with defined salient features has the potential as an alternative dosage form design.



Keywords: Oral cephalosporin; Powder for suspension; Alternate dosage form design; Flexible dispersible formulation; Swallowing difficulty; Chewing difficulty.

I. INTRODUCTION

Cephalosporin belongs to one of the most important classes of antibiotics known as Beta-lactam antibiotics and also read as β-lactam, they are called β-lactam antibiotics because having a β-lactam ring in their molecular structure Fig. 1. Since the first cephalosporin was discovered, scientists have been improving the structure of cephalosporin to make them more effective against gram-positive and gram-negative bacteria. Each time the structure changes, a new "generation" of cephalosporin is made, so far there are three generations of oral cephalosporin invented and commercialized. Antimicrobial potency and stability against hydrolysis by beta-lactamase producing bacterial strains increases from first to third generation [1-3], (Fig. 2). The oral cephalosporin was commercially approved in the form of a capsule, tablet, powder for oral suspension and chewable tablet. Among the commercialized cephalosporin oral dosage forms, powder for oral suspension (PFOS) is the only dosage form having the potential application in the condition of swallowing and chewing difficulty along with providing flexibility in dosage to cover the age groups from pediatric to the geriatric [4].

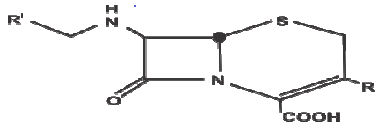


Fig. 1. Structure of Cephalosporin with β -lactam ring.

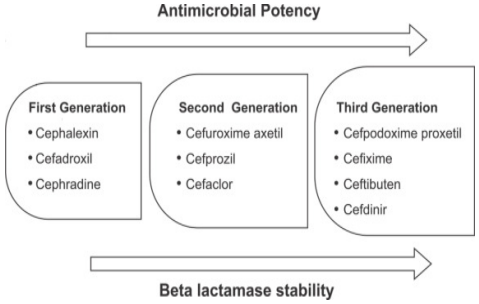


Fig. 2. Antimicrobial activity and beta lactamase stability of oral cephalosporin generations.

However, the limitations such as refrigeration requirement and reduced overall product shelf life after reconstitution limited its potential application and further stress the necessity to look for an alternate novel oral dosage form design avoiding the above-said limitations and covering the salient features of PFOS.

Safe and effective pharmacotherapy requires the development of dosage form with proper use that suits the age, physiological condition, disease state for example mental disorder, autism, and diabetic, body sizes of the targeted population and acceptable stability with respect both real-time & in-use [6], [47], (Table 1). Across the age groups from pediatric to the geriatric population, having a unique set of barriers to conventional oral solid dosage forms viz. tablet and capsule is the inability to swallow the dosage forms[12],[15],[16]. The most potential factors that can affect the pediatric population is the inability to swallow the medication due to the size of dosage forms [4], whereas in the geriatric population, the swallowing difficulty is the most common because of the aging process can have a worse impact the oral, pharyngeal and esophageal phases of the swallowing process [10]. To overcome the swallowing difficulty, the traditional practices are followed to administrating the adult dose by splitting the tablet even in the absence of splitting/scoring mark, by crushing the tablets or opening the capsule and administrating the powder to facilitate the ease of the administration which further deviates from the prescribed method of administration[9].

To overcome the impact of the size of the conventional tablet and capsule in the condition of swallowing difficulty, dispersible formulations and chewable tablet remains an alternative to ease of dosage form administration in the above said population [5, 17]. Chewing is one of the principles of oral functions and impairment in its ability across the age groups is the most immediate consequences of oral health problems and disorders, such as missing teeth, tooth-ache, cognitive impairment and impaired salivary secretion [11]. The impairment in one's chewing ability can have an impact on compliance with a chewing tablets for the betterment of therapy outcomes.

A variety of novel oral solid dosage forms commercially available make oral route extremely useful for the administration of medicinal products for the long term and short term treatments considering formulation design factors, age groups, patient acceptability and safety [5-9, 18-20, 39-42]. Further the scope of this review to find out the suitable novel oral dosage form design having the greater responsibility to deal with oral drug therapy in pediatric and geriatric population with swallowing and chewing difficulty against the commercially approved cephalosporin powder for the oral suspension dosage form.

Table 1: Potential clinical advantages and disadvantages of conventional and novel oral dosage forms.

Sr. No	Oral dosage forms	Potential advantages	Potential disadvantages
1	**Liquid preparations**		
A	Suspensions	* Acceptability * Maximum dose flexibility	*.Shorter shelf -life *More prone to microbial proliferation (solutions, drops) * Special storage condtion (at 2-8°C for reconstituted suspension and liquid dosage forms) *Bulky volumes and special storage condition which in turn increases the shipping cost
B	Solutions, syrup, drops	Good dosage uniformity	
C	Powders and granules for reconstitution	Long term stability as compared to liquid preparations	*Possibility of spillage *Non-Compatibility with food /drinks (sprinkles) *Limited control overdose intake * More number of excipients which inturn cause unwanted side effects / allergic reactions
2	**Solid dosage forms**		
A	Tablets	Long term stability as compared to liquid preparations	* Size of dosage forms * Risks of choking * Not feasible in mentally retarded subjects
B	Capsules		
C	Powders , granules, sprinkles	* Long term stability as compared to liquid preparations	* Dose-measuring device critical (for lower, subdivided dose) *Non-Compatibility with food /drinks *Limited control overdose intake
D	Dispersible (Powder,Tablet)	Long term stability as compared to liquid preparations	*The Restricted volume of solvent used for dispersibility * No risk of choking
E	Orodispersible/ Orally dsintegrating Tablets	Long term stability as compared to liquid preparations	*Impaired salivary secretion or dry mouth may impact or reduce the degree of dispersibility
F	Chewable Tablet preparations Administration	Long term stability as compared to liquid preparations	*Risks of choking and chewing *Not feasible in mentally retard and chewing difficulty subjects
G	Mini Tablets	Long term stability as compared to liquid preparations	*Size of dosage forms and handling *Risk of choking (non-disintegrating type) * More of tablets need to be administered in case of high dose drugs
H	Orodispersible Films	Long term stability as compared to liquid preparations	* Handling and dosage administration *Mechanical strength *Risk of medication errors requires particular attention *Child acceptability not clearly understood *Restricted in dose strength(<75 mg) to minimize the size of the film

II. LITERATURE SEARCH AND REVIEW

Literature search and review carried out with a focus on below outlines section which has potential application in the condition of swallowing and chewing difficulty.
(i) Commercially approved cephalosporin powder for oral suspension dosage form (Table 2)
(ii) Published articles dealing with current novel oral technologies and application (Table 3)
(ii) Commercialized novel oral technologies (Table 4)

A. Commercially approved Oral cephalosporin Dosage forms

Oral cephalosporin class of antibiotics is the most commonly prescribed antibiotics across the globe. Currently, there are 3 generations of cephalosporin available for oral use, providing a variety of choices for the treatment of common infections. Generally, these antibiotics are indicated for upper and lower respiratory tract infections (including otitis media, pharyngitis, and bronchitis), uncomplicated skin and soft tissue infections, and uncomplicated urinary tract infections. Traditionally, the first-generation agents are known to have greater activity against gram-positive organisms with little gram-negative activity. Second-generation cephalosporin typically retains their gram-positive activity and provides greater activity against gram-negative organisms. The third-generation agents lose some gram-positive activity but demonstrate superior activity against gram-negative organisms. Among commercially approved oral cephalosporin dosage forms (Table 2), powder for oral suspension is preferred formulation choice in the condition of swallowing and chewing difficulty across the age groups. Upon review of commercially approved cephalosporin powder for oral suspension (PFOS), the following potential advantages and limitations were observed.

Potential advantages:
(i) Provide flexibility in dosage based on age groups from pediatric to geriatric
(ii) Ease of administration in the condition of swallowing and chewing difficulty.

Potential limitations:
"Most of commercialized PFOS need to be stored at the refrigerator, i.e. at 2℃-8℃ after reconstitution, which seems to impossible to afford for less economic population, difficult to handle during traveling and far away from home.
(i) Shorter shelf life after reconstitution which impact on overall product shelf life.
(ii) Most of commercialized PFOS contains more amount of sugar-based diluent per dose which limits the application in the diabetic population.
(iii) More shipping cost due to bulky volume
(iv) More prone to breaking due to glass bottles as a primary packing materials

Table 2: List of commercialized oral cepahlosporin drug products (Ref: Drugs@FDA).

Sr.No	Cephalo-sporin generations	Spectrum type	Antibacterial activity	Approved drug & dosage form across the globe	Potential limitations of powder for oral suspension (PFOS) dosage form
1.	First Generation	Narrow Spectrum	**Gram Positive:** Optimum activity **Gram Negative** : Have little activity	**Cefadroxil:** Capsule/Tablet/ PFOS	*After reconstitution needs to be stored at refrigerator. To be used for not more than 14 days * High amount of sucrose limits to use in diabetic patients
				Cephalexin: Capsule/PFOS	*After reconstitution needs to be stored at refrigerator. To be used for not more than 14 days * High amount of sucrose limits to use in diabetic patients
				Cephradine: Capsule/PFOS	* After reconstitution needs to be stored at refrigerator. To be used not more than 14 days. If stored at room temperature, to be used not more than 7 days * High amount of sucrose limits to use in diabetic patients
2.	Second Generation	Intermediate Spectrum	**Gram Positive :** Lesser activity than first generation **Gram Negative :** Greater than first generation	**Cefuroxime:** Tablet/PFOS	* After reconstitution needs to be stored at refrigerator. To be used not more than 10 days * High amount of sucrose limits to use in diabetic patients
				Cefprozil: Tablet/PFOS	* After reconstitution needs to be stored at refrigerator. To be used not more than 14 days * High amount of sucrose limits to use in diabetic patients
				Cefaclor: Capsule/PFOS	After reconstitution needs to be stored at refrigerator. To be used not more than 14 days

3.	Third Generation	Broad Spectrum	**Gram Positive :** Limited activity **Gram Negative:** Greater activity as compare to other generations	**Ceftibuten:** Capsule/PFOS	* After reconstitution needs to be stored at refrigerator. To be used not more than 14 days * High amount of sucrose limits to use in diabetic patients
				Cefixime : Capsule/PFOS/ Tablet/Chewable Tablet	*After reconstitution needs to be stored at room temperature or under refrigerator. To be used not more than 14 days * High amount of sucrose limits to use in diabetic patients
				Cefpodoxime Proxetil: Tablet/ PFOS	After reconstitution needs to be stored at refrigerator. To be used not more than 14 days
				Cefdinir: Capsule/PFOS	*After reconstitution needs to stored at controlled room temperature. Use not more than 10 days * High amount of sucrose limits to use in diabetic patients

B. Current novel oral technologies from published articles

From the author's desk, the following technical points had got highlighted and summarized in Table 3.

[5],[27-30,32-33] Worldwide people would prefer liquid dosage forms when medicines have to be given orally. The syrups and suspensions can be dosed flexibly by increasing the volume with the age and weight of the child. From a pharmaceutical development and manufacturing point of view, liquid dosage forms have several potential limitations in many ways. A switch to solid oral formulations would be the best way to improve the availability of dosage form if they would accept them and be able to swallow them.

Further substituting oral liquid formulations with suitable flexible solid dosage forms would bring considerable cost savings even in rich countries. The acceptability was significantly higher for the mini-tablet than for the suspension.

Necessity of patient acceptability (stability, ease /cost of development, manufacture, and supply), safety and access of several novel oral dosage forms viz. multi-particulates /granules/sprinkles/powders, mini-tablets (1-4mm), orodispersible tablet/melt, chewable dosage forms, oral films (dispersible). Dispersible tablets offer an advantage over conventional tablets by overcoming swallowing difficulties faced by some pediatric and geriatric patients [6, 21-26, 34-38, 43-46].

Table 3: Oral dosage forms applicability and preferences as per age groups.

Age groups	Age in days / months/years	Oral dosage form acceptability
Full - term new born Infants	0-28 days	Solution/Drops
Infants and toddlers	1 month to 2 years	Solution/Drops/Emulsion/Suspension
Children, pre-school	2-5 years	Powders/Granules/sprinkles/Dispersible tablet/ Effervescent tablet/Orally disintegrating tablet / Chewable tablet/Mini tablet (1-4 mm)
Children, school	6-11 years	Tablet/Capsule/Dispersible tablet/Orally disintegrating tablet/Chewable/Orally disintegrating film
Adolescents	12 years to 18 years	Tablet/Capsule/Dispersible/Orally disintegrating tablet/ Chewable tablet
Geriatrics	> 65 years	Tablet/Capsule/Dispersible tablet/Orally disintegrating tablet/Chewable

About 25% of adult patients have difficulty in swallowing (dysphagia) intact tablets and capsules; in the pediatric population of the percentage is higher [9]. Dysphagia challenges may be overcome by developing solid dosage forms to be dissolved, dispersed or mixed with food before administration, or dosage forms for chewing or administered to the mouth. Besides highlighted about merits and demerits several novel oral technologies,

(i) Effervescent dosage forms are not suitable for patients having renal insufficiency because of the high content of potassium or sodium.

(ii) It is very important that chewable tablets are needed to be easy to break by chewing for the pediatric patient due to tablet high hardness.

(iii) Dispersible tablets are more advantageous as compared to effervescent tablets are that the problems with bicarbonate, sodium, and potassium are avoided.

(iv) Orodispersible dosage forms are orodispersible tablets, oral lyophilisates, and thin films to be placed on the tongue where they disperse rapidly or melt by dissolution in the saliva, whereafter the dissolved dose is swallowed. They are easy to administer, do not require additional water.

End-user needs regard to the supply chain consideration such as ease of transportation and storage requirements. Storage in a refrigerator by the user is not always possible. Multiparticulate flexible preparations are rounded granules of uniform size (often called pellets with a size range of 0.5-2 mm) and mini-tablets with a diameter of not less than 1.5 mm and not more than 4 mm. An age-related dose may be obtained by taking several pellets or mini-tablets. The Potential problem with chewable tablets is that they may be swallowed by a patient without proper chewing or

chewing at all. Dispersible and soluble tablets are flexible dosage forms [7], [31].
Orodispersible film having advantages of easy administration, no risk of choking. Also having the disadvantages of orodispersible film include poor mechanical strength, product packaging, risk of medication errors, the limited load of drug substance, higher production costs and lack of harmonized test methods [11].

C. Commercially approved novel oral solid dosage forms

Oral Solid drug delivery system design has been the formulation of choice for pharmaceutical industry due to the pros of well-established technology platforms enabling long-term stability, easing supply chain and maintaining low manufacturing cost. The oral solid dosage form design remains an alternative formulation design as compared to liquid dosage form design. As overviewed from the published journals, the highlighted novel oral dosage forms are sprinkles (powder, granules), mini- tablets, dispersible tablets, orally disintegrating/Orodispersible tablets, chewable tablets, and orodispersible films. Majority of the dosage forms were commercialized found to be orally disintegrating/orodispersible tablets [13-14], (Table 4). The majority of commercialized manufacturing technology involves conventional approaches, followed by freeze-dried/lyophilized technologies.

Table 4: List of commercialized novel oral solid dosage forms.

Sr.No	Drug products	Age groups covered	Dose flexibility across the age groups (from ≥2 years to ≥65 years)
1.	Alprazolam Orally Disintegrating Tablets 0.25/0.5/1.0/2.0 mg (scored)	* Above 18 years * Geriatric (at smallest dose)	Not Established
2.	Aripiprazole Orally Disintegrating Tablets 10/15 mg	6 - 18 years to >65 years	Flexible (low)
3.	Cetirizine Hydrochloride Orally Disintegrating Tablets 10 mg	* 6-17 years * <6 years with prescription	Not Established
4.	Clonazepam Orally Disintegrating Tablets 0.5/1/2 mg	Above 18 years & Geriatric	Not Established
5.	Donepezil hydrochloride orally disintegrating tablets 5/10 mg	* Pediatric : Safety not established * Geriatric 73 years mean age	Not Established
6.	Loratadine 10 mg orally Disintegrating Tablets	* > 6 years & older * <6 years with prescription	Not Established
7.	Ticagrelor 90 mg Orodispersible Tablets	>18 years & Geriatric	Not Established
8.	Lansoprazole 30 mg Orodispersible Tablets	>12 years & Geriatric	Not Established
9.	Meloxicam 15 mg Orodispersible Tablets	* >16 years to Geriatrics (Water may be used to moisten the buccal mucosa in patients with a dry mouth)	Not Established
10.	Rizatriptan benzoate Orally Disintegrating Tablets 5/10 mg (lyophilized)	* 6 to 17 years * >65 years with cautious	Flexible (low)
11.	Risperidone Orally Disintegrating Tablets 0.5/1/2/3/4 mg	13-17 years	Not Established
12.	Mirtazapine Orally Disintegrating Tablets 15/30/45 mg	*Pediatrics : Safety not established *25-74 years	Not Established
13.	Olanzapine Orally Disintegrating Tablets (freeze - dried) 5/10/15/20 mg	13-17 years	Not Established
14.	Loperamide hydrochloride 2 mg Orodispersible Tablet (lyophilized)	12 years to >65 years	Not Established
15.	Ondansetron 4/8 mg Orally Disintegrating Tablets (lyophilized)	> 4 years to > 65 years	*Flexible(low) *For adult dose, 3 tablets of 8 mg strength to be administered over 30 mins
16.	Ondansetron 4/8 mg Orally Dissolving Films	> 4 years to > 65 years (Multiple inactive ingredients used for fabrication will be possible for alarming the risk of excipients oriented adverse reaction)	*Flexible(low) * For adult dose,3 film of 8 mg strength to be administered over 30 mins

III. SUMMARY AND CONCLUSION

This review provides a comparative assessment in the selection of suitable novel oral solid dosage form without the necessity of refrigeration and has a potential application in the condition of swallowing and chewing difficulty in place of commercialized cephalosporin powder for oral suspension dosage form. Further, this review highlights that certain dosage form design parameters as identified below need to consider while designing flexible novel oral solid dosage form which is not addressed by the authors in any of literature review.

The oral route of administration is most commonly used for dosing medicinal products for the long term and short term treatments. Consequently, a variety of conventional and novel oral dosage forms available make this route extremely useful for the administration of medicinal products. For generations, it was considered that it would best be treated with oral liquid dosage forms, as these were easy to swallow in the condition of swallowing, chewing difficulty and would possible to provide adequate dosing flexibility across the age groups from pediatric to geriatric.The usage of oral liquid dosage forms, associated with numerous limitations such as poor chemical stability, inaccurate dosing, more prone to microbial degradation and special storage condition. Because of the above - said limitations of oral liquid dosage forms, solid drug delivery system design has been the formulation of choice for pharmaceutical industry due to the pros of well- established technology platforms, enabling long-term stability, easing supply chain and maintaining, low manufacturing cost. However, due to the impact of the size of conventional oral solid dosage forms such as tablet and capsule in the condition of swallowing difficulty, several novel oral solid dosage forms had been identified and commercialized (Table 1 & 4).

With referring to the current literature review about commercially approved oral cephalosporin powder for suspension dosage form (Table 2), it has the potential clinical application of providing flexibility in dosage across the age groups from pediatric to geriatric and also preferred dosage form in the condition of swallowing and chewing difficulty as compared to other commercialized cephalosporin oral dosage forms. However, necessity to refrigerate in order to stabilize the dosage forms and impact on overall shelf life after reconstitution tends to reduce its commercial application. Further, this review stresses the importance of looking for an alternate novel oral solid dosage form design with salient features of avoiding the necessity of refrigeration, flexible in the application concerning dosage, mode of administration across the age groups as per therapeutic dosage indication.

With referring to the current literature review about the dosage form preference across the age groups (Table 3) and commercially approved novel oral solid dosage forms (Table 4), the dispersible oral formulation in the form of dispersible tablets, orally disintegrating/ orodispersible tablets and mini-tablets showing more potential in terms of flexibility in dosage and mode of administration considering patient age groups from 4 years to ≥65 years, pathophysiology condition/patient requirements and also have the capability of application in the condition of swallowing and chewing difficulty as compared to other novel oral solid dosage forms. Further these salient features of dispersible oral formulation found to have the potential as an alternative dosage form design in place of commercialized cephalosporin powder for oral suspension dosage form.

However, from this current review about commercialized cephalosporin oral dosage forms except for powder for oral suspension dosage form, several novel oral solid dosage forms and novel technologies, none of the literature does address about the dosage form design parameters which need to consider while designing the dosage forms in terms of flexibility in application across the intended age groups as per therapeutic dosage indication. The following dosage form design parameters need to consider while designing the flexible dispersible oral dosage forms.

(i) Single dosage form design covering pediatric and geriatric age groups particularly from >2 years to ≥65 years without the necessity of different dosage form design

(ii) To facilitate flexibility in dosage administration based on the pathophysiological condition of salivary secretion & patients needs

(iii) To formulate with minimum and only the excipients known to be safe across the age groups

(iv) Dosage forms permitting safe, accurate dose administration, which enhances the compliance (convenient, easy, reliable administration) by parents or caregivers and reduces the risk of medication errors.

(v) Non-complex and cost-effective manufacturing process

(vi) Acceptable palatability and patient compliance

(vii) Stable at controlled room temperature condition

Finally to conclude that, flexible dispersible oral dosage forms such as a dispersible tablet, orally disintegrating/orodispersible tablets and, mini-tablets with above-intended dosage design parameters having the potential as an alternate flexible dosage form design choice in place of commercially approved oral cephalosporin powder for suspension dosage form across the age groups.

IV. FUTURE SCOPE

To explore the formulation design to understand the practical implications in the current scenario of novel oral dosage form design in terms of flexibility across the age groups.

ACKNOWLEDGMENT

This review did not receive any specific grant from funding agencies in the public, commercial or not for profit sectors.

Conflict of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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How to cite this article: Govindan, S.P., Senthamarai, R. and Anbarasu, K. (2019). Refrigeration and the Shelf Life of Oral Cephalosporin Powder for Suspension Dosage Form: Review and Proposal. *International Journal of Emerging Technologies*, **10**(2): 376–383.