AN ASSESSMENT ON BUCCAL MUCOADHESIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Buccal drug delivery system (BDDS) has won a variety of exposure and traction as it possesses plenty of advantages and benefits as evaluate to different mucosal drug delivery systems. Buccal path for systemic drug delivery, the use of mucosahesive polymers twill significantly increase the efficacy of many tablets, has been of outstanding interest over the previous couple of decades. This article affords a precis of BDDS mechanisms, consisting of a composition of the oral mucosa, delivery mechanism, numerous forms of BDDS, formulation, assessment and application of BDDS. Additionally, this text affords a precis over the patents, advertised products and destiny factors of BDDS. In this evaluation article, we’ve got tried to assemble the maximum significant reports (1988 to 2021) of formulation, assessment, application, patents of BDDS. This review will help pharmaceutical researchers to clarify the potential of BDDS to overcome the various existing drug delivery dispute like the efficiency of absorption, permeability and bioavailability of drugs.

Keywords: Buccal drug delivery, Mucoadhesive polymer, Formulation, Evaluation, Application, Patents

INTRODUCTION

Advancement and the progress made by the pharmaceutical industry that greatly contributed to treat the diseases, thus improving the quality of life [1]. With the passage of time researchers who are involved in the drug development industries focus on the alternative routes of administration of potentially capable pharmaceutical products and as well as to overcome defects that are associated with the oral route of administration. Though oral route is the most preferred route for the administration of major drugs, but it possesses certain drawbacks such as, the first pass metabolism in the liver, the local GI and enzymatic degradation inside the GI tracts [2].

In order to overcome the above mention drawbacks, one such strategy was used that is to deliver the drug through the alternative route such as Intranasal, Sublingual, Buccal, Pulmonary or Transdermal drug delivery systems [3]. Transmucosal method of drug transmission comprise of the mucosal lining of mouth, eye, vagina, rectum and nasal cavity which provides potential benefits over oral systemic drug delivery system. These features include the ability to bypass the first-pass metabolism, avoid the pre-elimination of the drug in the GI tract and dependence on the drug characters, it shows better enzymatic flora for the drug absorption [4].

Among the different mucosal pathways, the buccal mucosa has excellent accessibility, stretching of smooth muscle and relatively immobile mucosa; thus, this route of administration is suitable for controlled release of drugs from the dosage forms. By eliminating first-pass metabolism and enzymatic degradation owing to GI microbial flora, the oral mucosal drug delivery method is extensively applicable as a unique site for drug administration for immediate and controlled release action. Local and systemic action is provided through the oral mucosal medication delivery system. In addition, it exhibit great patient compliance as compare to other non-oral mucosal methods of drug administration. The Buccal drug delivery avoids acidolysis of the drug in GI system and bypasses the first-pass hepatic metabolism, which results the high bioavailability of the drug [5].

This article summarizes the advantage and disadvantages, application, evaluation, mechanism of the drug penetration, patents and marketed available pelletized drug delivery system. And also it will highlight the important terms and descriptions in the advantages, disadvantages, application, evaluation, mechanism of the drug penetration, patents and marketed available pelletized drug delivery system.

This review was conducted using Google search terms such as buccal mucoadhesive drug delivery system and articles relating to its formulation, evaluation, application and patents, which were collected from standard journals such as science direct, pubmed and scopus indexed journals.

Physiological, anatomical features of the oral cavity

The lips, hard palate (the bony front portion of the roof of the mouth), soft palate (the muscular back portion of the roof of the mouth), retromolar trigone (the area behind the wisdom teeth), front two-thirds of the tongue, gingiva (gums), buccal mucosa (the inner lining of the lips and cheeks), and floor of the mouth under the tongue are all parts of the oral cavity. In the following fig. 1 and table 1, it show the composition of the oral cavity and its respective role in drug penetration.

Fig. 1: (A) Anatomy of oral mucosa; (B) Transverse section of oral mucosa [2]
Table 1: Composition of the oral cavity and mechanism of permeation enhancers

| S. No. | Composition of the oral cavity and its role | Thickness | Drug permeation enhancement mechanism | Reference |
|--------|--------------------------------------------|-----------|--------------------------------------|-----------|
| 1.     | Epithelium Layer as shown in fig. 1 possesses two type keratinized epithelium, It covers the soft palate, ventral surface of the tongue, inner lip, floor of the mouth and inner cheeks | 500-800 µm | The pores of the protective layer can be enhanced by the addition of surfactant (Anionic: Sodium lauryl sulfate Cationic: Cetyl pyridinium chloride Nonionic: Poloxamer, Brij, Span, Myrj, Tween) by the agitation of intercellular Lipids and its protein (keratin) domain structure | [2, 3] |
|        | Keratinized epithelium It covers the gingiva, dorsal surface of the tongue and hard palate. Role: Protective layer |           |                                      |           |
| 2.     | Basement Membrane It forms a distinct layer between the epithelium and connective layer Role: Provides the adherence between the epithelium and connective tissue and provide mechanical support to the epithelium layer | 1-2 µm    | Addition of positively charged polymers like Chitosan, Cationic compounds like Poly-L-arginine, L-lysine will show an ionic interaction with the negative charge on the mucosal surface will pave the way to the enhancement of drug through the mcosa | [4, 5] |
| 3.     | Connective Tissue It consists of lamina propria and submucosa layer. The lamina propria consists of collagen fibers, supporting layers, blood vessels and smooth muscles. Role: Responsible for the blood supply to the oral cavity. The Buccal artery like facial artery and infraorbital artery are the predominant source of blood supply to cheek lining in the Buccal cavity. Which will be responsible for enhancement of drug penetration due to the predominant source of blood supply | 150-500 µm | By adding a surfactant, Cyclodextrins, Chelators, anionic and cationic polymers may interfere with Ca+ ions, negative charge on the mucosal surface will leads to enhancement of drug permeability. | [6, 7] |
| 4.     | Mucus Gel like secretion which was translucent and continuous; Composition • Water insoluble glycoprotein (Mucin): 1-5% • Water: 95-99% • Proteins, enzymes, electrolytes and nucleic acids. Role: It is a visco-elastic hydrogel which act as a protective layer to the cell below. | • Buccal (Nonkeratinized)-500-600 µm with 2.40 ml/min/cm² • Sublingual (Nonkeratinized)-100-200 µm with 0.97 ml/min/cm² • Gingival (keratinized)-200 µm with 1.47 ml/min/cm² • Palatal (Keratinized)-250 µm with 0.89 ml/min/cm² • Viscosity-1.05 cP and 1.29 cP, respectively | By adding anionic and cationic surfactant, bile salts (Sodium glycocholate, Sodium tauro deoxycholate, Sodium taurocholate), Fatty acids (Oleic acid, Caprylic acid, Lauric acid), Cyclodextrin, Chelator (EDTA, Citric acid, Sodium salicylate, Methoxy salicylates) will either increase the fluidity of phospholipid domains or agitate the intercellular Lipids and its protein (keratin) domain structure | [8, 9] |
| 5.     | Saliva Role: Protective fluid, Source of mineralization for the tooth enamel, Hydrate the oral drug delivery system | By adding anionic and cationic surfactant, bile salts (Sodium glycocholate, Sodium tauro deoxycholate, Sodium taurocholate), Fatty acids (Oleic acid, Caprylic acid, Lauric acid), Cyclodextrin, Chelator (EDTA, Citric acid, Sodium salicylate, Methoxy salicylates) will either increase the fluidity of phospholipid domains or agitate the intercellular Lipids and its protein (keratin) domain structure | Drug Permeation enhancement mechanism: Will either increase the fluidity of phospholipid domains by adding bile salt, fatty acids to the BDDS | [10, 11] |

Fig. 2: (A) Buccal mucoadhesive tablet [5]; (B) Administration sites of buccal mucoadhesive tablets [6]; (C) Schematic representation of bioadhesion mechanism [8]; Buccal mucoadhesive films [9]; (D) Contact of BDDS to buccal mucosa [8]; (E) Buccal patch [9]; (F) Scheme of route of permeation from BDDS through buccal mucosa [3]
Transport mechanism

Drug transport mechanism through the Buccal drug delivery is carried out by two mechanisms i.e. transcellular (intracellular) and paracellular (intercellular) as shown in fig. 2 (F). Paracellular route of permeation of the drug across the buccal epithelium is carried out through the passive diffusion. It is the most common route of permeation of the drug across the buccal epithelium is carried out by transferring the drug through the absorptive barrier i.e. cell membrane followed by the hydrophilic content of the series cell in order to reach the cytoplasmic content of the next cell. Example of the drug that penetrates via transcellular route of permeation is fentanyl [10]. Certain drugs may penetrate by using both the pathways which is possible only when the drug exhibit proper hydrophilic and lipophilic balance with a slight predominance of hydrophilic property. These drugs undergo faster penetration, apart from these pathways alternative pathway like carrier mediated transport also play an major role for the penetration of the certain drugs across the membrane [11]. The major factors that influencing the penetration and bioavailability of the drug through the Buccal drug delivery includes permeability and thickness of the epithelium, blood supply, metabolic activity, saliva and mucous, species difference and route of mechanism [12].

Novel buccal dosage formulations

| S. No. | Dosage form | Description | Example | Reference |
|--------|-------------|-------------|---------|-----------|
| 1.     | Buccal mucoadhesive tablets as shown in fig. 2(A,B) | Dry dosage form | Double layer tablet | [13, 14] |
| 2.     | Buccal patches as shown in fig. 2(E) It is of two types • Reservoir type • Matrix type | Must be moistened before use prior coming in contact with the Buccal mucosa | Zilactin | [15, 16] |
| 3.     | Semisolid dosage form(ointments and gel) Powders | Consists of two laminates with adhesive polymer(aqueous form) which is glued over the backing sheet | - | [17] |
| 4.     | It is increase the residence time of the drug in oral mucosa | - | Hydroxypropyl cellulose and beclomethasone combination | [18, 19] |
| 5.     | Sprays | It is made up of Mucoadhesive suspension, especially used through nasal route | - | [17-19] |

Advantages and disadvantages of Buccal drug delivery system

| Advantages | Disadvantages | Reference |
|------------|--------------|-----------|
| In contrast to the other mucosal tissues, the buccal mucosa is relatively permeable and has a good blood supply. | The total surface area of the oral cavity membranes usable for drug absorption is 170 cm², with non-keratinized tissues, such as the buccal membrane, accounting for 50 cm². | [16-20] |
| Bypass first pass metabolism | The mucosa’s barrier properties. | |
| Exhibits localized therapy | The medication is diluted as a result of the continuous secretion of saliva (0.5-2 l/day). | |
| Many medications would work better because they have a longer contact time with the mucosa. | The risk of choking if the delivery system is swallowed involuntarily is a concern. | |
| Patient acceptance is high as compared to other non-oral drug delivery methods. | Swallowing saliva may result in the loss of dissolved or suspended drugs, as well as the inadvertent removal of the dosage type. | |
| Lower administration frequency may result from increased residence time combined with controlled API release. | |
| API localization at the disease site can also result in substantial cost savings and a reduction in dose-related side effects. | |
| The formulation stays longer at the delivery site as a result of adhesion and personal touch, improving API bioavailability while using lower API concentrations for disease care. | |
| Buccal drug delivery removes the harsh environmental conditions that occur in oral drug delivery. | |
| It is a passive drug absorption mechanism that does not need any activation. | |
| In comparison to rectal or transdermal pathways, the presence of saliva guarantees a comparatively large volume of water for drug dissolution. | |
| Provides a various different ways to administer hormones, narcotic analgesics, steroids, enzymes, cardiovascular agents, and other medications. | |
| It allows for localized tissue permeability alteration, protease inhibition, and immunogenic response reduction. As a result, therapeutic agents such as peptides, proteins, and ionized species can be easily administered. | |
### Table 4: Types of excipients and their role in the buccal drug delivery system

| S. No. | Excipient | Role | Example | Reference |
|--------|-----------|------|---------|-----------|
| 1.     | Mucoadhesive polymer | Mucoadhesives are synthetic or natural polymers that bind with the mucus layer that coats the mucosal epithelial surface and the major molecules that make up mucus.  
• It is the main excipients for adhesion by attracting water, swells and adheres to the mucous through forming a channel by linking to mucin polymer  
• They bind with mucin with help of H-bonding group, hydrophilic group | Semi synthetic/Natural polymer: Agarose, gelatin, Hyaluronic acid, pectin and cellulose derivatives. Synthetic polymer: Poly(acrylic acid)-based polymers i.e. poly(acrylic acid-co-thylhexylacrylate), poly(methacrylate) Water soluble polymer: PAA, Sodium CMC, Sodiumalginate Water insoluble polymer: Chitosan (soluble in dilute aqueous acids), EC, PC Cationic polymer: Chitosan, Dimethylaminoethyl (DEAE)-dextran, trimethylated chitosan Non ionic polymer: poly(ethylene oxide), PVA, PVP, scleroglucan Anionic polymer: Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum | [21-23] |
| 2.     | Permeation enhancer | Permeation enhancer (<1%) enhances the permeation ability of the drug through the epithelium membrane. The permeation enhancer mechanism depends upon the fick’s first law of diffusion. Its mechanism is as follows:  
• Increasing fluidity and integrity of cell membranes  
• Extracting inter and intracellular lipids  
• Altering cellular proteins  
• Varying mucus rheology  
• Enhancing thermodynamic activity of drugs  
• Decreasing surface tension | Surfactant: Ionic: Dicetyl Sodium sulfosuccinate, Polyoxyethylene-20-cetyl ether Nonionic: Nonylphenoxypolyoxyethylene(NP-POE)(nonionic), Polyoxyethylene-9-lauryl ether (PLE) (nonionic) Fatty acids and derivatives: Acylcarnitine, Oleic acid, Caprylic acid, Mono(di)glycerides and Lauric acid Chelating agents: EDTA, Citric acid and Salicylates Polyols: Propylene glycol and Polyethylene glycol Bile salts and derivatives: Sodium deoxycholate), Sodium glycodydrofusidate and Sodium deoxycholate Sulfoxides: Dimethyl sulfoxide(DMSO) Others (non-surfactants): Urea and derivative Azone(1-dodecylazacycloheptan-2-one) (laurocapram) and cholines | [24-26] |
| 3.     | Enzyme inhibitor | Enzyme inhibitors are used in the formulation of BDDS in order to enhance the drug absorption by decrease the affect of the enzyme over the drug by altering the structural configuration of enzyme and in order to make the drug less susceptible towards the enzyme degradation. | Aprotinin, bestatin, puromycin, bile salts stabilize and polyacrylic acid. | [27-29] |

**Manufacturing methods of the buccal tablets [6, 10, 26]**

1. Tablet ingredients were screened through a 0.150 mm sieve before mixing to achieve a uniform particle size distribution.
2. Gildant and Lubricant were weighed carefully and mixed with a cubic mixer for 15 minutes and then added to the above powder mixture.
3. Blended for 3 minutes.
4. Buccal tablets were compressed by using a single or multiple punch tablet machine with with required mm round flat punch set.
5. Tablet weight was kept constant at 100 mg.
6.Thickness of tablets was adjusted to 2 mm.
Evaluation parameters of buccal drug delivery system

Table 5: Evaluation parameters of BDDS

| S. No. | Evaluation parameter            | Type of buccal dosage form | Method used                                    | Instrument                          | Reference   |
|--------|--------------------------------|----------------------------|-----------------------------------------------|-------------------------------------|-------------|
| 1.     | Surface pH                     | Patch, Tablets Films       | Visual colour change                          | pH meter                           | [32-35]     |
| 2.     | Morphology                     | Tablets, Patches Films     | Microscopy                                    | Scanning Electron Microscopy (SEM)  | [36-39]     |
| 3.     | Swelling index                 | Patches, Films Tablets, Wafers | Swelling of patch and tablet in pH 6.4 phosphate buffer | Agar gel plates                    | [39-43]     |
| 4.     | Folding endurance              | Patches, Films             | Repeated folding in same point                | Manually folded                    | [43-45]     |
| 5.     | Drug compatibility             | Patches, Films Tablets, Wafers | Thermal analysis, Spectral analysis         | FTIR, DSC, XRD                      | [46-48]     |
| 6.     | Thickness                      | Patches, Films             | Standard deviation                           | Vernier calipers, Screw guaze, Electronic digital micrometer | [49-51]     |
| 7.     | Mucoadhesive strength          | Patches, Films Tablets     | Tensile strength                             | Texture analyzer                   | [42, 58, 62]|
| 8.     | Water absorption capacity test | Patches Films              | Agar plate technique                         | Desicators                          | [52-54]     |
| 9.     | Invitro drug release           | Tablets, Patches, Films    | Beaker method; Dissolution method; Rotating paddle method | Kesary chein cell; Franz diffusion cell | [55-58]     |
| 10.    | Mechanical properties          | Patches, Films             | Wilthemy plate technique                     | Microprocessor Modified tensile strength tester | [59-62]     |
| 11.    | Residence time                 | Buccal hydrogels           | Disintegration                               | Modified disintegrator             | [63, 64]    |
| 12.    | Palatability test              | Patches Films              | Grading of taste                             | E-taste meter                      | [65-68]     |
| 13.    | Flatness                       | Patches Films              | Percent constriction                         | Vernier calipers                   | [69, 70]    |
| 14.    | Drug content                   | Tablets, Patches Films     | Traction                                     | RP-HPLC method, UV spectrophotometer | [71-74]     |
| 15.    | Hardness                       | Tablets Wafers             | Crushing force                               | Monsanto hardness tester           | [75-78]     |
| 16.    | Friability                     | Tablets                    | Weighing                                     | Roche fri briator                  | [79-83]     |
| 17.    | Contact angle                  | Films                      | Wetting                                      | Optical tensiometer                | [72, 84-86]|
| 18.    | Transparency                   | Films                      | Transmittance                                | UV spectrophotometer               | [87-89]     |
| 19.    | Water vapour transmission rate | Patches Films              | Dressing method                              | Ovens                              | [90, 91]    |
| 20.    | Drug entrapment                | Patches, Films, Microspheres | Coiloal gold staining method                 | UV spectrophotometer               | [82, 91,]   |
| 21.    | Bio-adhesion                   | Patches Films              | Floreence probe method                       | Dissolution cells                  | [92, 93]    |
| 22.    | Percentage moisture loss        | Patches Films              | Gravimetry method                            | Desicator                          | [94, 95]    |
| 23.    | Ex vivo residence time (RT)    | Patches Films Tablets      | Modified disintegration test apparatus        | disintegration tester              | [96-98]     |

Manufacturing methods of the buccal patches/films

Solvent casting

This method is widely used for the manufacturing of the controlled release matrix and liquid reservoir type buccal film, oral disintegrating films, pellets and granules [35, 39].

Direct milling

This method is widely used for the manufacturing of the oral buccal films and buccal wafers [54, 69].

Hot melt extrusion of films

This method is widely used for the manufacturing of the controlled release matrix tablets, oral disintegrating films, pellets and granules. The procedure of hot melts extrusion as follows [80, 97]:

Application of buccal drug delivery

Table 6: Applications of BDDS

| Applications                          | References |
|---------------------------------------|------------|
| Hypertension. Eg: Atenolol patches.   | [86-102]   |
| Hormone replacement therapy.          |            |
| Angina pectoris. Eg: Nitroglycerine patches. |        |
| Cancer. Eg: Opioid analgesics.        |            |
| Smoking cessation therapy. Eg: Nicotine patches. |      |
| Treatment of microbial infections associated with periodontitis. |   |
| Local therapy includes oral infections, moth ulcers, dental caries, gingivitis, stomatitis. | |
Patents of bdds formulations

Table 7: Patents of BDDS formulations

| S. No. | Title                                                | Author                                                   | Patent number          | Year |
|--------|------------------------------------------------------|----------------------------------------------------------|------------------------|------|
| 1.     | Buccal and/or sublingual therapeutic formulation     | Cumming Alisthair, Kannar david, Sparrow lance          | AU2016238901A                      | 2016 |
| 2.     | Bioadhesive films for oral and/or systemic delivery  | Mcconville Jason Thomas, Morales Javier O, Ross Alkstart | US2016128947A                   | 2016 |
| 3.     | Buccal delivery system                               | Rubina Mughal                                            | GB2568554A                     | 2017 |
| 4.     | Composition and method for Buccal administration of GNRH agonists | De groot Aldemar B, Taneya Rajneesh                           | WO2017208076A                   | 2017 |
| 5.     | Sublingual or Buccal administration for treatment of skin diseases | Scaife michael                                           | WO2018051183A                   | 2018 |
| 6.     | Transmucosal delivery devices with enhanced uptake   | Finn Andrew, Vasisht Niraj                              | US2018133210A                   | 2018 |
| 7.     | Chewable composition for rapid Buccal absorption     | Purcell Marc                                             | US2019015324A                   | 2019 |
| 8.     | Transdermal drug delivery systems for levonorgestrel and ethinyl estradiol | Liao Jun, Nguyen Viet, Patel Prashant                             | US10231977B2                    | 2019 |
| 9.     | Buccal swab delivery system                          | Azmi Nooshin, Cauley Thomas H, Cohen Bruce A, Schnipper Edward F | US2020376241A                   | 2020 |
| 10.    | Device and methods for ultrasonic delivery of an agent within an oral cavity | France Marion, Schoellhammer carl, Sheppard Norman                      | WO2020018866A                   | 2020 |
| 11.    | Enhancing drug activity through accentuated Buccal/sublingual administration | Banerjee Debasish, Banerjee Priyamgada                    | WO2021019278A                   | 2021 |

Marketed products of bdds formulation

Table 8: Marketed products of BDDS formulation

| S. No. | Marketed product | Active ingredient | Bioadhesive agent | Dosage form | Company/Manufacturer | Therapeutic class |
|--------|------------------|-------------------|-------------------|-------------|----------------------|------------------|
| 1.     | Buccastem®       | Prochlorperazine maleate | Xanthum gum      | Buccal tablet | Reckitt Benckiser | Antipsychotics |
| 2.     | Corosol® gel®   | Chlorhexidine     | HPMC              | Oral paste  | GlaxoSmith Kline    | Antimicrobial    |
| 3.     | Actiq           | Fentanyl citrate  | Magnesium stearate| Lozenge     | Celltech              | Analgesics       |
| 4.     | Sucard          | Glyceryl trinitrate| Hypermellase      | Tablet      | Forest laboratories  | Vasodilator      |
| 5.     | Corlan pellets  | Hydrocortisone    | Acacia            | Oral mucosal pellets | Noven | Corticosteroids |
| 6.     | Fastum          | Ketoprofen        | PEG               | Gel         | AMenarini industries | NSAIDS           |
| 7.     | Coreg           | Carvediol         | HPMC              | Buccal patch | GlaxoSmith Kline    | Hypertension     |
| 8.     | Loramyc         | Miconazole        | Corn starch       | Tablet      | BioAlance Pharma SA  | Antifungal       |
| 9.     | Bonjela®        | Cetabonium chloride, Choline salicylate | Hypermellose | Gel         | Reckitt Benckiser    | Analgesic        |
| 10.    | Dentipatch®     | Lidocaine         | Xanthum gum       | Patch       | Noven                | Analgesic        |

Future outcomes

Buccal drug delivery system offers advantages in accessibility, administration, economy, patient compliance. Novel preparations are focusing on the use of responsive polymeric system using copolymer with desirable hydrophilic/hydrophobic interaction, complexation networks, block or graft polymers from the natural edible sources. At the current global scenario, experts are finding ways to develop Buccal drug delivery with improved bioavailability of orally inefficient drugs by manipulating the formulation with enzyme inhibitors, inclusion of pH, permeation enhancers. At present solid dosage forms, liquids, patches and gels are commercially successful.

CONCLUSION

The Buccal drug delivery system predominantly serves more advantages when compared to controlled drug delivery. It was a promising area for the systemic drug delivery of orally inefficient drugs. It has significant advantages like avoidance of presystemic elimination in GIT and first pass metabolism in liver. Buccal drug delivery can be affected by thickness of mucosal layer, barrier properties of mucosa, area of absorption site and it can be enhanced by penetration enhancers, bio-adhesive agents. In this review we have concluded that with the right dosage form design, mucoadhesive polymers and ideal formulation, the permeability and the local environment of mucosa can be controlled and manipulated in order to enhance drug permeation. This review will help pharmaceutical researchers to clarify the potential of BDDS to overcome the various existing drug delivery dispute like efficiency of absorption, permeability and bioavailability of drugs.

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AUTHORS CONTRIBUTIONS

Mrs. V. L. V. Lakshmi was involved in review of literature and collection of data and preparation of the manuscript. Mr. Umashankar MS, Mr Alagusundaram M was involved in reviewing, and editing of the manuscript.

CONFLICT OF INTERESTS

There is no conflict of interest for this review.

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