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An insight into the use and advantages of Carbopol in topical mucoadhesive drug delivery system: A systematic review

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ABSTRACT

Introduction: In recent years, mucoadhesive topical application of mucous membrane has gained considerable interest among formulation researchers in advanced drug delivery systems. It has been identified as a potential route for both local and systemic drug delivery. A mucoadhesive agent is usually incorporated in the formulation to overcome the disadvantages associated with the conventional topical formulation. These disadvantages include low residence time of the medication on the site of application due to tongue movement and salivary washout in the intraoral formulation, mucociliary clearance in the intranasal application, and rapid precorneal elimination in the intraocular formulation. Carbomer or known as Carbopol is a mucoadhesive polymer that is widely studied for topical delivery of pharmaceutical agents to the mucous membrane. The use of Carbopol and its advantages in the mucoadhesive topical application has gained considerable interest with several published studies and is available in various grades. In this study, a systematic review was performed on the available literature that investigates the Carbopol application in mucoadhesive topical drug delivery. **Method:** A systematic searching strategy was performed in Scopus, ProQuest, and PubMed databases using predetermined search strings. A total of 778 articles were retrieved, however, only 25 articles met the inclusion criteria and were used for data synthesis. **Results:** The results showed that incorporation of Carbopol as mucoadhesive polymer hold multiple advantages in drug delivery namely excellent mucoadhesion effect, the prolonged residence time of the formulation, enhanced drug permeation, prolonged release of drug, pseudoplastic behaviour of the formulation, pH compatibility with all mucosal site, and biocompatible. **Conclusion:** This suggests that the incorporation of Carbopol can be an effective mucoadhesive agent for topical drug delivery systems.

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Introduction

Mucoadhesive topical application is an interesting field among formulation researchers in advanced drug delivery systems (Duarah, Durai, & Narayanan, 2017; Kapileshwari et al., 2020; Matos et al., 2020). It is an external drug's introduction to the mucous membrane of the body part that exploits the property of bioadhesion of certain polymers (Kore, Shete, Desai, & Dnyanpeeths, 2013). Mucous membranes are found in many body parts including the eyes, respiratory tract, gastrointestinal tract, and reproductive tract (Netsomboon & Bernkop-Schnürch, 2016) that serves as a potential route for both local and systemic drug delivery (Kumar, Naik, Pradhan, Ghosh, & Rath, 2020; Srikrishna et al., 2017). Mucoadhesive drug delivery is adopted to resolve the disadvantages associated with the conventional topical formulation including low residence medication time on the site of application due to tongue movement and salivary washout in the intraoral formulation, mucociliary clearance in the intranasal application, and rapid precorneal elimination in the intraocular formulation (Netsomboon & Bernkop-Schnürch, 2016; Pagano, Giovagnoli, Perioli, Tiralti, & Ricci, 2020; Saisree et al., 2019; Sheshala, Ming, Kok, Singh, & Dua, 2019). Carbomer or is typically called Carbopol and and polyacrylic acid is a mucoadhesive polymer with the formula (CH2-CHCO2H)n that is widely incorporated for topical delivery of pharmaceutical agents to the mucous membrane (Arun Karthick, Ramya Devi, & Vedha Hari, 2018; M. N. A. Rahman, Qader, Sukmasari, Ismail, & Doolaanea, 2017; Sheshala et al., 2019; Suzilla, Izzati, Isha, Zalina, & Rajaletchumy, 2020).

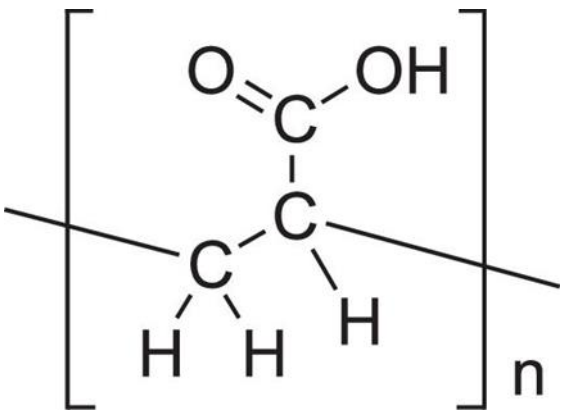

Figure 1. General structure of Carbopol polymer.

The most attractive properties of Carbopol as a mucoadhesive agent for topical application are biodegradable, bioadhesive, non-irritant, not absorbed into the body, and less expensive (Bera, Mazumder, & Khanam, 2016; Suzilla et al., 2020). Carbopol possesses several grades and is classified according to the degree of crosslinking, viscosity, and manufacturing condition, which offers flexibility in drug release profile as well as mucoadhesion (Singla, Chawla, & Singh, 2000). It is incorporated in various dosage form and various strength for topical oral, nasal, ophthalmic, and vaginal drug delivery. The main aim of this study is to systematically review the use of Carbopol according to its grade and formulation dosage form as mucoadhesive topical drug delivery particularly on the oral mucosa, nasal mucosa, ophthalmic mucosa, and vaginal mucosa based on recent studies. This review also aims to discuss the merits of Carbopol in topical mucoadhesive drug delivery.

Methodology

This section discusses the chosen method used to select articles related to the use of Carbopol in topical drug delivery. The reviewers used the PRISMA method that includes Scopus, ProQuest, and Pubmed to perform a systematic review in identifying, screening, eligibility, quality appraisal and data abstraction, and analysis.

1. The review protocol – PRISMA

This systematic review was guided by the PRISMA Statement.

2. Formulation of research question

The formulation of the research question for this review was based on PICo. It is a tool that facilitates the authors in generating relevant research question for the review. PICo is based on three key concepts namely Problem, Interest, and Context. Based on these concepts, the authors chose three primary aspects for the review namely Carbopol grade and strength based on the formulation dosage form (Problem), advantages of Carbopol in the topical application on mucous membrane such as oral, nose, eye and vagina (Interest), and drug delivery system (Context). These concepts have guided the authors to formulate the key research question namely what is the grade, strength, and advantages of Carbopol in topical mucoadhesive drug delivery system?

3. Systematic searching strategies

There are three main processes in the systematic searching strategies that include identification, screening, and eligibility.

3.1 Identification

Identification of the keywords followed by the process of searching for the synonym of the keywords was performed. The search string was developed including ((Carbopol OR caborpol OR cabormer OR cabormer OR carbapol) AND (mucosa* OR "mucosa layer" OR "mucosa membrane") AND (eye* OR ophthalmic* OR ocular* OR optic* OR oral* OR mouth* OR lingual OR periodontal OR gum* OR vagina) AND (mucoadhesive OR mucoadhesion OR bioadhesive OR bioadhesion)). The search string was performed on three databases in which 300 articles were

retrieved in Scopus, 468 articles in ProQuest, and 10 articles in PubMed.

3.2 Screening

Screening of the articles was conducted automatically based on the sorting function available in the databases according to the inclusion and exclusion criteria as shown in Table 1. A total of 615 articles was excluded after the sorting function whereas 3 duplicate articles were removed.

Table 1: Inclusion and exclusion criteria of this systematic review

Criteria	Inclusion	Exclusion
Publication timeline	2016 - 2020	2015 and before
Document type	Original research articles	Conference proceeding, chapters in book, book series, books etc
Language	English	Non-English
Nature of the study	Focus on topical drug delivery	Focus on other than topical drug delivery

3.3 Eligibility

Eligibility is the third process whereby the authors read the full text of the articles to ensure that the articles met the inclusion criteria. A total of 160 articles were assessed and 87 articles were excluded due to lack of details regarding Carbopol used on the mucous membrane in the topical application. This resulted in only 73 articles proceeded to the quality appraisal step.

4. Quality appraisal

Quality appraisal was conducted to ensure the quality content of the articles. All 73 articles were assessed individually by 3 authors and these articles were ranked to either high, medium, or low-quality article based on the predetermined criteria. The criteria were established based on the research questions. Mutual agreement between the authors was practised in this process to reduce bias. The authors concluded to only include high-quality articles hence, only 25 articles proceeded to the data abstraction and analysis step (Figure 2).

5. Data abstraction and analysis

This study used a qualitative technique to analyse the data. Data abstraction was conducted based on the research questions in which 2 of the authors categorised each article into the dosage design, the drug used, site of application, Carbopol grade and strength, and the advantages of Carbopol based on the summary of the article.

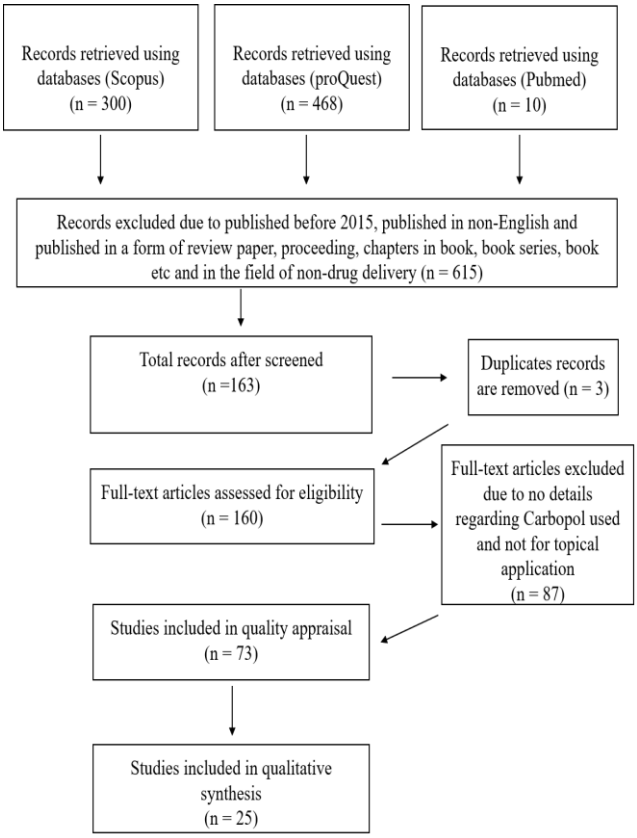

Figure 2. The PRISMA flow diagram.

Results

1. Background of the selected articles

The total selected articles were 25 of which 2 articles were published in 2020, 6 in 2019, 4 in 2018, 8 in 2017, and 5 in 2016. These articles were evaluated for Carbopol application to the oral mucosa, nasal mucosa, eye mucosa, and vaginal mucosa. The results showed that 14 articles incorporated Carbopol for oral mucosa application, 5 studies in the nasal mucosa, 5 studies in vaginal mucosa while only 1 study in eye mucosa. This review has identified 7 formulated dosages, which is in situ gel, gel, tablet, patches, film, aerosol, and wafer. There were 5 grades of Carbopol polymer were documented namely Carbopol 940, Carbopol 974P, Carbopol 934P, Carbopol 971P, and Carbopol 980. The most frequently used Carbopol grade was Carbopol 940 in which it was reported in 10 articles followed by 8 articles utilised Carbopol 934P, 6 articles used Carbopol 974P, and 1 article each used Carbopol 971P and Carbopol 980. Table 2 summarises the included studies.

Table 2: Summary of the included studies.

Year	Ref	Dosage design	Drug	Site	Carbopol type and strength	Advantages
2020	(Li, Bao, Shen, Lalla, & Burgess, 2020)	In situ gel	Bupivacaine	Oral	974P (0.08%)	Superior mucoadhesion and greater swelling
2019	(Mohamad, Abdelkader, Elrehany, & Mansour, 2019)	Tablets	Cyanocobalamin	Oral	971P (50% and 49% w/w)	Superior mucoadhesion, exhibit slow-release, good swelling rate
2016	(Patel, Prabhu, Dubey, & Kamath, 2016)	Buccal patches	Hydrochlorothiazide and atenolol	Oral	934P (100 mg – 300 mg)	Superior mucoadhesion, greater swelling, better permeation and biocompatible
2017	(Marques, Rocha, Leal, Estanqueiro, & Lobo, 2017)	Buccal gel of lipid nanoparticle	Ibuprofen	Oral	980 (1.5% w/w)	Superior mucoadhesion, higher firmness and exhibit pseudoplastic behaviour
2017	(Pham, Van Vo, Tran, Tran, & Tran, 2017)	Microemulsion-based wafer	Prednisolone	Oral	940 (1.5%)	Exhibit slow-release and superior mucoadhesion
2017	(Azeran et al., 2017)	Gel	Moxifloxacin	Oral	940 (0.3%)	Superior mucoadhesion, exhibit slow-release, and exert permeation enhancing effect
2017	(Sadeq & Rajab, 2017)	Patches	Captopril	Oral	934 (93.75mg and 18.75mg)	Superior mucoadhesion, greater swelling index, exhibit slow release and compatible
2016	(Kumria, Nair, Goomber, & Gupta, 2016)	Film	Prednisolone	Oral	940 (100mg, 75 mg and 50 mg)	Improved viscosity, superior mucoadhesion, slow and steady hydration, exhibit slow-release, and great drug permeation
2019	(Jain, Gilhotra, & Kori, 2019)	Hydrogel	L-glutamine	Oral	934P (0.25-1%)	Good consistencies and homogeneity, compatible, and exhibit slow release
2020	(T. A. Ahmed, Bawazir, Alharbi, & Safo, 2020)	Film	Simvastatin	Oral	940 (5% and 10%)	Uniform distribution, compatible (drug and excipient) superior mucoadhesion and exhibit slow release.
2017	(Ali, Sabati, & Ali, 2017)	Film	Baclofen	Oral	940 (1-5%)	Biocompatible, greater swelling, superior mucoadhesion, exhibit slow release and greater in vivo residence time
2018	(Aslani, Zolfaghari, & Fereidani, 2018)	Gel	Herbs	Oral	940 (0.5% and 1%)	Superior mucoadhesion and exhibit slow release
2017	(Calixto et al., 2017)	Liquid-crystaline system with in situ gelling	Peptide p1025	Oral	974P (2.5%)	Superior mucoadhesion and good pseudoelasticity and elasticity
2018	(Chaiprateep, Khobjai, & Noysang, 2018)	Film	Clinacanthus nutans	Oral	934P (7.5 to 24 g)	Superior mucoadhesion, increased elongation and tensile strength and greater swelling
2019	(Mahajan, Shende, Dumore, & Nasare, 2019)	In situ gel	Tapentadol	Nasal	934P 0.1% w/v	Effective gelation viscosity and gel strength, good drug release and good mucoadhesive strength

2019	(Abdelnabi, Abdallah, & Elghamry, 2019)	In situ nanovesicular gel	Buspirone	Nasal	974P (0.3% & 0.5 % w/v)	Increased muchoadhesiveness, sustained drug release, increased bioavailability and has penetration enhancing effect
2016	(Ayoub, Ibrahim, Abdallah, & Mahdy, 2016)	Microemulsion based gel (mbg)	Sulpiride	Nasal	940 (0.5% - 2%)	Uniform spreadability, increased mucoadhesive force, enhanced nasal bioavailability, has penetration enhancing effect and prolong residence time
2017	(Malekar, Gondkar, Bhairav, Paralkar, & Saudagar, 2017)	In situ nasal gel	Naratriptan	Nasal	934 0.2% w/v	Prolong residence time, better mucoadhesive property and improved bioavailability
2016	(Shelke et al., 2016)	Thermoreversible nanoethosomal gel	Eletriptan	Nasal	934 (0.4% w/v)	Increased mucoadhesive strength, prolong retention, Increased absorption and better drug permeation

2. Grade and strength of Carbopol for oral mucosa application

Oral mucosa topical application reported 6 types of dosage forms namely in situ gel, oral gel, buccal mucoadhesive tablet, patches, film, and wafer. Different concentration of Carbopol was used according to the type of formulation. Carbopol ranging from 0.25% to 1.5% was used in the oral gel formulation whereas 1.5% of Carbopol 980 was used as a single gelling polymer in nanoparticle loaded gel formulation (Marques et al., 2017). A lower concentration was reported in 1 study whereby 0.3% of Carbopol 940 was used as a single gelling agent for oral gel formulation (Azeran et al., 2017). 0.25% to 1% of Carbopol 934P was used in combination with HPMC polymer and 0.5% to 1% Carbopol 940 was used in combination with Na-CMC carbomer for intraoral gel formulation (Aslani et al., 2018; Jain et al., 2019). Carbopol 974P was used in 2 articles for in situ gel formulation with 0.08% and 2.5% in combination with pluronic polymer and as single polymer, respectively (Calixto et al., 2017; Li et al., 2020). In addition, 3 articles utilised Carbopol 940 in mucoadhesive film formulation ranging from 1% to 10% and 1 article used 7.5 g to 24 g of Carbopol 934P with the combination of various polymers such as gum acacia, sodium alginate, polymethacrylates, and HPMC (T. A. Ahmed et al., 2020; Ali et al., 2017; Chaiprateep et al., 2018; Kumria et al., 2016). 1.5% of Carbopol 940 was employed in microemulsion based mucoadhesive buccal wafer (Pham et al., 2017) and 2 articles utilised 18.75 mg to 300 mg of Carbopol 934 for buccal patches formulation (Patel et al., 2016; Sadeq & Rajab, 2017). Meanwhile, 1 study incorporated 49% and 50% of Carbopol 971P in combination with HPMC and chitosan for mucoadhesive buccal tablet formulation (Mohamad et al., 2019).

3. Grade and strength of Carbopol for nasal mucosa application

For intranasal application, 0.5% to 2% of Carbopol 940 was used as a single mucoadhesive polymer for gel formulation (Ayoub et al., 2016). Meanwhile, 3 studies used Carbopol 934P with a concentration of 0.1% to 0.4% for in situ gel formulation with a combination of other polymers such as HPMC, gellan gum, xanthan gum, and poloxamer 407 (Mahajan et al., 2019; Malekar et al., 2017; Shelke et al., 2016). Furthermore, 1 study used 0.3% and 0.5% of Carbopol 974P with a combination of HPMC for in situ intranasal formulation (Abdelnabi et al., 2019). It can be observed that the incorporation of Carbopol as the only gelling polymer requires a higher concentration of up to 2%. In contrast, a lower concentration of Carbopol is needed below 0.5% when used in combination with other polymers.

4. Grade and strength of Carbopol for vaginal mucosa application

In single gelling agent for intravaginal gel formulation, 2 articles incorporated 1% Carbopol 974P (S. S. Rahman & Ahmed, 2019; Takalkar & Desai, 2018) while another study used 0.8% Carbopol 940 (Salah, Awad, & Makhlouf, 2018). An article studied 2 grades of Carbopol namely Carbopol 934 and Carbopol 940 both ranging from 0.5% to 1% with the combination of HPMC polymer for vaginal gel formulation (Choudhury & Roy, 2016).

5. Grade and strength of Carbopol for eye mucosa application

0.1% and 0.2% Carbopol 940 was used in in situ gel ophthalmic application in combination with HPMC polymer (Kouchak, Mahmoodzadeh, & Farrahi, 2019). Based on the results, it can be concluded that HPMC was the most frequently used polymer in combination with Carbopol for topical application on the mucosal membrane. Table 3 summarises the Carbopol use according to site of application and dosage form.

Table 3: Summary of the Carbopol use according to the site of application and dosage form.

Application site	Dosage form	Carbopol type	Concentration /amount
Oral mucosa	In situ gel	974P	0.08%, 2.5%
	Gel	980	1.5%
	Gel	940	0.3% - 1%
	Gel	934P	0.25% - 1%
	Tablet	971P	49%, 50%
	Patches	934	18.75 mg - 300 mg
	Film	940	1% - 10%
	Film	934P	7.5 g - 24 g
	Wafer	940	1.5%
Nasal mucosa	Gel	940	0.5% - 2%
	Gel	934	0.1% - 0.4%
	In situ gel	974P	0.3% and 0.5%
Eye mucosa	In situ gel	940	0.1% and 0.2%
Vaginal mucosa	Gel	974P	0.8% - 1%
	Gel	934/934P	0.5% -1%
	Gel	940	0.5% - 1%

6. Advantages of Carbopol used in mucoadhesive topical drug delivery system

There were 7 advantages of Carbopol in topical drug delivery namely excellent mucoadhesion effect, the prolonged residence time of the formulation, enhanced drug permeation, prolonged release of drug, pseudoplastic behaviour of the formulation, pH compatibility with all mucosal site, and biocompatible with mucous membrane. The most reported benefit is the excellent mucoadhesion property.

Discussion

Carbopol is a mucoadhesive polymer that is extensively used in drug delivery studies. There are several types of Carbopol in which dominantly applied in a specific part of the body based on their rheological properties. The availability of the various grades of Carbopol depends on the manufacturing condition namely polymerisation and degree of cross-linking of the polymer reflected by the viscosity. Carbopol that carry the letter P after the number means that they are of high purity that makes them suitable for oral use (Mariageraldrajan, 2007; Panzade & Puranik, 2010). The summary of findings of this systematic review is summarised in Figure 3.

1. Mucoadhesive effect

Mucoadhesion is a characteristic of a dosage form that can interact with the mucous layer covering mucosal epithelial cells (Ahmed & Bhaduri, 2017). It plays an important role in the drug absorption and bioavailability (Ahmed et al., 2020). Besides this property is also important to preserve high level of drugs at the application site and to prevent expulsion of the formulation. For example, in buccal patch or buccal film, adequate mucoadhesion is prerequisite for optimal performance because low mucoadhesion would result in spitting or ingestion of the formulation (Kumria et al., 2016). Strong mucoadhesion of formulation incorporated with Carbopol were reported in various formulations types such as buccal patch, buccal film, buccal wafer, oral gel, nasal in situ gel, vaginal gel and in situ eye gel (Ahmed et al., 2020; Choudhury & Roy, 2016; Kouchak et al., 2019; Kumria et al., 2016; Mahajan et al., 2019; Malekar et al., 2017; Marques et al., 2017; Patel et al., 2016; Shelke et al., 2016). Mucoadhesive effect of Carbopol is attributed to the strong interaction that exists between carboxyl group (COOH) of Carbopol and a component of mucous membrane called mucin. Mucin are large glycoprotein expressed by epithelial membranes and are a component of the mucous secretions that covers epithelial. Mucin has a protein core with carbohydrate side chain and is the target to improve drug retention. Chemically, Carbopol polymer having abundance of carboxyl groups

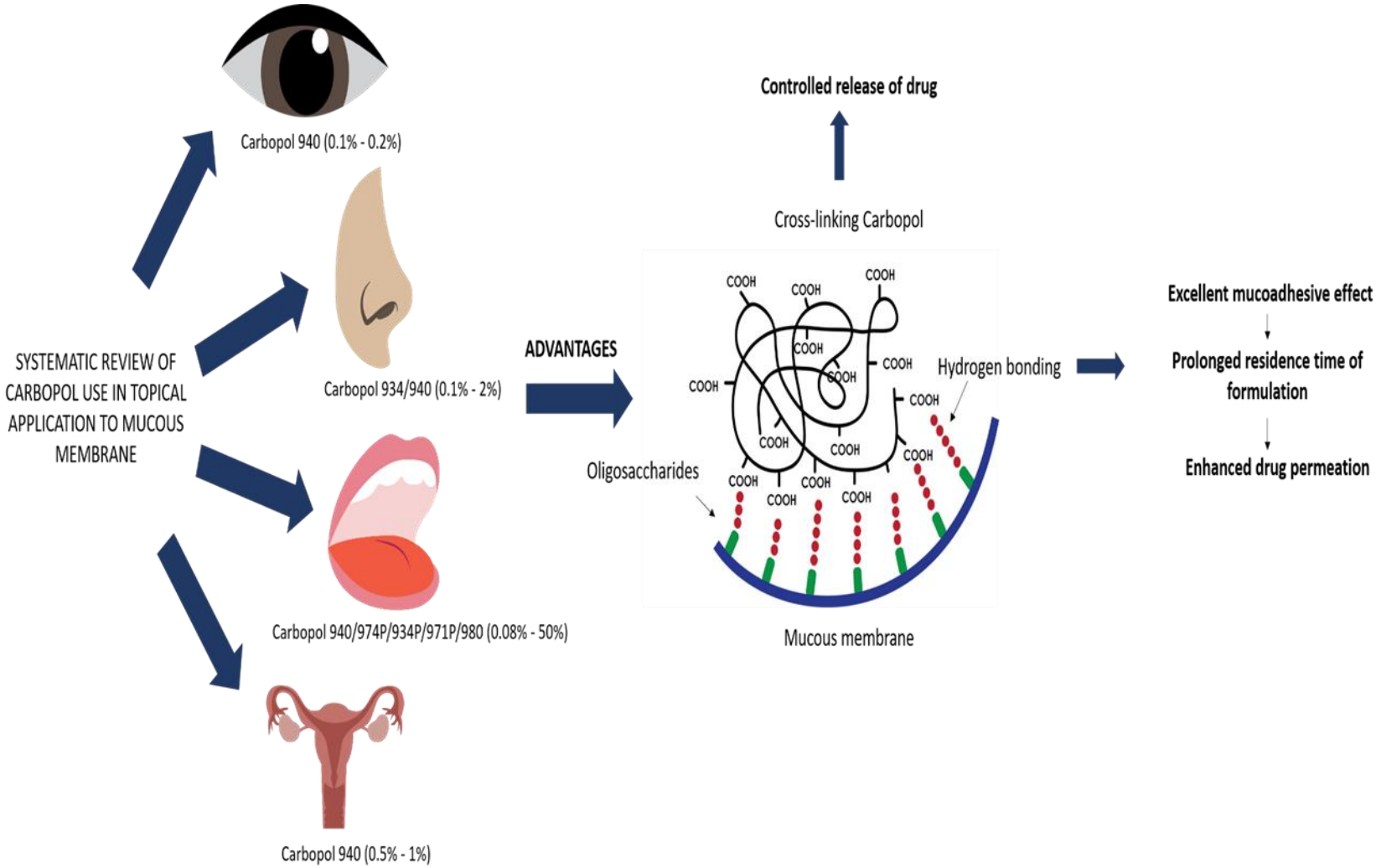

Figure 3. Summary of findings of this systematic review.

tend to form hydrogen bonding with amide group of mucin as proton accepting group (Shelke et al., 2016). Besides, studies showed that mucoadhesion of formulation were directly proportional with Carbopol concentration present in formulations (Ayoub et al., 2016). The plausible explanation is at higher Carbopol concentration, more interactions would be formed between Carbopol and mucous membrane leading to increase in mucoadhesion strength (Shelke et al., 2016). However, too strong mucoadhesive would damage the mucosal membrane (Kouchak et al., 2019).

2. Prolonged residence time of the formulation

At high Carbopol concentration, more compact lattice structure and more hydrogen bonding will be formed led to an increase in mucoadhesive strength. High mucoadhesive strength prolongs drugs retention and eventually inprove the absorption of drug across the mucosal tissue (Ayoub et al., 2016; Malekar et al., 2017).

In oral application, the retention time of prednisolone buccal wafer containing 1.5% Carbopol in ex vivo study was longer which is about 5 hours compared to formulation with lower Carbopol concentration (Pham et al., 2017). Similarly, another study found that the formulation of oral buccoadhesive films using Carbopol possesses greater mucoadhesive retention compared to without Carbopol content (Kumria et al., 2016). Dissolution of buccal film influences the retention time of the film. The high viscosity of Carbopol retard the dissolution of the film and subsequently increasing the film retention time (Kumria et al., 2016).

In nasal application, adequate mucoadhesive strength is important as this could help improving nasal drugs delivery as it prevents drainage from the nose cavity (Malekar et al., 2017). A pharmacodynamic study on the paw test was conducted to compare intranasal microemulsion based gel (MBG) over intranasal microemulsion (ME) of sulpiride. It was found that MBG has higher hind limb refraction time (HRT) values compared to ME of sulpiride. This demonstrated the role of Carbopol 940 incorporated in MBG in reducing the mucociliary clearance (MCC) and subsequently prolonging the residence time of sulpiride (Ayoub et al., 2016).

In the ophthalmic preparation, the drug's residence time plays a major concern in the formulation as it may influence the effectiveness of the drug. Prolonged residence time could result in a long duration of intraocular pressure (IOP) reduction and increase the efficiency of the in situ gel. The incorporation of Carbopol 940 (0.1 w/v) and HPMC (0.1% w/v) for in situ gel of dorzolamide HCl showed a longer and higher intra ocular pressure-lowering activity compared to dorzolamide solution and marketed drop. The prolonged residence time of the drug is attributed to its high viscosity and mucoadhesive property of the polymers. This subsequently increases the bioavailability and reducing administration frequency (Kouchak et al., 2019).

3. Drug permeation enhancing effect

Several studies have shown that the concentration of Carbopol improves the bioavailability and permeation of the drugs in certain formulations of oral and nasal application (Ayoub et al., 2016; Kumria et al., 2016; Mohamad et al., 2019). The administration of cyanocobalamine buccoadhesive tablet with 20% - 50% Carbopol 971P in combination with HPMC polymer exhibited a significant increase in the total amount of cyanocobalamin that enter systemic circulation that reflected by the estimated area under the curve (AUC) value (Mohamad et al., 2019). Similarly, enhancement in the rate and absorption of prednisolone have been reported in a study of prednisolone buccal film that use combination of HPMC and 50 mg of Carbopol 940. Higher AUC value of 2 folds was observed with buccal route compared to oral suspension formulation of prednisolone (Kumria et al., 2016). Good permeation ability of drug also reported with combination of 300 mg Carbopol 934 and HPMC in mucoadhesive buccal patch formulation of anti-hypertensive agents (Patel et al., 2016). The penetration enhancing effect are mainly due to the mucoadhesive properties as the residence time of formulation on mucosa also improved with the drug's permeation across the oral mucosa (Azeran et al., 2017).

The permeation enhancing effect of Carbopol was also reported with nasal application. Microemulsion based gel with 0.5% to 2% Carbopol 940 showed greater permeation of sulpiride compared to microemulsion after 24 hours. Carbopol exert the penetration enhancing effect by opening the tight junctions of the nasal mucosa thus promoting the transport of drugs via a paracellular pathway (Ayoub et al., 2016).

4. Prolonged release of drug

Carbopol plays important roles in sustaining the drug release for hours. Prolonged release formulation is desirable as it allows reduction of medication administration frequency and improving patient compliance (da Silva, Ferreira, Reis, Cook, & Bruschi, 2018). Various studies reported that incorporation of Carbopol polymer would retard the release of drugs from many formulations such as buccal tablet, buccal patches, buccal wafer, buccal film, in situ nasal gel and microemulsion based gel (Ali et al., 2017; Ayoub et al., 2016; Mahajan et al., 2019; Mohamad et al., 2019; Patel et al., 2016; Pham et al., 2017). It was found that, with

increase in concentration of Carbopol the release rates decrease gradually. Theoretically, drug was trapped by higher Carbopol concentration in which would exert resistance for the drug to travel through it. Additionally, drug movement area also would be limited by the density of chain structure especially at higher Carbopol concentration. Subsequently producing slower drug release rate for a longer duration (Ahmed et al., 2020; Ayoub et al., 2016; Mahajan et al., 2019; Patel et al., 2016; Pham et al., 2017).

A slow-release rate of cyanocobalamine reported from buccal tablet up to 5 hours duration (Mohamad et al., 2019). Meanwhile, longer release duration of more than 6 hours were reported with the formulations of combination antihypertensive agents (hydrochlorothiazide and atenolol) and prednisolone from buccal patches (100-300 mg Carbopol) and microemulsion based gel buccal wafer (1.5% Carbopol) respectively (Patel et al., 2016; Pham et al., 2017).

For nasal delivery, extended release of tapentadol for duration of 5 hours have been shown with in situ nasal gel formulation with 0.2% Carbopol (Mahajan et al., 2019). A longer release duration of naratriptan up to 8 hours was reported with formulation of in situ nasal gel that use combination of 0.2% Carbopol with 0.1% xanthan gum (Malekar et al., 2017).

For vaginal mucosa application, formulation of fluconazole gel with combination of HPMC and 0.5% Carbopol 940 show a constant and uniform drug release with around 80 – 85% drug release after 10th hour compared to formulation fabricated with sodium CMC and guar gum that complete the drug release within 10 hours (Choudhury & Roy, 2016). Besides, a study of nanogel of nevirapine formulated with 1% Carbopol 974P reported a zero-order kinetics suggesting the system release the drug at a constant rate for 6 hours duration (Rahman & Ahmed, 2019).

5. pH compatibility

The pH of oral cavity is maintained by the saliva with the normal pH range of 6.2 to 7.6 (Baliga, Muglikar, & Kale, 2013). It is advisable to keep the surface pH of the formulation similar to the buccal and salivary pH to minimise irritation to the oral mucosa (Kumria et al., 2016). In this review study, various forms of topical oral formulations namely buccal tablets, buccal patch, wafer, oral gel and buccal film have been successfully developed within the saliva pH value (Ali et al., 2017; Jain et al., 2019; Kumria et al., 2016; Mohamad et al., 2019; Patel et al., 2016; Pham et al., 2017; Sadeq & Rajab, 2017).

The normal nasal mucosa pH ranges between 5.5 - 6.5 (England, Homer, Knight, & Ell, 1999). The pH of nasal formulation reviewed in this study were within the physiological pH of the nasal mucosa (Ayoub et al., 2016; Mahajan et al., 2019; Malekar et al., 2017; Shelke et al., 2016). The slight acidic pH is necessary for lysozyme activity (Takalkar & Desai, 2018). Lysozyme is produced in nasal secretions and is responsible for killing bacteria at an acidic pH and is ineffective under alkaline pH and could promote the nasal tissue to be vulnerable to microbial infection (Salah et al., 2018).

Similarly, the normal vaginal pH ranges between 3.8 to 5.0, which is moderately acidic. This slight acidic pH of vaginal mucosa is crucial to protect the vagina mucosa from pathogenic organism (Lin, Chen, Cheng, & Shen, 2021). Nevirapine nanoparticle loaded 1% Carbopol 974P gel and fluconazole gel (1.5% Carbopol 934) were formulated with desired physicochemical characteristics within the vaginal physiological pH (Choudhury & Roy, 2016; Rahman & Ahmed, 2019). In contrast, another study of miconazole microsponge gel was formulated with slightly higher pH which is 7 to prolong the retention of the gel at the vaginal mucosa to allow complete drug release as the maximum viscosity of Carbopol gel achieved at pH 6-7. The plausible explanation is that the neutral pH is not harmful to the vaginal mucosa as the pH of the semen ranged between 7.2-8 and also higher vaginal pH was reported in fungal infection (Salah et al., 2018).

Meanwhile, the normal pH range of tear lies between 6.5 to 7.6 (Abelson, Udell, & Weston, 1981). pH is an essential parameter of the eye's acceptance and tolerance with the formulation. With buffering capacities that tolerate the pH around 4-8, the pH of the tear is about 7.4. A pH value beyond this range will reduce the drug's bioavailability due to the stimulation of blinking and tearing (Kouchak et al., 2019). pH triggered in situ gel under was successfully formulated with combination of 0.1% carbomer and 0.1% HPMC and desired viscous gel formed under the physiological tear pH (Kouchak et al., 2019).

6. pH compatibility

Biocompatibility refers to the ability of a formulation in not causing toxicity or injury effects on living tissue (L. Guy, 1988). Carbopol is biocompatible to be administered since it does not irritate the mucous membrane. A study showed that after removal of buccal film containing (1-5% Carbopol 940), visual inspection of the mucosal tissue showed no evidence of mucosal injury to any of the polymers. No discomfort was reported by the volunteers during or after in vivo study of baclofen buccal film (Ali et al., 2017). Besides, sheep's nasal mucosa photomicrographs were observed for histopathological changes after permeation tests with in situ gel containing opioid for nose to brain delivery. No sign of remarkable destructive effect of formulations on the treated nasal mucosa was observed (Mahajan et al., 2019). In another study,

histopathological photographs were conducted where nasal mucosal membranes treated with thermoreversible gel revealed minor epithelial cell destruction, meanwhile, intact cellular integrity was seen in the untreated mucosal membrane. The physical impact caused by the application of gel and pH shock could be related to the cause of this injury. That may be attributed to the swollen aspect of Carbopol resulting in mild damage to the intact columnar cells of the epithelial cells. The absence of damage to the glands that secrete mucus, cell necrosis, and columnar cells indicated that these ethosomal thermoreversible gels were healthy for nasal mucosa and could be used to treat migraine through intranasal path (Mei et al., 2017). For the vaginal drug delivery, histopathological findings concluded an absence of vaginal mucosal irritation indicated by normal cell lining without any vaginal mucosa injury. Another study also reported no clinical symptoms of irritation involving rash, inflammation, swelling, scaling, and irregular tissue formation hence suggesting that the Carbopol-based formulation is free from any irritation (Malekar et al., 2017). Additionally, there were no signs of clinical irritation of rabbit's eye with the application of pH triggered in situ gel in the ophthalmic drug delivery (Kouchak et al., 2019).

7. Pseudoplastic behaviour

The incorporation of Carbopol in the formulations exhibit a non-Newtonian pseudoplastic behaviour with yield stress. Pseudoplastic behaviour helps to facilitate liquid flow out from its container. In the formulation of in situ gel for dorzolamide, Carbopol 940 NF and HPMC showed a lower pseudoplastic behaviour in the physiological condition compared to the non-physiological condition (Kouchak et al., 2019). Force application on the buccal mucosa causes the breakdown of the gel network structure hence making it easier to spread on the mucosa (Marques et al., 2017). In order to sustain the site-specific action for a longer period, pseudoplastic behaviour is desired for topical application (Azeran et al., 2017).

Conclusion

The result of this systematic review revealed that Carbopol 940 is the most frequent carbomer grade incorporated in mucoadhesive topical drug delivery formulation. The concentration of Carbopol polymer incorporated in a formulation varies according to the type of pharmaceutical dosage form and application site. Carbopol polymer exhibits various advantages in mucoadhesive topical drug delivery systems apart from mucoadhesive behaviour alone. Carbopol as a mucoadhesive polymer benefits drug delivery in various ways namely excellent mucoadhesion effect, the prolonged residence time of the formulation, enhanced drug permeation, prolonged release of the drug, pH compatibility with all mucosal sites, biocompatible and pseudoplastic behaviour of the formulation. Thus, it is suggested that the incorporation of Carbopol can be an effective mucoadhesive agent for topical drug delivery systems.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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