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Evaluation and Development of Domperidone Mucoadhesive Patches for Buccal Drug Delivery

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Abstract:

Mucoadhesion is a state in which two components, one of which is of biological origin, are held together for extended periods of time with the assistance of interfacial forces. This state can be characterized as mucoadhesion. The buccal mucosa has excellent accessibility and is rather immobile, making it suited for the administration of retentive dosage forms. Comparatively speaking, the other transmucosal routes do not possess these characteristics. From a theoretical vantage point, the purpose of this paper is to conduct a review of the work that has been done in the subject of mucoadhesive buccal drug delivery systems, abbreviated MBDDS. This article begins with a brief introduction of the mucoadhesive drug delivery systems, oral mucosa, and the theories of mucoadhesion. It then proceeds to detail the works that have been done so far in the field of MBDDS, categorizing them depending on what they are intended to treat. In addition, we concentrate on the numerous patents, recent advancements, and obstacles in the field, as well as the opportunities that exist for mucoadhesive buccal drug delivery systems.

Keywords: buccal mucosa, clinical perspective, mucoadhesion, patents, transmucosal route.

1. INTRODUCTION

Domperidone mucoadhesive patches for buccal drug delivery refer to a pharmaceutical formulation designed to deliver the drug domperidone through the buccal mucosa (inner lining of the cheek) for systemic or local therapeutic effects. The patches are typically thin and flexible and adhere to the buccal mucosa, allowing the drug to be absorbed directly into the bloodstream [1–3].

2. A FEW SALIENT FEATURES OF THIS METHOD OF DISPENSING DRUGS:

2.A. Domperidone: Domperidone is a medication used to treat nausea and vomiting, particularly in cases of gastrointestinal disorders and certain medications that can cause these side effects. It works by blocking dopamine receptors in the brain and gastrointestinal tract, which leads to

increased motility of the stomach and intestines [1, 2].

2. B. Buccal Drug Delivery: Buccal drug delivery is an alternative route of drug administration that involves placing the drug in the oral cavity, where it dissolves or is absorbed through the mucosal tissues of the cheek or gum. This method allows for direct absorption into the bloodstream, bypassing first-pass metabolism in the liver [1, 4].

2. C. Mucoadhesive Patches: Mucoadhesive patches are designed to stick to the moist surfaces of the oral mucosa and remain in place for an extended period. The patches are formulated with mucoadhesive polymers that interact with the mucosal surfaces, promoting prolonged drug release and enhancing drug absorption [1–5].

2.D. Advantages of Buccal Drug Delivery: Delivering drugs through the buccal mucosa offers several advantages, including rapid onset of action due to direct absorption, avoidance of the gastrointestinal system, and bypassing the first-pass metabolism, which can enhance the bioavailability of certain drugs [1].

2. E. Potential Applications: Domperidone mucoadhesive patches could be beneficial in cases where oral administration is challenging, such as patients experiencing nausea and vomiting or those who cannot swallow oral medication. They can also be used to maintain a steady drug concentration in the bloodstream, allowing for sustained therapeutic effects [1].

3. AIM OF THE WORK:

At present, the oral route is the most prevalent method of drug administration. While this has the advantage of being simple to administer, it has significant disadvantages, including poor bioavailability due to hepatic first-pass metabolism and the tendency to produce rapid blood level spikes (both high and low), necessitating high and/or frequent dosing, which can be expensive and inconvenient. To surmount these obstacles, it is necessary to develop new drug delivery systems. For many years, the buccal route has been used to administer drugs that undergo first-pass metabolism. The buccal route benefits from a relatively robust mucosa, exceptional accessibility, and reasonable patient compliance. The buccal region of the lingual mucosa is an attractive route of administration for local or systemic drug delivery. The mucosa has an abundant blood supply and is permeable. Domperidone is used to treat nausea and vomiting, gastrokinetics (to accelerate gastric evacuation), dyspepsia, and gastroesophageal reflux disease (GERD). Domperidone inhibits the action of the dopamine receptor at both the chemoreceptor trigger zone just outside the blood-brain barrier and the gastric level [6–80].

Presently, it is available as a conventional oral tablet or suspension, and after oral administration, it undergoes a significant first-pass metabolism. It is metabolized by CYP3A4, which is involved in the N-dealkylation of Domperidone, whereas CYP3A4, CYP1A2, and CYP2E1 are involved in Domperidone's aromatic hydroxylation. Its bioavailability is only 15%. So domperidone is chosen as a model drug for the buccal drug delivery system with the following objective:

- To enhance drug bioavailability.
- To avoid the first-pass metabolism.
- To eliminate gastrointestinal irritation.
- To reduce dosing frequency.
- To rapid termination of the drug's action.
- To improve patient compliance.

3.2 PLAN OF WORK:

The proposed work was performed on the following lines:

3.2.1. PRE-FORMULATION STUDIES [1-3]:

Identification of drugs

(i) Physical appearance

(ii) Melting point

(iii) UV Absorption maxima

(iv) IR spectrum
1. Determination of partitioning studies.
2. Determination of loss on drying
3.2.2. Preparation of the calibration curve
6. Phosphate buffer solution (pH 6.8)
7.Phosphate buffer solution (pH 5.8).
3.2.3. Interference study of poly emulsifiers

4. The Characterization of prepared mucoadhesive buccal patches will be evaluated for the following parameters [1, 5].

A. Thickness
1. Weight variation
C. Folding endurance
1. Percent swelling index
2. Surface pH
3. In vitro residence time
G. Mucoadhesive strength

5. RESULT AND DISSUSSION

5.1. In-vitro drug release and kinetic study of buccal patch formulations

5.2. A. PHARMACODYNAMIC PARAMETERS:

5.2.1 Mechanism of Action:

Domperidone blocks the action of dopamine receptors. It has strong affinities for the D2 and D3 dopamine receptors, which are found in the chemoreceptor trigger zone, located just outside the blood-brain barrier, which, among others, regulates nausea and vomiting (area postrema on the floor of the fourth ventricle and rhomboid fossa) (Tripathi, K.D. 2007). [1].

5.2.2 Indication:

Domperidone is a first-choice antiemetic drug. Domperidone is used together with metoclopramide, cyclizine, and 5HT3 receptor antagonists (such as granisetron) in the treatment of nausea and vomiting. It can be used in patients with Parkinson's disease because doperidone does not cross the blood-brain barrier. Domperidone has also been found effective in the treatment of gastroparesis, a stomach motility condition, and pediatric gastroesophageal reflux (infant vomiting). Domperidone, by acting as an anti-dopaminergic, results in increased prolactin secretion and thus promotes lactation (Goodman & Gilman 2006) [1, 8–10].

Table 1: Partition coefficient of Domperidone

Water: n-Octanol (ml)	Concentration Of drug in water (g/ml)	Concentration Of the drug in n-Octanol (g/ml)	Log P (Partition coefficient)	Reference value of Log P
1:1	7.44	12.35	1.66	
1:1	7.39	12.43	1.68	1.67
1:1	7.38	12.48	1.69	

5.2.3. Physical Appearance and surface texture of patches: These parameters were checked simply with a visual inspection of patches and by feel or touch. The observation suggests that the patches are having smooth surfaces and they are elegant enough to see.

5.2.4. Weight uniformity of patches:

The weight of the patches was determined by using a digital balance. The weight variation was found to be in the range of 233.33±1.26 to 260.45±Formulationlation D1 had minimum average weight while formulation D5 was having maximum average weight. The value of all six formulations is tabulated in Table 2. In all the cases the calculated standard deviation values are very low and they suggest that the prepared patches were uniform in weight.

5.2.5. Thickness of patches

The thickness of the patches was measured by using a screw gauge and thickness varied from 0.25±0.03 to 0.36±0.20 mm

respectively. The value obtained from all formulations is given in Table:2.In all the cases the calculated standard deviation values are very low which suggests that the prepared patches were uniform in thickness.

Table 2: Physical evaluation of mucoadhesive buccal patches of Domperidone

Formulation Code	Avg. Thickness (mm)±SD, N=3	Avg. Weight (mg)±SD, N=3	Avg. Folding Endurance±SD, N=3	Avg. Swelling Index (%)±SD, N=3
D1	0.25±0.03	233.33±1.26	265±3.31	54.09±1.23
D2	o.3o±0.01	243.8±0.46	300±2.46	49.81±1.54
D3	0.35±.01	244.21±2.07	289±1.22	52.84±3.22
D4	0.36±0.20	246.05±1.72	291±2.00	54.28±1.89
D5	0.30±0.015	260.45±1.32	283±1.63	53.31±2.67
D6	0.29±0.023	241.1±1.54	282±2.56	51.19±3.12

5.2.3. Folding endurance of patches

The folding endurance was found to be in the range of 2653.31 to 3002.46. The value for all six formulations is given in Table 2. The maximum average folding was found to be the highest for formulation D2 and the lowest for formulation D1. It was found that the folding endurance values of sodium alginate patches were increased by the addition of polymers in the following order: Carbopol934>Polyvinylpyrrolydine>Sodium carboxymethylcellulose>ssodium alginate. This data revealed that the patches had good mechanical strength and flexibility.

5.2.4. Swelling index of patches

It was observed that the percentage swelling indices of various formulations were in the order of D1>D4>D2>D3>D5>D6. Formulation D1 has the highest swelling index because it contains sodium carboxymethylcellulose, which has more hydroxyl groups when compared to other formulations. Formulation D6 showed a lower swelling index; all values of the patches are given in Table 2. The percentage swelling of all formulations This was reduced by the addition of carpool and increased by the addition of PVP K-30. The PVP K-30-containing patches showed a higher percentage of swelling due to being freely soluble in water-ssoluble hydrophilic polymers, which dissolve rapidly, resulting in high porosity. From all these patches, NaCMC and PVP K-30 containing pashow show a high degree of swelling index due to the presence of more hydroxyl groups in the NaCMC molecule. The void of volume is thus expected to be occupied by the external solvent diffusing into the patch and thereby accelerating the dissolution of patches. In all the cases, the calculated standard deviation values are very low, which suggests that the prepared patches show a uniform swelling index.

5.2.5 Surface pH of patches:

The surface pH of the patches was determined by allowing them to come into contact with 10 ml of distilled water. The surface pH was noted by bringing a combined glass electrode near the surface of the patches and allowing for equilibrium for 1 min, and the average surface pH is given in Table 6.5. Attempts were made to keep the surface pH as close to buccal or salivary pH as possible. No significant difference was found in the surface pH of different patches. The standard deviation values calculated for all the patches are very low, which concludes that the surface pH of all patches was uniform within the range.

5.3.DRUG CONTENT:

The drug content of each formulation was evaluated, and the results are shown in Table 4. Drug content in all formulations was found

to be uniform, ranging from 90.2% to 91.9%. This indicates that the drug was dispersed uniformly throughout the patches.

Table 3: Mucoadhesive Properties of patches

Formulation	Surface pH	Drug Content (%)	Mucoadhesive strength (gm)	Mucoadhesive Time (min.)
F1	6.8±23	91.3±0.23	36.76±0.72	219±15.76
F2	6.95±0.4	92.1±1.6	31.92±1.13	198±19.54
F3	6.60±1.26	91.9±1.5	35.39±5.10	220±9.01
F4	6.61±0.05	91.2±2.4	32.43±0.64	222±23.12
F5	6.86±0.67	90.43±1.6	33.34±0.23	225±12.54
F6	6.89±0.02	92.3±1.2	32.78±21	224±23.56

5.4 MUCOADHESIVE STRENGTH:

The mucoadhesive strength of different formulations was determined. All the formulations showed good mucoadhesive strength. Among the formulations, F3 showed maximum mucoadhesive strength, while formulation F2 showed less mucoadhesive strength (Table 3).

5.5 MUCOADHESIVE TIME:

All formulations showed satisfactory mucoadhesive time. Formulation F3 showed maximum mucoadhesive time, while Formulation F2 showed less mucoadhesive time (Table 3).

6. IN-VITRO DRUG RELEASE THROUGH DIALYSIS MEMBRANE:

In vitro drug release experiments were performed for a total of eight hours on each of the domperidone buccal patches that were manufactured. In vitro drug release experiments of various formulations were carried out at a temperature of 285 degrees Celsius in a phosphate buffer solution having a pH value of 6.8. The release pattern of domperidone patches that contained polymers such as sod alginate, carpool, PVP K-30, and sod CMC was shown to be distinct from one another. As can be seen in the picture, the results from the detailed in-vitro drug release study were plotted between the percentage of medication released from the formulation and the passage of time. During the process of diffusion, patches that contained PVP K-30 expanded, resulting in the formation of a dense gel layer on the exposed patch surfaces. It is possible to explain the increased drug release of domperidone from NaCMC with PVP K-30 by referring to the viscosity of the polymer as well as its hydrophilicity at the 8th hour, respectively. At the conclusion of 8 hours, the detailed in-vitro release data of each of the created formulations was presented in the form of tablets. The results of an investigation into the in vitro drug release that occurred across the dialysis membrane are shown in Figure 1. A biphasic release pattern was discovered when researchers measured the rates at which various formulations were released through the dialysis membrane. An initial burst effect occurs, which is then followed by the completion of a steady phase, which controls the release of the medication from the delivery device. The effect of the formulation D4 with simply sodium alginate produced a more rapid initial burst, but the formulation with carbopol-934, PVP K-30, and sodium CMC demonstrated a sustained release. This suggests that there is a decrease in the release rate of domperidone whenever there is a rise in the viscosity of the formulation. The formulation D3 is the best one to employ because it has a satisfactory swelling index

and a manageable residence period. This makes it the optimal formulation. In addition, a promising medication release pattern was observed. All of our formulations, which are mucoadhesive buccal patches, were evaluated to determine the proportion of medication that was released up to eight hours after application. For the ex-vivo release research, formulation D3 was chosen as the drug of choice. Because it was unable to control the release of the D4 formulation and it acted more like an immediate-release formulation, it was eliminated from consideration. At the conclusion of 8 hours, the cumulative drug release of the formulation that contained sodium alginate with a secondary polymer was found to be in the order of sodium alginate > carbopol-934 > sodium carboxymethylcellulose >polyvinylpyrroliidine [1, 11, 12]. Sodium alginate was determined to be the most effective drug delivery agent. Additionally, the kinetics of a variety of formulations were investigated, and Table 5 illustrates the R2 values that were found.

Table 4: Drug release data at the end of 4hrs and 8hrs from domperidone buccal patches

Formulation Code	% Drug release in 4 hours	% Drug release in 8 hours
D1	70.69	85.78
D2	63.94	82.60
D3	73.08	89.35
D4	65.53	74.66
D5	67.92	80.62
D6	63.55	73.47

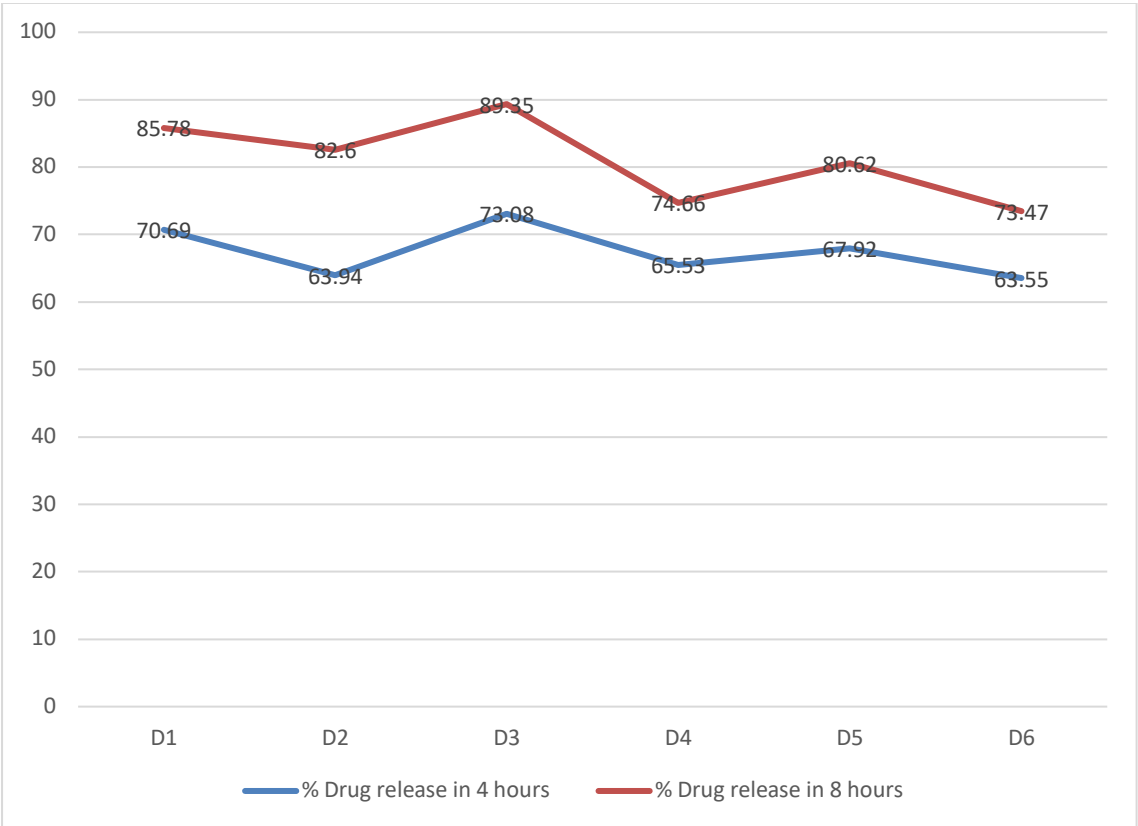

Figure 1: Drug release data at the end of 4 hours and 8 hours from domperidone buccal patches.

7. Summary and Conclusion

The present study made an effort to successfully develop buccal patches for a mucoadhesive drug delivery system of an antiemetic medication such as domperidone for buccal administration. This was done to increase the drug's bioavailability. Based on the experiment's findings, one can draw the following conclusions: 1. The IR spectra demonstrated no contact between the polymers and the medications; hence, the two are compatible.

2. The finished patches had a refined appearance and a silky smooth texture.

3. The patches had a decent amount of flexibility.

4. There is an even swelling throughout the spots.

5. The patches have a consistent level of mucoadhesive strength.

6. The medicinal substance was dispersed evenly throughout the entire patch.

7. By the end of August, almost seventy per cent of the medication had been extracted from all the formulations.

8. The percentage of entrapment efficiency was shown to be more significant for carbopol-based buccal parches than that of soc alginate, sod CMC, and PVP.

9. An increase in the mucoadhesive polymer led to a rise in oedema. However, carbopol had a higher mucoadhesion and swelling index than the other substances.

10. The amount of medication released similarly increased as the concentration of mucoadhesive polymer rose.

11. When it comes to the drug release mechanism, all formulations, except D4, follow the sustained release. In addition, they all follow the first order, zero order, Higuchi and Peppas model with non-fiction release. Based on the research findings and the discussion of its implications, we can conclude that domperidone can be administered in buccal form.

References:

1. Panda, P. K., Dixit, P. K., & Mishra, U. S. Review on mucoadhesive drug delivery system: an essential means in designing of innovative controlled drug delivery system for the effective delivery of pharmaceuticals. Eur. Chem. Bull. 2023, 12(Special Issue 4), 3761-3779.
2. Rocha, B., de Morais, L. A., Viana, M. C., &Carneiro, G. (2023). Promising strategies for improving oral bioavailability of poor water-soluble drugs. Expert Opinion on Drug Discovery, 18(6), 615-627.
3. Morales-Burgos, A. M., Beltran-Juarez, E., Carvajal-Millan, E., & Campa-Mada, A. (2023). Plant polysaccharides in buccal drug delivery. In Plant Polysaccharides as Pharmaceutical Excipients (pp. 311-328). Elsevier.
4. Malik, M. K., Bhatt, P., Kumar, T., Singh, J., Kumar, V., Faruk, A., ... & Kumar, S. (2023). Significance of chemically derivatized starch as drug carrier in developing novel drug delivery devices. The Natural Products Journal, 13(6), 40-53.
5. Malik, M. K., Bhatt, P., Kumar, T., Singh, J., Kumar, V., Faruk, A., ... & Kumar, S. (2023). Significance of chemically derivatized starch as drug carrier in developing novel drug delivery devices. The Natural Products Journal, 13(6), 40-53.
6. Dey, T., Bera, D. K., Samanta, B., Mahanti, D. B., &Abhipublications, L. (2020). mucoadhesive drug delivery system: A review article. International Journal of Pharmacy and Engineering. T. Dey. et al, 8(2), 944-960.
7. Ashoor, J. A., Mohammed, J., &ALAayedi, M. (2021). The Principle of Mucoadhesion, Classifications of Mucoadhesive Polymers, Applications

and Methods of Evaluation: A review Article. kerbala journal of pharmaceutical sciences, 1(19).

8. Tangri, P., &Madhav, N. S. (2011). Recent advances in oral mucoadhesive drug delivery systems: a review. International Journal of Pharmaceutical Research and Development, 3(2), 151-161.
9. Sharma, D., Singh, M., Kumar, D., & Singh, G. (2012). Novel paradigms in mucoadhesive drug delivery system. Int J Pharm Sci Res, 3(08), 2455-71.
10. Parmar, H. K., Pandya, K. K., Pardasani, L. J., Panchal, V. S., &Tandel, T. (2017). A systematic review on mucoadhesive drug delivery system. World J Pharm Res, 6(9), 337-66.
11. Mahajan, P., Kaur, A., Aggarwal, G., &Harikumar, S. L. (2013). Mucoadhesive drug delivery system: a review. Int J Drug Dev Res, 5(1), 11-20.
12. Banerjee, R., Kumar, K. J., & Kennedy, J. F. (2023). Structure and drug delivery relationship of acidic polysaccharides: A review. International Journal of Biological Macromolecules, 125092.