IJBPAS, September, 2022, 11(9): 4368-4376

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

FORMULATION DEVELOPMENT AND IN-VITRO EVALUATION OF DOXOFYLLINE MUCOADHESIVE BUCCAL TABLETS

R. VINOTH[1*], S. RANI[2] AND V. MANIKANDAN[3]

1, 3: PG Student, Department of Pharmacy, Annamalai University, Chidambaram, Tamil Nadu, India

2: Associate Professor, Department of Pharmacy, Annamalai University, Chidambaram, Tamil Nadu, India

***Corresponding Author: R Vinoth: E Mail: vinothbpharm16@gmail.com**

Received 19th Oct. 2021; Revised 25th Nov. 2021; Accepted 1st Feb. 2022; Available online 1st Sept. 2022

https://doi.org/10.31032/IJBPAS/2022/11.9.6422

ABSTRACT

The formulation of Doxofylline buccal tablets was the primary goal of this research, which used different acceptable mucoadhesive polymers, such as Carbopol 934P and HPMC. An impermeable backing layer of ethyl cellulose was used. The direct compression technique was used to make six batches of doxofylline mucoadhesive buccal tablets. Physicochemical characteristics like tablet thickness, friability, drug content, weight variation, surface pH and swelling index were then assessed and in vitro dissolution test were also carried out in accordance with IP 2018. All of the prepared tablets were under the permitted limit as stated in IP 2018. The batch 1 (95.81 percent) guaranteed a long-term release of the medication and a proper swelling index (73.70 percent). Thus, the findings showed that doxofylline can be made into a buccal mucoadhesive tablet. Furthermore, the properties of the tablet are not only influenced by the concentration of the polymers, but also by their behaviour.

Keywords: Doxofylline, Mucoadhesive Buccal tablet, Carbopol 934P, HPMC

INTRODUCTION :

The Drug administration by oral route is the common and most recommended method due to the ease of ingestion, the ability for patients to take their own medicine and the accuracy of the dose, as well as the ability for most adaptable and regulated dosage options and patient compliance **[1]**. First pass impact, GI enzymatic breakdown, and late beginning of effective action are some of the

significant drawbacks of them **[2]**. Researchers have been working on intraoral delivery systems over the past several decades in order to provide the best possible therapeutic impact. Using the mouth cavity and its extremely permeable mucosa to transport drugs to the systemic circulation (oral transmucosal administration) and to local tissues (oral mucosal tissue) has been a common practise for decades **[3]**. The direct flow of blood from the buccal mucosa directly into the jugular vein is advantageous, since it prevents medicines from being processed by either the digestive tract or the liver **[4]**. Taking medicine via mouth means that it will be absorbed through the buccal cavity's mucosal lining. A systemic medication delivery strategy other than injection or enteral administration, oral mucosal drug delivery has various benefits. Variety of mucoadhesive polymers such as synthetic, semi-synthetic and natural polymers are employed in this drug delivery method. It is the swelling and spreading of the mucoadhesive product that the mucosal membrane is initially penetrated by the substance, after that the moisture-activated the polymers in the mucoadhesive materials (polymers), resulting in the delayed release of the medicine. Among the many benefits of this drug delivery system are its simplicity, the ability to be quickly terminated in the event of unanticipated adverse effects or emergencies, and the ability to include enzyme inhibitors or permeability enhancers **[5, 6]**. A hydrogel is formed when the mucoadhesive tablet is hydrated, allowing the medicine to be released via the buccal mucosa. Direct compression is the most common method for making mucoadhesive tablets. Tablets have two layers: an impermeable ethyl cellulose backing and a core medication layer **[7]**. This research aimed to prepare six batches of mucoadhesive doxofylline tablets for later use.

MATERIAL AND METHODS:

Drugs and Chemicals:

Doxofylline was provided as a free sample from Harikrishna Enterprise Pt. Ltd., India. A sample of Carbopol 934 (CP) was given by Maruti Chemicals, India. The HPMC, Magnesium stearate, talc, Lactose (anhydrous), and Ethyl cellulose were purchased from Nice chemicals Pt. Ltd., India, respectively. Analytical-grade chemicals and reagents were employed in this experiment.

Instruments:

Single Stroke tableting machine, Dissolution apparatus IP Type 1 – Paddle apparatus, UV Spectrophotometer, Digital weighing machine, Friabilator.

Formulation of doxofylline mucoadhesive tablets:

Buccal mucoadhesive tablets were made with an existing technology with a few changes **[8]**. The doxofylline mucoadhesive tablet was manufactured and compressed using the Direct Compression Method. A scale was used to properly weigh each ingredient, and placed in a separate container for transportation. The required quantity of doxofylline and carbopol 934P were mixed together and this mixture is named as (Drug Polymer mixture) mixture 1 and mix the required quantity of Hydroxypropyl methyl cellulose (HPMC) and Talc and Lactose anhydrous in separate container and named this mixture as (Excipient mixture) Mixture 2. Mix the Mixture No.1 (Drug-polymer mixture) and Mixture No.2 (Excipient mixture) together for 5 minutes and pass through the 40 mesh and then add a required quantity of magnesium stearate and kept it separate container, after that gone for blending and compression. In a single stroke tableting machine, the core layer of this mixture was compressed at the lowest possible compaction force. It is necessary to add an impermeable backing layer of ethyl cellulose, which is then compressed at 5-7 kg/cm^2 force to the core tablet. The top punch, which had not disturbed the core tablet, was lifted and the impermeable backing layer was attached. **Table 1** outlined the content of each batch in milligrams.

Evaluation:

In accordance with Indian Pharmacopeia 2018, all batches of buccal mucoadhesive tablets were tested for various quality control criteria.

Table 1: Composition of various batches of doxofylline mucoadhesive buccal tablets

Materials	B1	B2	B3	B4	B5	B6
Doxofylline	100	100	100	100	100	100
Hydroxypropyl methyl cellulose (HPMC)	60	55	50	45	27.5	22.5
Carbopol 934P	25	30	35	40	30	40
Magnesium Stearate	5	5	5	5	5	5
Lactose anhydrous	15	15	15	15	42.5	37.5
Ethyl Cellulose	40	40	40	40	40	40
Talc	5	5	5	5	5	5
Total	250	250	250	250	250	250

PREFORMULATION STUDIES:

Bulk Density:

It is necessary to break up agglomerates that may have formed during storage by passing the powder through an aperture greater than or equal to 1 millimetre. This must be done gently to avoid altering the material's characteristics. Approximately weigh the 100 grams of the test sample (m) and place it in an empty graduated cylinder of 250 millilitres (ml) that is read to 2 millilitres. After carefully

levelling and reading the unsettled apparent volume (V0) to its nearest graduated unit. Using the formula m/V0, determine the bulk density in gram per millilitre. Repeated measurements are generally preferable for this property's determination.

Tapped Density:

The bulk volume may be determined in the same manner as mentioned before (V_0). Set it in its place and tighten it. Tap the same powder sample 10 times, 50 times, and 100 times, and record the volumes of V10, V50, and V100 to the closest graded unit. V100 is the tapped volume if the significant difference between V50 and V100 is less than or equal to 2 ml. The difference between the two measures should be less than or equal to 2 ml at all times. If not repeat the procedure until the difference between the next two measures is less than or equal to 2 ml. Using fewer taps may be reasonable for certain powders, provided that they have been shown to work. The tapped density (g/ml) is determined by using the formula m/Vf, where Vf is denoted as final tapped volume. For this attribute, it's best to do many tests. The drop height may be specified in the results.

Angle of Repose:

Mount the graph paper on a horizontal, level surface and a funnel is mounted vertically in a stand at a certain height above it. Sample powder is poured into a funnel after the funnel's bottom has been sealed. A sample weighing between 10 and 50 grams may be used for the experiment. As soon as the funnel is uncorked, the powder is poured onto a sheet of graph paper, where it forms a conical pile. Measuring in various directions yields the average radius of the conical heap's base. Using a scale, we can find out how high the pile rises. The same sample is used each time to do the experiment again. The results of the preformulation studies were shown in **Table 2**

POST COMPRESSION PARAMETERS:

Thickness:

Vernier caliper were used to determine the thickness of each batch of randomly taken tablets, and the average thickness was recorded for each batch.

Weight Variation:

Randomly weigh 20 units of chosen doxofylline buccal tablets separately, and determine its average weight of the tablets for each batch. As per IP limit, only two of individual tablets is allowed to deviate from the average weight by a larger proportion than the percentage and nothing more than twice that amount deviates from the average **[9]**.

Friability:

Full tablet samples equivalent to 6.5 g should be taken, if tablets with an average weight of 0.65g or less or Ten tablet samples should be taken for tablets with an average weight of 0.65g or more **[9]**. Doxofylline tablets are below 0.65 g in weight, thus use 6.5 g of sample tablets to do the test. Set the RPM to 25 and allow to revolve the drum for 4 minutes after thoroughly dusting and properly weighing the tablets. Ensure that the tablets are dust-free before weighing them and determining the percentage loss at the conclusion of the procedure.

$$\% \textbf{ Friablity} = \frac{\textbf{Initial weight} - \textbf{Final weight}}{\textbf{Final weight}} * \textbf{100}$$

Assay:

Using a mortar and pestle, break up the 20 tablets from each batch. Dissolve 100 mg equivalent weight of doxofylline drug powder in 20 ml of freshly prepared pH 6.8 phosphate buffer under sonification and then make up to volume of 100 ml with phosphate buffer pH 6.8 (Dilution-I), after that filter with what man filter paper No. 41, from there take 10 ml and then transfer to 100 ml volumetric flask and make up to volume with phosphate buffer pH 6.8 (Dilution-II). From that take 50 ml and then the Phosphate buffer pH 6.8 is added to bring the volume to 100 ml in a volumetric flask. (Dilution-III). At 272 nm, the drug's absorbance should be tested against a blank solution to determine its purity.

In Vitro Dissolution Test:

The invitro dissolution test was performed using IP type-I apparatus [Paddle apparatus]. The dissolution test apparatus vessel was filled with 900 ml of phosphate Buffer pH 6.8, which had been warmed to 37°C. Doxofylline tablets are inserted in each basket and the dissolution apparatus is allowed to run for 45 minutes at a time. Using a cotton-edged pipette, aliquot of samples (1 ml) for every 10 minutes, 20 minutes, and 30 minutes is withdrawn and put it into a 100 ml volumetric flask. Then, using a UV-Spectrophotometer at 272 nm, analyse the samples. The same method is used to determine the drug release in subsequent batches to determine its drug release.

Mucoadhesion Test:

Surface pH Studies:

The tablet was kept in contact with 1 ml distilled water in a Petri dish at room temperature for 2 h to permit it to swell. The pH was determined by putting the pH paper on the core surface of the enlarged tablet and permitting the surface to reach equilibrium for 1 min.

Swelling Index Studies:

Doxofylline Buccal tablets which prepared are weighed separately and

immediately transferred to 2 percent agar gel plates (which is previously prepared) with core surface of the tablet facing towards the gel surface and it should be allowed to incubate at 37± 0.1˚C for 1 hr. Using a filter paper, surplus water was gently removed from the petri dish. Swelled tablets were then reweighed and the swelling index of the tablets was computed using the formula below; the same technique was applied for subsequent batches.

$$\%\ \textbf{Swelling Index} = \frac{\textbf{Final weight (W2)} - \textbf{Initial weight (W1)}}{\textbf{Initial weight (W1)}} * 100$$

RESULT:

Preformulation Studies:

Table 2: Preformulation Studies

S. No	Formulation	Angle of Repose	Tapped Density	Bulk Density
1	B1	20.353	0.563571	0.464118
2	B2	20.851	0.519259	0.438125
3	B3	21.053	0.552121	0.506111
4	B4	22.777	0.693706	0.560452
5	B5	22.82	0.684783	0.572727
6	B6	21.382	0.505612	0.450455

Post Compression Parameters:

Table 3: Post Compression Parameters

S. No	Formulation	Thickness	Weight Variation	Friability	Assay
1	B1	4.438	0.3028	0.277	96.72
2	B2	4.364	0.3068	0.74	93.27
3	B3	4.037	0.3075	0.44	94.65
4	B4	4.138	0.3016	0.416	93.96
5	B5	4.007	0.2985	0.879	95.17
6	B6	4.405	0.2968	0.37	92.75

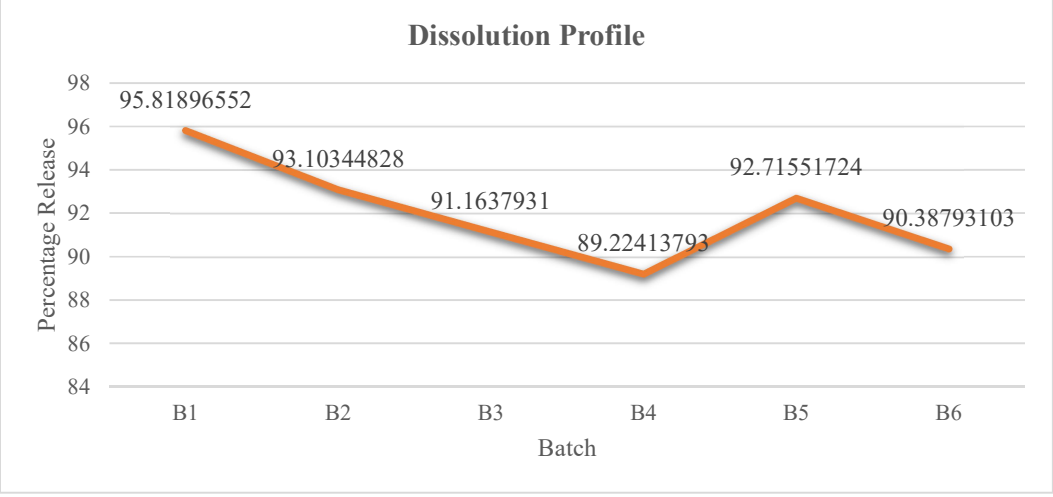

Figure 1: Dissolution Profile of Various batches

Mucoadhesion test:

Surface pH:

Table 4: Surface pH Studies

S. No	Formulation	Surface pH
1	B1	6.47
2	B2	6.49
3	B3	6.42
4	B4	6.39
5	B5	6.4
6	B6	6.47

Swelling Index:

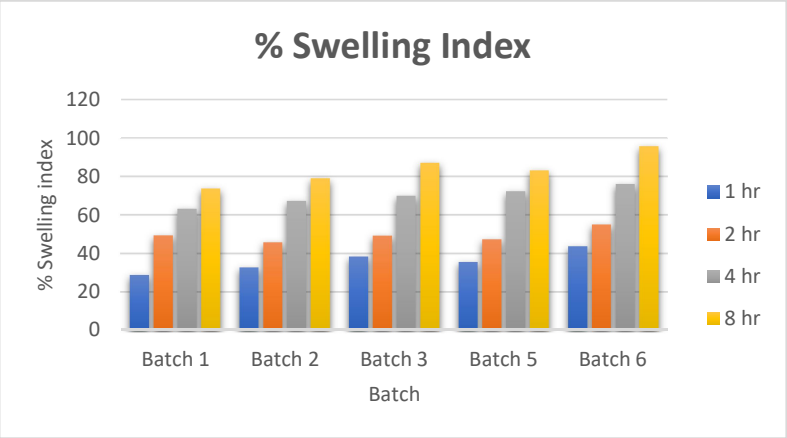

Figure 2: Swelling Index of Various batches

DISCUSSION:

A smooth, flat-faced, white, spherical tablet was found in all prepared samples. The pharmacopeial criteria for weight variation, thickness, and friability of the entire batch was achieved, confirming that the manufactured tablets were of acceptable quality **[10]** and it shows in detail in **Table 3**. The drug content was determined to be between 92.75 percent (B6) and 96.72 percent (B1) in each batch.

Doxofylline drug release is dependent on the kind and percentage of polymers used, according to in vitro drug release experiments. High amount of carbopol 934P presented formulation has been shown to reduce the drug release profile in a formulation **[11]**. When carbopol 934P is exposed to water, it expands and becomes viscous, making it difficult for the drug to be released. From the **Figure 1** we found that the amount of HPMC in the formulation has a direct correlation to the amount of drug released.

The **Table 4** shows the tablets surface pH and it was in the range of 6.39–6.49, virtually exactly matching the buccal cavity's pH. Because of this, all the formulated batches are free from irritation and pain at the buccal cavity, which leads to increased patient compliance **[12, 13]**.

Optimal swelling of the buccal tablet is essential, to guarantee that the

medicine which is released over a sustained period of time and that it adheres to the mucosa. **Figure 2** explains the swelling index of various batches. As part of the study, all formulated batches, swelling index is increased as time increases and it is because of, hydrophilic polymers utilised gradually absorb water[14]. The hydrophilicity of cellulose derivatives has an effect on the swelling behaviour. The polymers used in this formulation may be the most important determinant of swelling index. Further study is needed to verify this conclusion **[15]**.

CONCLUSION:

Studies were carried out to develop and assess mucoadhesive buccal doxofylline tablets having a sustained release feature for the treatment of asthma. No capping or chipping was observed in any of the prepared tablet formulations. In a study of six batches, B1 was found to have the satisfaction result of drug release, swelling index, and good surface pH. Swelling index, in-vitro dissolution, and surface pH experiments all showed that this B1 formulation performed well across a range of parameters. Drug release and swelling behaviour can be greatly affected by HPMC. Doxofylline mucoadhesive buccal tablet formulation is a successful approach to avoid the first pass effect and also to boost the absorption of Doxofylline across the mucous barrier. Long-term pharmacokinetic and pharmacodynamic investigations in humans are needed to evaluate the drug's effectiveness and safety.

REFERENCES:

[1] Gilhotra, R. M., Ikram, M., Srivastava, S., & Gilhotra, N., A clinical perspective on mucoadhesive buccal drug delivery systems. Journal of biomedical research, 2014, 28(2), 81–97.

[2] Bhowmik, D., Chiranjib, B., Pankaj, K., Chandira, R.M., Fast dissolving tablet: an overview, Journal of Chemistry and Pharmaceutical research, 2009, 1(1), 163–177.

[3] Swarbrick, J., Ghosh, T.K., Pfister R.W., Drug delivery to the oral cavity molecules to market, Francis Publishing House, New York, 2005, 36-48.

[4] Madhav, N. V., Shakya, A. K., Shakya, P., & Singh, K. Orotransmucosal drug delivery systems: a review. Journal of controlled release: official journal of the Controlled Release Society, 2009, 140(1), 2–11.

[5] Smart J. D. Buccal drug delivery. Expert opinion on drug delivery, 2005, 2(3), 507–517.

[6] Shanker, G., Kumar, C. K., Gonugunta, C. S., Kumar, B. V., & Veerareddy, P. R. Formulation and evaluation of bioadhesive buccal drug delivery of

tizanidine hydrochloride tablets. AAPS PharmSciTech, 2009, 10(2), 530–539.

[7] Hao, J., & Heng, P. W. Buccal delivery systems. Drug development and industrial pharmacy, 2003, 29(8), 821–832.

[8] Patel, V. M., Prajapati, B. G., & Patel, M. M. Formulation, evaluation, and comparison of bilayered and multilayered mucoadhesive buccal devices of propranolol hydrochloride. AAPS PharmSciTech, 2007, 8(1), 22.

[9] Government of India, Indian Pharmacopoeia, vol. I, controller of publications, Delhi, 2018, pp. 308-309.

[10] Vaidya, V., Manwar, J., Mahajan, N., & Sakarkar, D. Design and In-Vitro Evaluation of Mucoadhesive Buccal Tablets of Terbutaline Sulphate. International Journal of PharmTech Research, 2009, 1(3), 588-597.

[11] Hassan, N., Khar, R. K., Ali, M., & Ali, J. Development and evaluation of buccal bioadhesive tablet of an anti-emetic agent ondan-setron. AAPS Pharm Sci Tech, 2009, 10(4), 1085–1092

[12] Peddapalli, H., Bakshi, V., & Boggula, N, Formulation, in vitro and ex vivo characterization of mucoadhesive buccal tablets for antihypertensive drug. Asian Journal of Pharmaceutical and Clinical Research, 2018. 8(11), 402-411.

[13] Aframian, D. J., Davidowitz, T., & Benoliel, R. The distribution of oral mucosal pH values in healthy saliva secretors. Oral diseases, 2006, 12(4), 420–423.

[14] Chinna Reddy, P., Chaitanya, K. S., & Madhusudan Rao, Y. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. Daru: Journal of Faculty of Pharmacy, Tehran University of Medical Sciences, 2011, 19(6), 385–403.

[15] Bhanja, S., Ellaiah, P., Kumar, S., Sahu, P., Tiwari, S., Panigrahi, B., & Das, D. Formulation and in vitro evaluation of mucoadhesive buccal tablets of Timolol mal-eate. International Journal of Pharmaceutical and Biomedical Research, 2010, 1(4), 129-134.