JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

OPTIMIZING DRUG RELEASE: FORMULATION AND EVALUATION OF BI-LAYERED BUCCOADHESIVE TABLETS WITH MODIFIED POLYMERS FOR PROPRANOLOL HYDROCHLORIDE DELIVERY

[1]Israel Babu B J, [2] Adarsh B Patil, [3]Ganesh Hebbar.

[1]Assistant Professor, [2]Assistant Professor, [3]Assistant Professor.

[1]Department of Pharmaceutics

National College of Pharmacy,

Balraj Urs Road, Shimoga, Karnataka, India.

Abstract

The bi-layered buccoadhesive tablets were formulated with different ratios of natural and modified polymers using Propranolol hydrochloride as a model drug to achieve optimum drug release with good bioadhesive properties. The modification of chitosan was achieved with acetaldehyde (polymer-I) and propionaldehyde (polymer-II) to form a Schiff base. Modification and compatibility confirmed by FR-IR and DSC analysis. Ethylcellulose was used to provide an impermeable cap to achieve unidirectional drug release. The tablets were evaluated by different physical parameters such as swelling index, moisture uptake, ex vivo bioadhesion strength, adhesion time, hardness and friability and in-vitro drug release studies. The prepared formulation followed zero order, first order and Fickian-type drug release kinetics.

Keywords: bucoadhesive drug delivery system, Propranolol hydrochloride, modified chitosan, polymer-I, polymer-II.

The oral route of drug administration is the most popular route for drug delivery owing to ease of access, cost-effectiveness and high patient compliance. However, slow onset of action, lack of absorption and poor bioavailability due to first pass metabolism are prominent disadvantages. Hence, the drugs possessing these drawbacks are administered by developing alternative drug delivery routes such as mucosal drug delivery system; using oral mucosa for drug delivery of drugs was noted as one of the major routes because of its many advantages, such as having highly vascularized tissue, being easily accessible, having low enzymatic activity, allowing for painless administration and easy withdrawal, and enabling the addition of permeation enhancers,

enzyme inhibitors, or pH modifiers in buccal formulations. Buccal dosage forms also offer versatility in design, allowing for multidirectional or unidirectional release systems for local or systemic action, and can result in increased patient compliance due to prolonged retention time of the drug on the absorption site and controlled release, which reduces dosing frequency.[1]

Various types of bucoadhesive dosage forms have been developed in recent years because of their major benefits like prolonged retention time of drug on absorption site, also able to achieve controlled release which results in increased patient compliance due to reduction in dosing frequency.[2]

In recent years, there has been a significant focus on various mucoadhesive buccal delivery systems, with notable attention given to gels, films, tablets, and microparticles. Specifically, buccal tablets, easily prepared through direct compression, have garnered interest for their potential to dissolve or erode slowly and their user-friendly nature. Moreover, buccal tablets facilitate the unidirectional release of the drug toward the mucosa, ensuring a controlled and predictable manner of delivery to evoke the necessary therapeutic response. This targeted drug release can be accomplished through fabricating the bilayer devices.[3]

Propranolol HCl, a non-selective beta blocker, is extensively utilized in treating conditions such as hypertension, angina pectoris, arrhythmia, thyrotoxicosis, and migraine prophylaxis. Despite its widespread use, the drug experiences a significant first-pass effect, leading to low systemic bioavailability. With a half-life of approximately 3 to 5 hours and a relatively low molecular weight (295.81 g/mol), propranolol HCl stands as a suitable candidate for a buccoadhesive drug delivery system.[4]

The diverse mucoadhesive polymers employed in this delivery system, whether natural, semi-synthetic, or synthetic, exhibit adhesive properties upon hydration. Upon initial contact with the mucosal membrane, the mucoadhesive product undergoes swelling and spreading, establishing profound contact with the mucosal layer. Subsequently, the mucoadhesive materials, represented by polymers, are activated in the presence of moisture, leading to a gradual release of the drug.[5]

In the current investigation, efforts were undertaken to formulate and assess mucoadhesive bilayer buccal tablets containing propranolol HCl. This involved the utilization of both natural and modified mucoadhesive polymers, with the addition of ethyl cellulose (EC) as an impermeable backing layer.

MATERIALS AND METHODS

Materials

Propranolol HCl was received as a gift sample from Micro Labs Ltd (Bangalore, India). Polymers Chitosan and Pectin were provided by Sigma Aldrich Chemicals (India). HPMC K4M, Ethyl Cellulose and Microcrystalline cellulose (S.D Fine Chemicals, Mumbai, India) were obtained from commercial sources. All other reagents and chemicals employed in this study were of analytical reagent grade.

Methodology

Chemical modification of chitosan [6,7.]

To prepare a chemically modified chitosan, an 2% w/v chitosan solution was prepared by dissolving the polymer in a 1% acetic acid solution that had been prepared in distilled water. Once the chitosan was fully

dissolved, 50 ml of the solution was mixed with either 2 g of acetaldehyde (to make polymer A) or 2 g of propionaldehyde (to make polymer B). The mixture was stirred for about 3 hours at 60°C. After that, the chemically modified chitosan was precipitated by subsequently adding the polymer solution to acetone.

Preparation of bilayered buccal tablets of Propranolol HCl.

Materials	Formulation code			
	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)
Propranolol HCl	50	50	50	50
Chitosan	50	75	-	-
Polymer I (modified chitosan with acetaldehyde)	-	-	50	-
Polymer II (modified chitosan with propionaldehyde)	-	-	-	50
HPMC K4 M	25	-	25	25
Ethylcellulose	50	50	50	50
Magnesium stearate	5	5	5	5
Total	180	180	180	180

Table 1: Composition of mucoadhesive buccal tablets of Propranolol HCl. [8]

Bilayer buccoadhesive tablets were prepared by a direct compression procedure involving 2 steps.

Step 1: The adhesive layer was prepared by homogeneously mixing the drug with chitosan, modified chitosan, and HPMC K4M and all the ingredients, and excipients were weighed accurately according to batch formula and triturated in a glass mortar for 15 minutes. The mixture (130 mg) was then compressed using a 9-mm-diameter die in the rotary multi-station tablet machine.

Step 2: The upper punch was raised and the backing layer of EC DC (50 mg) was placed on the above compact and the 2 layers were then compressed into a mucoadhesive bilayer tablet. Each tablet weighed 180 mg.

Thickness and diameter

The thickness and diameter of tablets of all the prepared formulations were measured using a dial meter (Mitutoyo, Japan).

Hardness of tablets

Tablets required to have a certain level of mechanical strength and resistance to breakage in order to withstand the mechanical stresses during manufacturing, packaging and shipping. The hardness of the tablets was measured using a Monsanto Hardness tester, which expresses the force required to break tablets in Kg/cm^2. Three tablets were randomly selected from each formulation and the mean and standard deviation values were calculated to determine the overall hardness of the tablets.

Weight variation test

The tablets were characterized for weight uniformity by weighing 20 tablets of each formulation using an electronic balance (citizen balance CY 220). The obtained results were compared with IP standards of uniformity weight.

Friability of tablets

Tablet friability was determined by using Roche friabilator. Pre-weighed tablets (10 numbers) were allowed to fall from a height of 6 inches for 100 revolutions, taken out and were dedusted. The percentage of weight loss was calculated by rewriting the tablets. The % friability was then calculated by:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

Where, W = weight of tablet.

Swelling studies[9]

To determine the swelling index of the prepared tablets, each tablet was weighed individually (W1) and then placed in 8ml of phosphate buffer (pH 6.6) in a Petri dish. The dish was then incubated at 37°C. At different time intervals, the tablets were removed, blotted with filter paper and re-weighed (W2). The swelling index was calculated using the formula

$$swelling\ index = \frac{w1 - w2}{w1}\ X\ 100$$

W1= initial weight of the tablet

W2= final weight of the tablet

In vitro Bioadhesion strength.[10, 11]

Modified balance is used to determine mucoadhesive strength of tablets. A section of sheep buccal mucosa was attached to the bottom of the weighing pan with glue. The weight on the right-hand side of the balance was slowly increased in increments of 0.5 g until the tablet just separated from the membrane surface. The excess weight on the right pan, which is the total weight minus 5 g, was taken as a measure of the mucoadhesive strength.

$$\text{The force of adhsion} = \frac{\text{bioadhesion strength} * 9.8}{1000}$$

$$\text{Bond strength} = \frac{\text{force of adhesion (N)}}{\text{surface area}}$$

In vitro drug release study

The study was carried out in USP XXIII tablet dissolution test apparatus-II (Electrolab TDT-06), employing a paddle stirrer at 50 rpm and 900 ml of phosphate buffer pH 6.6 as dissolution medium maintained at 37 0.5 0C. At different time intervals, 5 ml of the sample was withdrawn and replaced with fresh medium. The samples

were filtered through 0.25 µm membrane filter paper and analyzed for propranolol hydrochloride after appropriate dilution at 289nm using a Shimadzu-1700 UV-visible spectrophotometer.

FT-IR Spectrophotometric analysis

The sample of the drug and the drug-polymer mixture were subjected to attenuated total refraction and scanned from 4000 cm^{-1} to 500 cm^{-1} using an FT-IR spectrophotometer (8400S FT-IR Shimadzu, Japan).

Differential scanning calorimetric analysis

Approximately 2 mg samples of the drug and the drug–polymer mixture were taken in an aluminum pan. The pan was sealed with an aluminum cap and kept in a nitrogen-purging atmosphere. The samples were scanned from 50-300 ^0C with a heating rate of 10 ^oC rise/min using differential scanning calorimeter (DSC-60 Shimadzu, Japan).

Results and Discussion

Physical properties of tablets

Formulation code	Hardness (Kg/cm^2)	Thickness (mm)	Fragility %
F1	4.93±0.11	2.76±0.05	0.961±0.73
F2	5.11±0.09	2.33±0.03	0.744±1.06
F3	4.55±0.15	2.88±0.01	0.88±0.42
F4	4.95±0.05	2.58±0.02	0.584±0.67

Values are mean ±SD, n=3

Table 2: physico-mechanical properties of prepared Propranolol HCl bilayered mucoadhesive tablets

Tablet diameter: 9.2mm

All tablets were prepared by direct compaction method and their physical characteristics them were evaluated (Table 2). The thickness of tablets, depending on the type of polymer, was found to be in the range of 2.33 ± 0.03 mm to 2.88 ± 0.01 mm. The results of the tablets hardness evaluation indicated that all tablets had the adequate mechanical strength for resistance to fracture during handling. All the formulations had the desired friability value (less than 1%). Weight variations of different formulations were found to be satisfactory.

Swelling studies

The swelling of all the tablets increased over time as the polymer gradually absorbed water, driven by its inherent hydrophilicity. The outermost layer of the hydrophilic polymer hydrated and swelled first. As this hydrated layer progressively dissolved or dispersed, the process of hydration-induced swelling continued,

exposing new surfaces. The swelling index was 21.07% to 52.78% in F1 and 29.07% to 5860.52% in F2 indicates as the concentration of chitosan increased the swelling behavior increased in contrast to the formulation containing modified chitosan showed less percentage of swelling index (Table 3).

Measurement of the mucoadhesive strength

The mucoadhesive strengths of propranolol HCl are given in the table. The mucoadhesion strength was in the range of 5.83±0.81 to 12.33±0.13 given in (Table 4). The study revealed that both the type and quantity of the polymer had a significant impact on mucoadhesive strength. An increase in the amount of the polymer resulted in a corresponding rise in mucoadhesive strength. This effect was attributed to the heightened presence of active functional groups, which played a crucial role in forming connections and links with the mucous membrane.

Time (h)	Swelling index (%)			
	F1	F2	F3	F4
0	0	0	0	0
1	21.07±0.84	29.07±0.83	12.36±0.72	9.82±0.99
2	28.47±0.97	38.16±0.44	24.96±1	20.40±0.95
3	34.54±0.71	44.84±1.17	31.46±0.59	27.61±1.25
4	39.24±0.66	47.86±1.04	37.41±0.92	34.9±0.95
5	42.68±0.76	50.57±0.76	41.74±0.88	38.93±1.19
6	46.52±0.74	55.34±0.74	44.97±0.81	41.65±0.95
7	50.60±1.73	58.53±0.89	46.58±1.1	42.56±0.72
8	52.78±0.59	60.52±0.98	49.19±1.07	44.52±0.72

Table 3: Swelling index of bi-layered mucoadhesive tablets

Formulation code	Bioadhesion strength (g)	Force of adhesion (N)	Bond strength (N/m^2)	Bioadhesion time (h)
F1	5.83±0.81	0.0571	72.01	>24
F2	10.28±0.41	0.1008	127.13	>24
F3	12.33±0.13	0.1209	152.47	>24
F4	9.66±0.72	0.0947	119.43	>24

Values are mean ±SD, n=3

Table 4: ex-vivo bioadhesion strength and ex-vivo bioadhesion time of bi-layered time of bi-layered mucoadhesive tablets

Drug release studies

To investigate the influence of polymer composition and proportion on drug release behavior, an in vitro dissolution study of the formulated batches of mucoadhesive tablets was conducted, and the outcomes are depicted in (Figure 1). The result indicated that the F2 tablets, prepared with plain chitosan, have shown a higher drug release rate in the hours, 81% drug was released at the end of 8hrs, this may be due to rapid hydration and swelling of chitosan, creating a gel-like layer through which water-soluble drugs were transported via a pore mechanism. This phenomenon was further enhanced by the formation of a soluble erosion matrix. While the tablets with modified chitosan F3 to F4 have shown progressively slower drug release. The tablets prepared with modified chitosan with acetaldehyde F3 showed 50% and modified chitosan with propionaldehyde F4 showed 58% drug release at the end of 8 hours. This could be due to the formation of a stiffer polymeric network, there may be a reduction in the movement of drug molecules through the polymeric network.

Time (h)	**Cumulative %drug release**			
	F1	**F2**	**F3**	**F4**
0	0	0	0	0
0.25	1.57±0.88	1.97±0.16	9.26±0.14	4.95±0.24
0.5	5.13±0.68	5.83±0.68	10.91±0.27	8.41±0.37
0.75	6.34±0.12	8.58±0.88	14.77±0.15	13.02±0.25
1	9.52±0.35	12.77±1.25	17.08±0.16	17.20±0.26
1.5	15.69±0.97	17.77±0.74	24.54±1.08	18.44±1.18
2	20.89±0.74	26.25±0.65	28.91±1.27	22.20±1.37
3	26.33±0.44	30.25±1.41	34.42±1.34	25.06±1.44
4	33.57±1.02	40.39±1.02	39.96±1.88	33.87±1.98
5	39.86±1.24	55.57±0.99	42.18±1.2	37.03±1.3
6	46.58±0.96	64.94±0.58	44.64±1.06	43.85±1.16
7	55.50±0.25	75.04±1.06	46.22±1.37	51.40±1.47
8	62.31±0.12	81.34±0.89	50.04±0.25	58.76±0.47

Values are mean ±SD, n=3

Table 5: In-vitro drug release of bi-layered bucoadhesive tablets

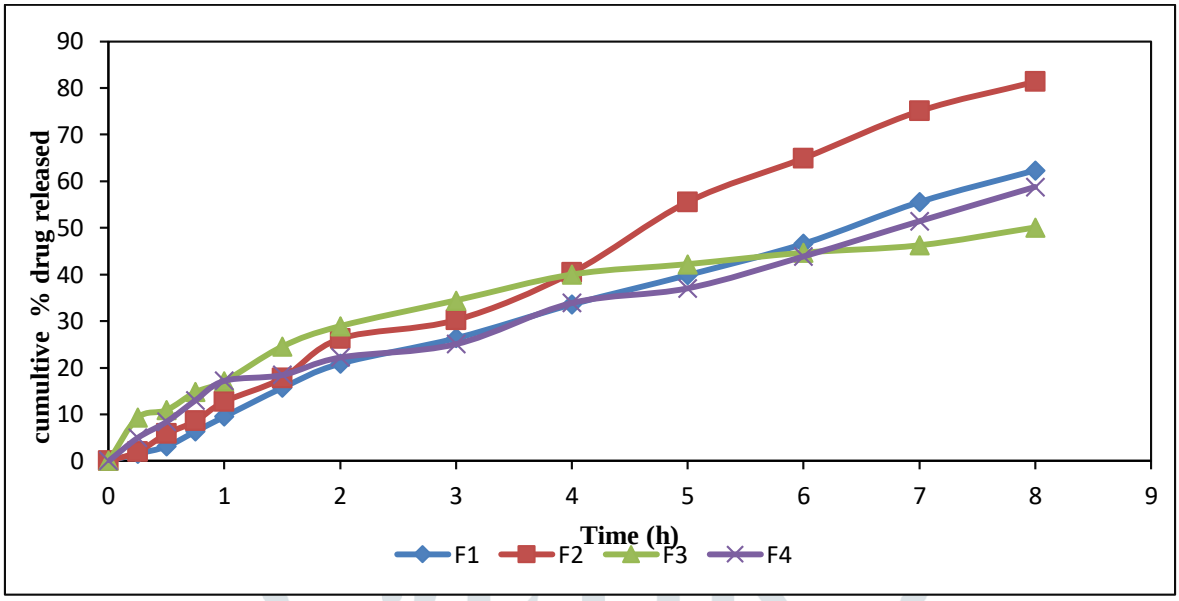

Figure 1: In vitro cumulative percent drug release studies

Drug release kinetics

Formulation code	Zero order equation (r^2 value)	First order equation (r^2 value)	Higuchi's equation (r^2 value)	Korsmeyer's Peppas equation (n value)
F1	0.992	0.958	0.993	0.877
F2	0.994	0.943	0.996	0.918
F3	0.950	0.981	0.951	0.560
F4	0.888	0.987	0.903	0.473

Table 6: Kinetics of drug release from bi-layered mucoadhesive buccal tablets.

To determine the mechanism of drug release, the in vitro drug release data was subjected to a goodness of fit test by linear regression analysis according to zero order, first order kinetic equations, Higuchi and Korsmeyer models. The results of linear regression analysis of data including regression coefficient are given in Table 6. The formulations F1 and F2 shown zero order release kinetics and the formulations F3 and F4 showed first order release kinetics. Most of the formulations follow Fickian-type drug release kinetics.

The formulations F1 and F2 show zero order release kinetics and the formulations F3 and F4 show first order release kinetics. Most of the formulations show non-Fickian release kinetics.

FT-IR Spectrophotometric analysis

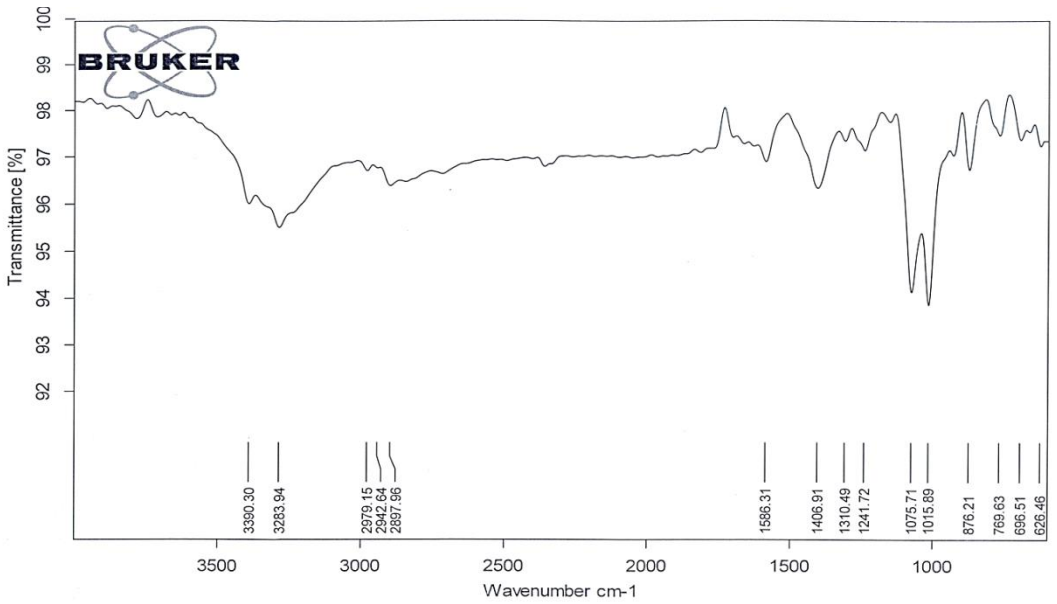

Figure 2: FT-IR spectra of propranolol hydrochloride

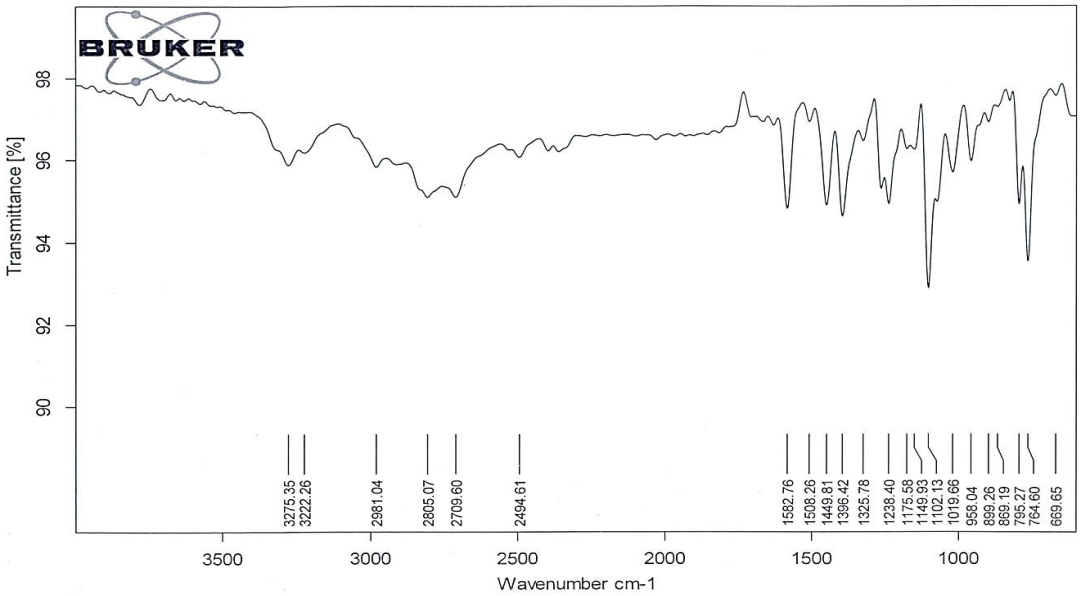

Figure 3: FT-IR spectra of drug with chitosan

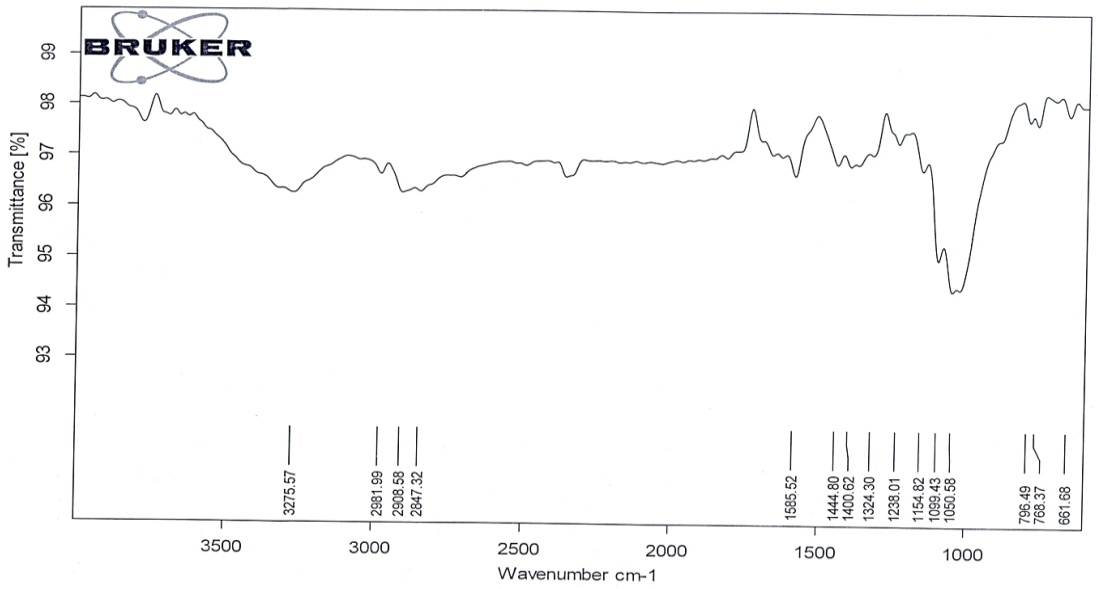

Figure 4: FT-IR spectra of drug with modified chitosan with acetaldehyde

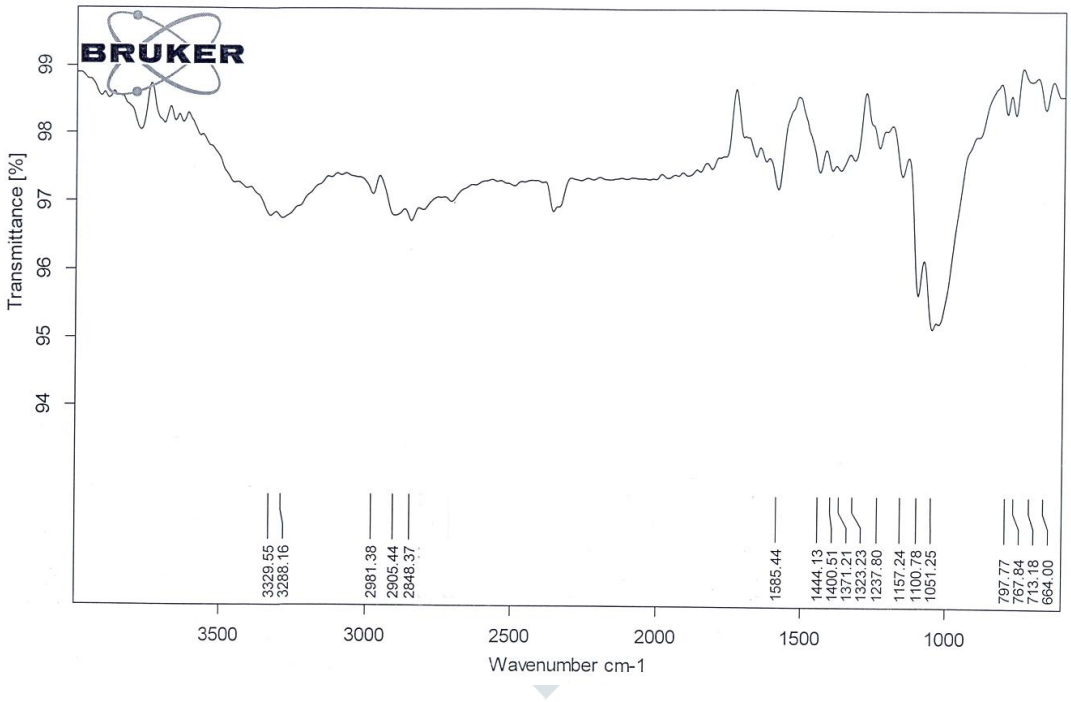

Figure 5: FT-IR spectra drug with modified chitosan with propionaldehyde

The compatibility studies of drug and polymers were determined by FTIR studies. The reaction was confirmed by performing FT-IR on plain chitosan with drug, drug with modified polymers, polymer-I and polymer-II, respectively.

The FT-IR spectra of pure drug Propranolol hydrochloride alone show peaks at 3293cm^{-1} and 2979cm^{-1}. Analysis of Propranolol hydrochloride with chitosan, polymer-I and polymer-II did not alter the drug peak.

Differential scanning calorimetric analysis

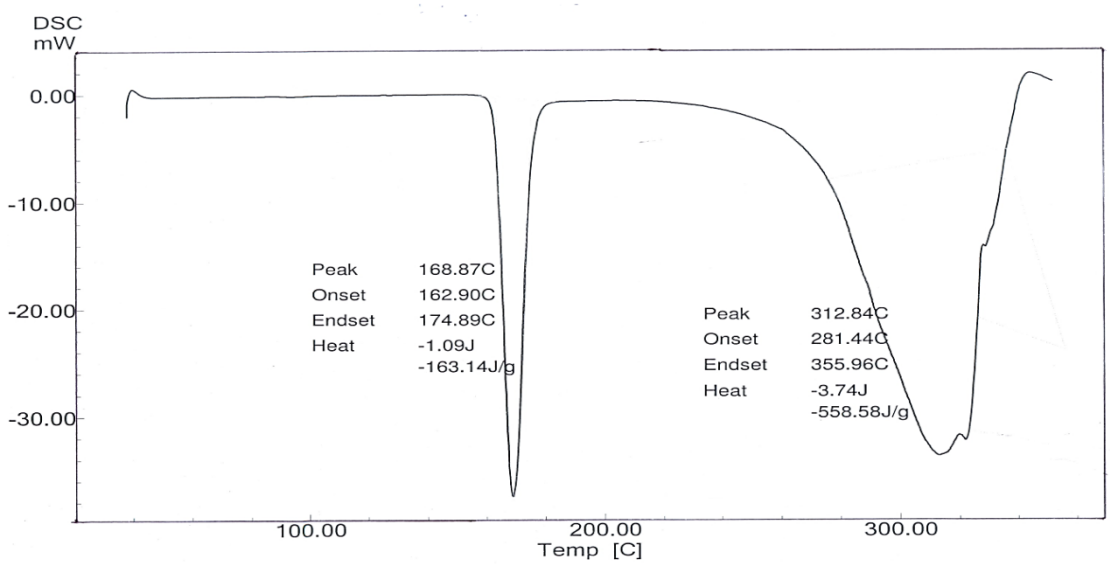

Figure 6:DSC thermograph of propranolol hydrochloride

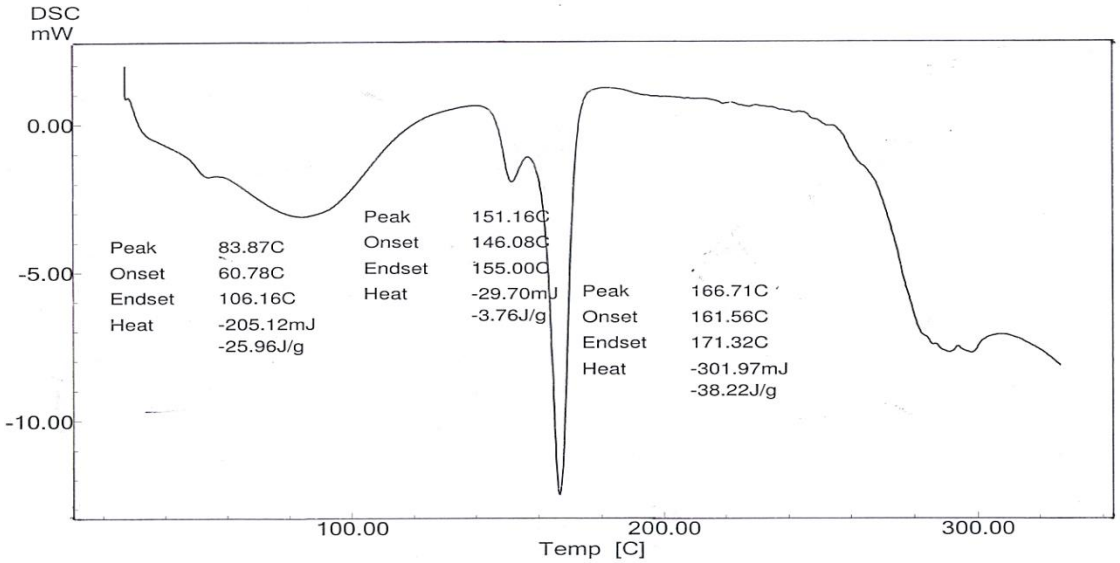

Figure 7: DSC thermograph of propranolol hydrochloride with chitosan

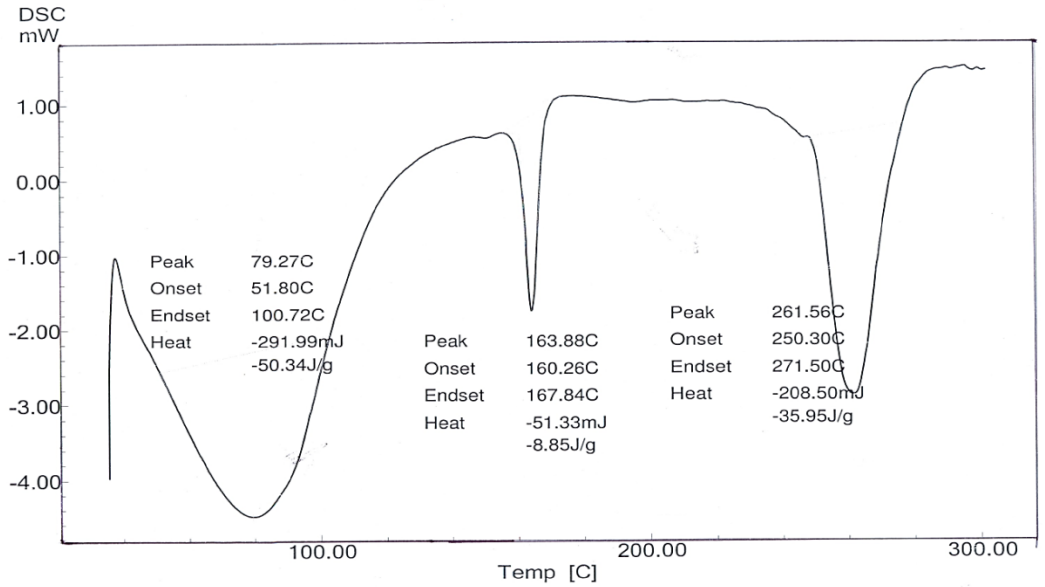

Figure 8: DSC thermograph of propranolol hydrochloride with modified chitosan (acetaldehyde)

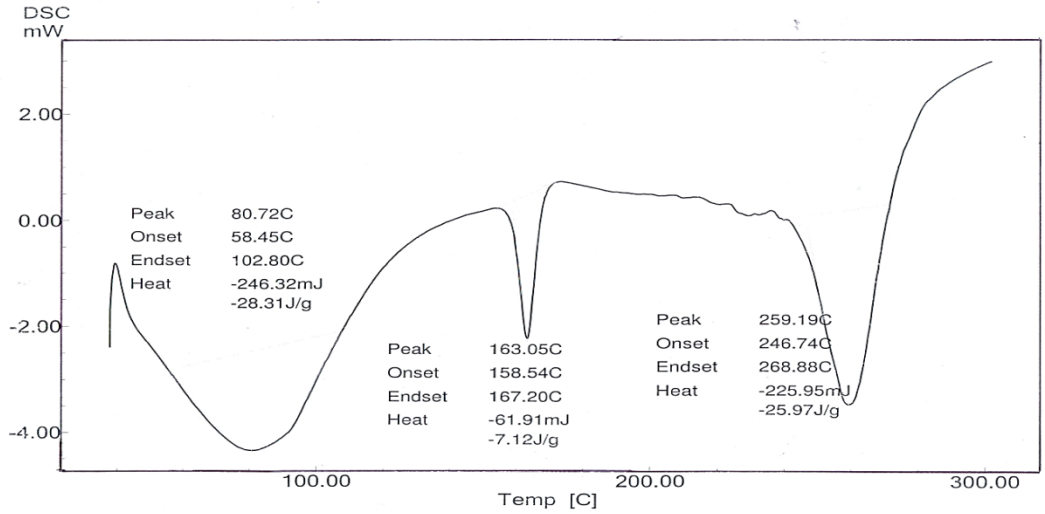

Figure 9: DSC thermograph of propranolol hydrochloride with modified chitosan (propionaldehyde)

The DSC thermograph of pure Propranolol HCl showed a sharp endothermic peak at 168.87° C (fig.6) corresponding to its melting point range of 163-169° C. To assess any change in the property of propranolol hydrochloride as a result of thermal treatment DSC studies were performed on the substance. The DSC thermographs of the physical mixture of propranolol hydrochloride and the polymers plain chitosan (figure 7) showed a sharp endothermic peak at 166.71^0 C and modified chitosan shown 163.88 C (figure 8) and 163.05 C (figure 9). As a result, it can be concluded that the drug is compatible with the polymer used in the present study.

CONCLUSION

The literature survey on the buccal drug delivery system reveals that the drug delivery system gives promising results for the drug which undergoes extensive first-pass metabolism. Propranolol hydrochloride is a non-selective beta adrenergic blocking agent and antihypertensive activities which possess low plasma half-life and which undergo extensive first pass metabolism. This makes it a very suitable drug candidate for incorporation into the buccal mucoadhesive drug delivery system. In the present study, we have formulated mucoadhesive tablets using chitosan, modified chitosan and a blend of modified chitosan/HPMC.

The modification of chitosan with aldehydes (Acetldehyde and Propionaldehyde) was confirmed by FT-IR and DSC analysis. The drug and polymer were also subjected to compatibility study using FT-IR and DSC, which suggested that there was no significant interaction between the drug and polymers.

The various formulations of bi-layered mucoadhesive buccal tablets of propranolol hydrochloride were prepared using chitosan and modified chitosan in different proportions. The bi-layered design of the tablets was modified from the conventional bi-layered tablet design to achieve perfect unidirectional drug release by incorporating the impermeable cap of ethylcellulose over the polymeric core containing the drug by leaving only one side of the core to release the drug. This design was able to provide perfect unidirectional drug release directly toward the buccal mucosal lining and prevent drug loss in saliva.

The tablets were evaluated for different physical parameters such as weight uniformity, hardness, thickness and drug content; bioadhesion parameters such as swelling index, moisture uptake, ex-vivo bioadhesion strength, ex-vivo bioadhesion time and in vitro drug release studies. The modified polymers showed progressively slower drug release when compared to plain chitosan. Most of the formulations showed non-Fickian drug release kinetics.

The present study concludes that the bi-layered bucoadhesive tablets of Propranolol hydrochloride and different proportions of chitosan, modified chitosan and HPMC in combination were successfully developed to provide unidirectional drug release with improved bioadhesive properties and drug release. The bi-layered buccoadhesive tablets can be a good approach to improve drug bioavailability by preventing extensive hepatic first pass metabolism of the drug and also by preventing drug loss in saliva.

Reference

1. Jung JH, Jin SG. Microneedle for transdermal drug delivery: current trends and fabrication. J. Pharm. Investig. 2021; 51:503–517.
2. Boddupalli BM, Mohammed ZN, Nath RA, Banji D. Mucoadhesive drug delivery system: an overview. J Adv Pharm Technol Res. 2010; 1(4):381-7.
3. Çelik B. Risperidone mucoadhesive buccal tablets: formulation design, optimization and evaluation. Drug Des Devel Ther. 2017; 11: 3355-3365.

4. Milind MG, Yogesh G, Yadav A. Formulation and evaluation of mucoadhesive buccal tablets of propranolol prepared using natural polymer. Int J Pharm Sci Res. 2018; 9(7): 2905-2913.
5. Jawadi Z, Yang C, Haidar ZS, Santa Maria PL, Massa S. Bio-inspired mucoadhesive polymers for drug delivery applications. Polymers. 2022; 14(24): 5459.
6. Kulkarni VH, Keshavayya J, Shastry CS, Preeti VK. Transdermal delivery of anti-asthmatic drug through the modified chitosan membrane. Indian J Pharm Sci. 2005; 67(5): 544-47.
7. Wahid A, Sridar BK, Shivakumar S; Preparation and evaluation of transdermal drug delivery system of etoricoxib using modified chitosan. Ind j Pharm Sci.2008; 70(24): 455-460.
8. Shirsand S, Suresh S, Keshavshetti G, Swamy P, Reddy PV. Formulation and optimization of mucoadhesive bilayer buccal tablets of atenolol using simplex design method. Int J Pharm Investig. 2012; 2(1): 34-41.
9. Desai KG, Kumar TM. Preparation and evaluation of a novel buccal adhesive system. AAPS Pharm Sci Tech. 2004; 5(3): 35.
10. Deshmukh VN, Jadhav JK, Sakarkar DM. Formulation and in vitro evaluation of theophylline anhydrous bioadhesive tablets. Asian J Pharm. 2009; 3: 54–8.
11. Choi HG, Kim CK. Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva. J Control Release. 2000; 68: 397–404.