Research Article

Design and Development of Buccal Mucoadhesive Tablets of Metoprolol Succinate by using Cashewnut Tree Gum

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ABSTRACT

In the present work, the mucoadhesive tablets of Metoprolol succinate were prepared by using cashewnut tree gum as a binder. The four tablet formulation were prepared by using drug and cashew nut tree gum ratios of 1:0.5, 1:0.75, 1:1, 1:1.25 by direct compression technique. Tablets were subjected for evaluation of uniformity of weight, hardness, friability, drug content uniformity, Swelling studies, Surface pH study, Ex-vivo mucoadhesion time, Ex-vivo Bioadhesive Strength and In vitro drug release study. Drug polymer interactions were evaluated by Fourier Transform Infrared Spectroscopy. All the formulations hardness, weight variation, friability and drug content values were found to be within pharmacopoeia limits. As the amount of polymer in the tablets increases, the drug release rate decreases, whereas swelling index and mucoadhesive strength increases. Based on the results F4 was found to be optimized formulation. The in-vitro drug release of all formulations exhibits complete release of Metoprolol succinate with zero order release kinetics and followed by Higuchi mechanism. From the study it can be conclude that the cashew nut tree gum used as a binding agent in mucoadhesive buccal tablet.

Keywords: Cashew nut, Metoprolol, Mucoadhesive, Zero-order, Higuchi.

INTRODUCTION

Cashew nut tree gum is obtained from the incised trunk of the tree *Anacardium occidentale* belonging family Anacardeaceae. The gum is a complex polysaccharide comprising galactose, arabinose, rahmnose, glucose, and other sugar residues. This study investigated the efficacy of cashew nut tree gum as a release retardant in the Mucoadhesive buccal tablets of metoprolol succinate[1].

Among the various transmucosal routes, buccal mucosa has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms. Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. Other advantages such as low enzymatic activity painless administration, easy drug withdrawal, facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation and versatility in designing as multidirectional or unidirectional release systems for local or systemic actions. Mucoadhesion is not new; there has been increased interest in recent years in using mucoadhesive polymers for drug delivery. Substantial effort has recently been focused on placing a drug or a formulation in a particular region of the body for extended periods of time [2].

Metoprolol succinate was used in the treatment of anti-hypertension and cardiovascular diseases and it is known to have low oral bioavailability (50%) due to an extensive high first-pass effect. Hence, it is suitable for buccal drug delivery. The aim of the present study was to design and develop mucoadhesive buccal tablets of Metoprolol succinate that could be applied to the buccal mucosa to release the drug unidirectional in buccal cavity in order to decrease gastric irritation and avoid first pass effect for improvement in bioavailability, to reduce the dosing frequency and to improve patient compliance. First pass effect for improvement in bioavailability, to reduce the dosing frequency and to improve patient compliance.

MATERIALS

Metoprolol succinate (It is obtained as gratis sample from Hetero pharmaceuticals). All other materials used in this study were of A.R.grade purchased from S.D.fine chemicals Mumbai.

Cashew nut tree gum was collected from authenticated plant fruits in local area of Guntur district of Andhra Pradesh.

METHOD

Isolation of water- soluble fraction of cashew nut tree gum

The collected crude cashew nut tree gum (100g) was ground by using mortar and pestle. The ground gum was dissolved in water (300ml). The solution was filtered through several folds of muslin cloth and the filtrate was collected. To the filtrate, alcohol (90% v/v) was added in 1:1 ratio and precipitate was obtained. The precipitate was filtered and dried in a hot air oven at 45^0 c. 100 g of powder obtained was dissolved in 100 ml water, filtered through several folds of muslin cloth. Then the filtrate was centrifuged at 3000 rpm for 10 minutes and the supernant layer was collected, evaporated and dried to obtain solid mass, which was ground. This mass was passed through sieve no. 80 and stored in an airtight container for further studies[3].

Preparation and evaluation of Tablet

Buccal tablets were prepared by direct compression procedure involving two consecutive steps. The mucoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug and polymers in a glass mortar for 15 mins. Magnesium stearate was added as a lubricant in the blended material and mixed. The blended powder was then lightly compressed on 9 mm flat punched using sixteen station tablet compression machine (Cadmach), the upper punch was then removed and backing material ethyl cellulose was added over it and finally compressed at a constant compression force. The tablets composition was shown in the table 3. All ingredients were dried, passed through 100 mesh sieve and mixed manually in mortar. The tablet formulation was developed for 250 mg tablet weight using 50 mg of Metoprolol succinate (drug) and varying concentration of cashew nut tree gum. The tablets were compressed by using sixteen station tablet machine fitted with flat faced punches.

Evaluation of the prepared buccal tablets

All the tablets were evaluated for different parameters such as hardness, weight variation and friability [4].

Drug content

Twenty tablets were collected and powdered. The powder equivalent to 50 mg of drug was weighed accurately, dissolved in 100 ml of phosphate buffer pH 6.8. The solution was filtered, suitably diluted and an aliquot was analyzed at 224nm.[5]

Swelling studies

Three buccal tablets were weighed individually (W1) and placed separately in 2% agar gel plates and incubated at 37 ± 1^0c. After every 2h time interval until 6h the tablet was removed from the petridish and excess surface water was removed carefully with blotting paper. The swollen tablet was then reweighed (W2) and the swelling index were calculated by using the formula given in equation[6]

Swelling index = (W2-W1)/W1 X 100

Where,
W1 = initial weight of the tablet
W2 = final weight of the tablet

Surface pH study

The tablet was allowed to swell by keeping in contact with 1 ml, of distilled water for 2h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min[7]

Ex-vivo mucoadhesion time

The ex vivo residence time was found using a locally modified USP disintegration apparatus.
The disintegration medium was composed of 800-ml pH 6.8 phosphate buffer maintained at 37°C. The sheep buccal tissue was glued to the surface of a glass slab using cyanoacrylate adhesive, vertically attached to the apparatus. The buccal tablet was hydrated from one surface using 0.5-ml of pH 6.8 phosphate buffer and then the hydrated surface was brought in contact with the mucosal membrane. The glass slide was vertically fixed to the apparatus and allowed to run in such way that the tablet completely immersed in the buffer solution at the lowest point and was out at the highest point. The time taken for complete erosion or dislodgment of the tablet from the mucosal surface was noted [8].

Ex-vivo Bioadhesive Strength

Ex-Vivo Bioadhesive strength of the buccal tablet was measured on the modified physical balance method. The fresh goat buccal mucosa obtained from slaughter house was cut in to pieces and washed with phosphate buffer pH

6.8. A piece of mucosa was tied to the glass slide which was moistened with phosphate buffer pH6.8. The tablet was stuck to the lower side of second glass slide with glue. The both pans were balanced by adding an appropriate support, so that the tablet touches the mucosa. Previously weighed beaker was placed on the right hand pan and water (equivalent to weight) was added slowly to it until the tablet detach from the mucosal surface. The weight required to detach the tablet from the mucosal surface it give the mucoadhesive strength[9].

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength} \times 9.81}{1000}$$

In vitro drug release study

The USP dissolution test apparatus (apparatus II paddle type) was used to study the drug release from the tablets. The dissolution medium was 500ml, of phosphate buffer pH 6.8 of 50 rpm. The buccal tablets were allocated to the bottom of the dissolution vessel. 5ml sample were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were analysed after appropriate dilution by UV spectrophotometer at 224nm[10].

Drug-excipient interaction studies

Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with cashew nut tree gum, diluents and lubricants used in tablet formulations. In the present study 1:1 ratio was used for preparation of physical mixtures and analyzed for compatibility studies [11].

RESULT AND DISCUSSION

The gum isolated from cashew nut tree was evaluated for flow properties and the results were shown in table 1. The results indicated that the gum have good flow property. The swelling property of gum was shown in table 2. The swelling behavior of gum reveals, it was suitable candidate for sustained release. Mucoadhesive buccal tablets of Metoprolol succinate with cashew nut tree gum were prepared by using different drug: gum ratios. The compositions of the tablets and the results of the physical characterization of tablets are summarized in Table 3 and 4. All the formulations hardness, weight variation, friability and drug content values were found to be within pharmacopoeia limits. The swelling behavior is important for bioadhesion. Water sorption increases with increase in the concentration of hydrophilic polymers. Swelling index, Mucoadhesive strength and Ex-vivo residence time were shown in table 5.

The cashew nut tree gum swells slowly and dissolves in presence of water. As hydrophilicity of the hydrogel increases, the interaction between water and hydrogel will increase too; this facilitates water diffusion and leads to greater swelling. The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity as acidic or alkaline pH was bound to cause irritation to the buccal mucosa. Surface pH of all formulations was found to be in the range of 6.27 to 6.79 which were nearer to the salivary pH 6.8 Hence it was assumed that these formulations do not cause any irritation to the mucous layer of oral cavity.

Mucoadhesion is determined by Mucoadhesive strength and duration of mucoadhesion. Formulation F1-F4 shows good mucoadhesive strength. As the viscosity gum increases swelling increases and mucoadhesion force depends on the swelling of the gum. This improves the consolidation step that increases the mobility of molecule and facilitates the interpretation with mucus layer, thus mucoadhesion increases. F4 shows maximum mucoadhesive strength this is due to tremendous increase in viscosity.

The ex-vivo residence time was determined using USP disintegration apparatus. Among the four formulations subjected for this study F4 showed maximum residence time of 9.35 Hrs. It was found that an increase in concentration of polymer increases the residence time. This was mainly due to the strong mucoadhesion nature of the polymer used. The results of in vitro drug release studies of different formulation are depicted in Figure 1. Tablet formulations prepared by using drug and gum in ratios of 1:0.5, 1:0.75, 1:1, and 1:1.25 shown drug release for a period of 6.5 hours, 8.5 hours, 9.5 hours and 11 hours respectively. The initial burst release decrease with increase in concentration of gum. The dissolution kinetics values were shown in table 6.The in-vitro drug release of all formulations exhibits complete release of Metoprolol succinate with zero order release kinetics and followed by Higuchi mechanism. IR spectroscopic studies indicated that there were no drug-excipient interactions. All the principle peaks observed for the drug alone were also observed in the tablet formulation also.

Table 1: Flow properties of dried cashew nut tree gum

Formulation	Evaluation parameters				
	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's Ratio	Angle of Repose (θ)
F_1	0.439 ± 0.018	0.512 ± 0.026	14.24 ± 0.71	1.16 ± 0.011	24.02 ± 0.22
F_2	0.445 ± 0.011	0.522 ± 0.019	13.94 ± 0.52	1.17 ± 0.08	25.22 ± 0.16
F_3	0.478 ± 0.017	0.580 ± 0.023	17.58 ± 0.45	1.21 ± 0.010	27.36 ± 0.15
F_4	0.496 ± 0.015	0.594 ± 0.020	16.49 ± 0.56	1.19 ± 0.14	28.85 ± 0.18

Table 2: Swelling property of Cashew nut tree gum

Natural gum	After 5 min(ml)	After 10min(ml)	After 15 min(ml)	After 20 min(ml)	After 25 min(ml)	After 30 min(ml)	After 35 min(ml)
Cashew nut tree gum	0.7	0.8	1.1	1.3	1.4	1.5	1.5

Table 3: Composition of tablets containing cashew nut tree gum

Content of tablet	1:0.5 (F1)	1:0.75 (F2)	1:1 (F3)	1:1.25 (F4)
Metoprolol succinate	50	50	50	50
Cashew nut tree gum	25	37.5	50	62.5
Microcrystalline cellulose	121	108.5	96	83.5
Magnesium stearate	2	2	2	2
Talc	2	2	2	2
Ethyl Cellulose	50	50	50	50
Total weight (mg)	250	250	250	250

Table 4: Evaluation of tablets prepared from cashew nut tree gum

Formulation	Parameters			
	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F_1	250 ± 1	4.3 ± 0.02	0.31	99.56
F_2	250 ± 3	4.0 ± 0.01	0.48	99.34
F_3	250 ± 2	4.2 ± 0.03	0.54	99.47
F_4	250 ± 1	4.1 ± 0.01	0.67	100.02

Table 5: Drug release kinetic studies of tablet formulation

Formulation	Correlation coefficient				T_{50} (hr)	T_{90} (hr)
	Zero order	First order	Higuchi	Peppas		
F_1	0.9969	0.8604	0.9840	0.8408	3.1	5.5
F_2	0.9917	0.8664	0.9865	0.8886	4.3	7.8
F_3	0.9934	0.8673	0.9836	0.9054	4.8	8.6
F_4	0.9962	0.8761	0.9819	0.9139	5.5	9.7

Table 6: Mucoadhesion strength, swelling index, retention time, surface pH of buccal tablets

Formulation	Swelling index	Ex-vivo mucoadhesion time	Ex-vivo bioadhesive strength	Surface pH
F_1	7.62 ± 3.82	3 hours 10 minutes	15.52 ± 0.32	6.27 ± 0.36
F_2	8.56 ± 3.60	4 hours 46 minutes	15.86 ± 0.10	6.39 ± 0.07
F_3	9.61 ± 2.92	6 hours 12 minutes	16.20 ± 0.44	6.48 ± 0.09
F_4	9.95 ± 2.36	9 hours 35 minutes	17.61 ± 1.20	6.79 ± 0.12

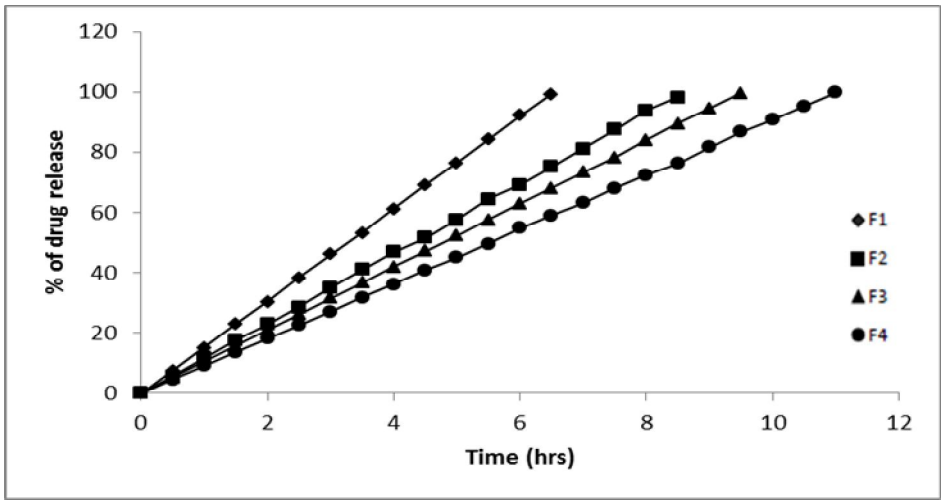

Fig. 1: Zero order plot Mucoadhesive tablets of Metoprolol succinate

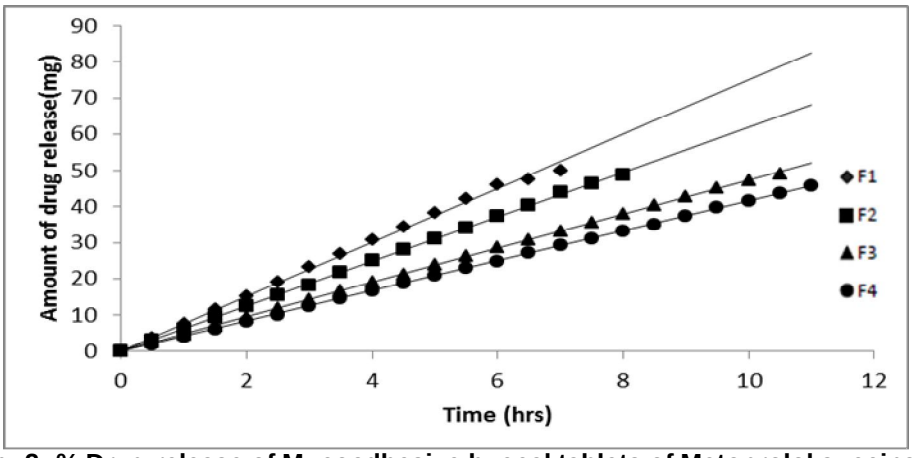

Fig. 2: % Drug release of Mucoadhesive buccal tablets of Metoprolol succinate

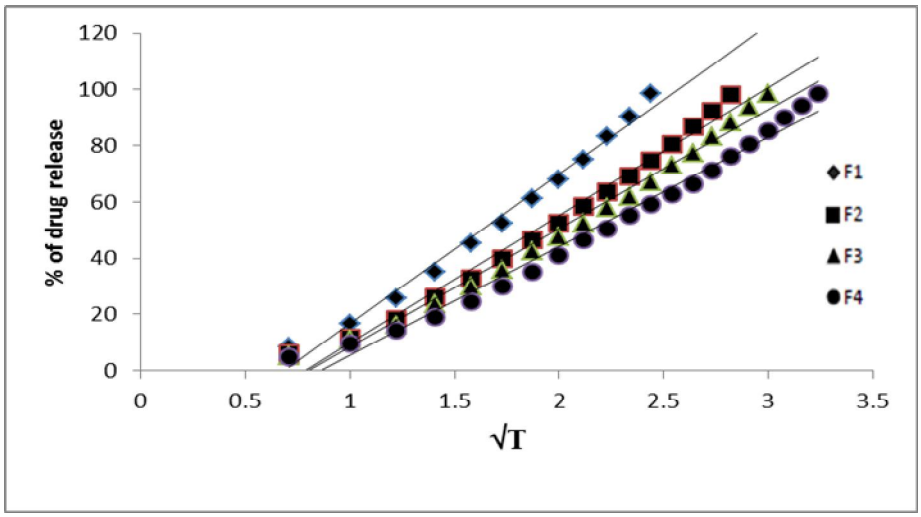

Fig. 3: Higuchi plot of Mucoadhesive buccal tablets of Metoprolol succinate

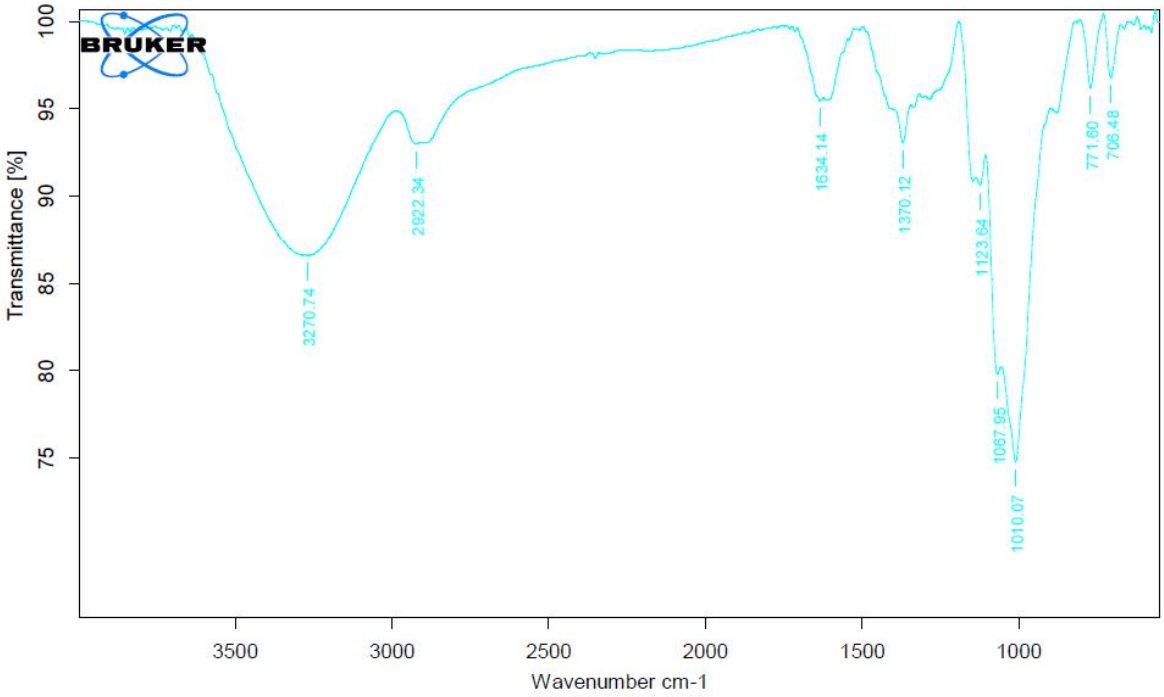

Fig. 4: FTIR of cashew nut tree gum

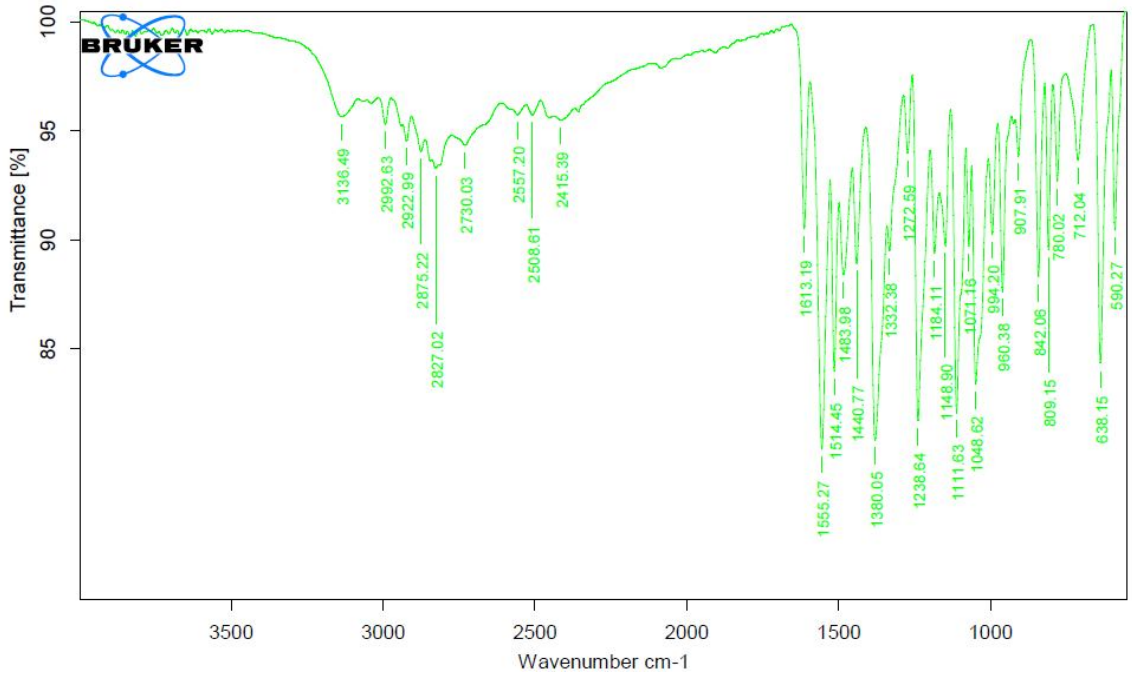

Fig. 5: FTIR of Metoprolol succinate

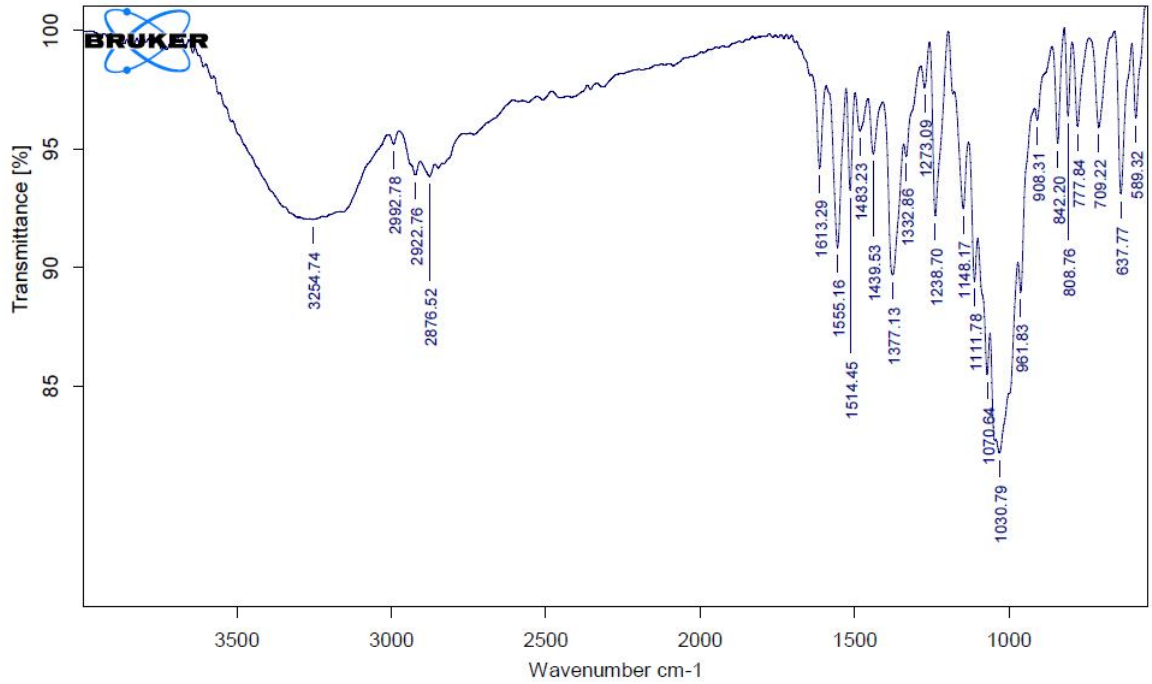

Fig. 6: FTIR of optimized formulation (F4)

CONCLUSION

The present study revealed that cashew nut tree gum appears to be suitable for use as a release retardant in the manufacture of matrix tablets because of its good swelling, good flow rate and suitability for mucoadhesion formulations. As the amount of polymer in the tablets increases, the drug release rate decreases, whereas swelling index and mucoadhesive strength increases. Ex-vivo residence test for mucoadhesion indicated good mucoadhesive property of the prepared tablets. From the results, it was concluded that dried cashew nut tree gum can be used as an excipient for making mucoadhesive buccal tablets of Metoprolol succinate.

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