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Research Article

FORMULATION AND EVALUATION OF ION EXCHANGE RESIN MATRIX TABLETS OF PROPRANOLOL

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ABSTRACT
In the present study, an attempt was made to prepare and evaluate Indion 254 ion exchange resin based matrix tablets by using sodium alginate, carrageenan and tamarind seed polyose for controlled release of propranolol HCl. The tablets were prepared by wet granulation method. The weight and drug contents of all the tablets were found to be uniform with the low SD values. The hardness and friability were within specified range. The pure drug propranolol HCl has shown complete dissolution within 60 min, whereas, drug-resin complex has shown drug release for 2.5 hrs. With the increase in concentration of carrageenan, the drug release was decreased whereas with the increase in concentration of tamarind seed polyose drug release was increased. The DSC and XRD analysis indicated that the drug was uniformly dispersed in an amorphous state in the polymer matrix. The FTIR analysis ruled out the interaction between drug and polymers used in the preparation. Swelling of the tablets decreased with an increased amount of carrageenan and it further decreased when the tablets were treated with glutaraldehyde. Swelling of the tablets increased with an increased amount of tamarind seed polyose. The in vitro drug release study indicated that the tablets containing tamarind seed polyose were capable of releasing the drug for 24 hrs. Drug release mechanism followed anomalous transport. The stability studies indicated that the formulations were stable, with respect to drug content and physical changes.
Keywords: Propranolol hydrochloride, Indion 254, Carrageenan, Sodium alginate, Tamarind seed polyose, Matrix tablets.

INTRODUCTION

The basic purpose of this study is to provide uniform release of a drug over a prolonged period may be obtained ,if it is chemically bound to a solid carrier, from which it slowly released by the action of gastrointestinal tract fluid and more uniform blood concentration. Examples of such carriers are ion- exchange resins, which have been used for several drugs in order to sustain or control the release rate. Ion exchange resins are also used in pharmaceuticals for taste improved stability and to improve physical characteristics[1].

When the drug resin complex reaches GIT, the reverse reaction takes place and the drug is released slowly. The controlled release systems have made significant progress in terms of clinical efficacy and patient compliance and reduced dosing frequency. Controlled release systems have many advantages like, improved efficacy, reduced toxicity and improved patient compliance and convenience. Controlled release of drugs is beneficial for drugs that are rapidly metabolized and eliminated from the body after administration. In recent years, hydrophilic matrices of natural polymers have been very popular for controlling the release of soluble drugs from solid dosage forms.

It is completely absorbed from GIT; however, the plasma concentrations are variable. It is having a shorter biological half life of 4 hrs and undergoes first pass metabolism[3]. Hence, it requires frequent administration. This suggest that propranolol is a suitable candidate for the development of oral controlled release system using ion exchange resins and natural polymers, which reduces the bitter taste of drug and avoids the need of repeated administration, this improves the patient compliance[4]. So lesser total dose required, improved efficacy/ safety factor, less fluctuating plasma drug level and uniform drug effect In the present study, it is therefore proposed to develop ion-exchange matrix tablets of propranolol. The developed formulation will be evaluated for its physicochemical and in vitro drug release behaviour[2].

MATERIALS AND METHODS

Propranolol hydrochloride, Indion 254 was gift sample from Cipla Pvt, Ltd. Mumbai, India. Carrageenan, Glutaraldehyde, Sodium Alginate from S.D. Fine Chemicals, Mumbai, India. Tamarind seed Polysaccharide Locally Obtained. Hydrochloric acid, Menthol, Acetone from Qualigens Fine-Chemicals, Mumbai, India.

Preparation of ion exchange resin

An accurately weighed amount of propranolol HCl 500 mg was taken in 100 ml of distilled water. Then a known weight 500 mg of ion-exchange resin Indion 254 was added to the solution and stirred on a magnetic stirrer until equilibrium was achieved. Time to reach equilibrium was determined by measuring concentration of drug in solution. Resinates obtained were separated by filtration, washed with copious quantity of de-ionized water to remove un-complexed drug. The complexes were dried overnight in a hot air oven at 40°C and then stored in tightly closed desiccators. The amount of drug loading was determined by finding the difference between the amount of drug present in the stock solution and the amount remaining in filtrate at the end of equilibrium[9].

Matrix tablet preparation

The tablets were prepared by wet granulation technique. All the powders were passed through 80 mesh. Required quantities of propranolol resinate, sodium alginate, carrageenan and tamarind seed polysaccharide were mixed thoroughly and a sufficient volume of granulating agent starch paste 5% w/v was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22/44 mesh. The granules were dried at 40°C for 12 hrs and thereafter kept in a desiccators for 12 hrs at room temperature. Once dry, the granules retained on 44 mesh

were mixed with 10% of fines granules that passed through 44 mesh. Talc and magnesium stearate were finally added as glidant and lubricants. The tablets were compressed using a rotary tablet compression machine. Further the tablets were cross-linked by exposing the tablets to glutaraldehyde solution for 15 min, 30 min and 45 min at 50°C. The total weight of tablets was 500 mg and each tablet contained 40 mg of propranolol. Composition of the prepared matrix tablet formulations of propranolol HCl were shown in Table 1 and 2.

Evaluation of buccal tablets

Thickness

The thickness of buccal tablets was determined using digital micrometer. Ten tablets from each batch were evaluated and the results averaged.

Weight variation

Weight variation was performed for twenty tablets from each batch using an electronic balance and average values were calculated[8].

Hardness

Hardness was conducted for three tablets from each batch using Monsanto hardness tester and average values were calculated[5,6].

Friability

Friability test was conducted by testing twenty tablets from each batch, using Roche friabilator.

Content uniformity

Ten tablets were weighed and grounded in a mortar with pestle to get fine powder; powder equivalent to the mass of one tablet was dissolved in methanol by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 224 nm using an UV spectrophotometer.

Equilibrium swelling study

The equilibrium swelling of the tablets was studied by mass measurement. Accurately weighed tablets were incubated with 100 ml phosphate buffer solution pH 7.4 at 37°C. The tablets were taken out after 10 hrs and blotted carefully without pressing hard to remove the excess surface liquid. The swollen tablets were weighed using the electronic microbalance. The percent water uptake (Q) after 10 hrs was calculated.

In vitro drug release study

In vitro drug release study was carried out using a USP-II rotating Paddle type dissolution tester. The dissolution was measured at 37° ± 0.5°C and 50 rpm speed. Drug release from the tablets was studied in 900 ml acidic medium (pH 1.2) for 2 hours and in alkaline medium (pH 7.4 phosphate buffer) till end of the study. At predetermined fresh solution. The amount of drug released was analyzed using UV- visible spectrophotometer at a max of 290 nm[7].

Release kinetics and mechanism

To know the release mechanism and kinetics of propranolo HCl, optimized formulation was attempted to fit in to mathematical models and n, r^2 values for zero order, First order, Higuchi and Peppas models were represented in Table 6 .The peppas model is widely used, when the release mechanism is not well known or more than one type of release could be involved. The semi-empirical equation was shown as equation[10].

$$Mt/M\infty = ktn$$

Where, $Mt/M\infty$ is fraction of drug released at time't', k represents a constant, and n is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-fickian release, the value of n falls between 0.5 and 1.0; while in case of fickian diffusion, n = 0.5; for zero-order release (case II transport), n = 1; and for supercase II transport, n > 1. Observation of all the r^2 values indicated that the highest r^2 (value was found for Zero order release. According to 'n' value it is one, so it follows non-fickian diffusion with zero order release (case II transport).

Fourier transforms infrared spectroscopy

The samples were crushed with KBr to make pellets under hydraulic pressure of 600 kg, and then the FTIR spectra were recorded between 400 and 4000 cm^{-1}.

RESULTS AND DISCUSSION

The present study was to formulate controlled release ion exchange resin matrix tablets of propranolol HCl using polymers such as carrageenan, tamarind seed polyose with different concentrations by wet granulation method.

The prepared tablets were evaluated for physiochemical properties, weight variation, differential scanning calorimetric analysis, drug content uniformity, x-ray diffraction, swelling index, in vitro dissolution, and stability studies and show acceptable results.

Pre-compression parameters

The Indion 254 ion exchange resin based matrix tablets of sodium alginate and carrageenan were prepared by wet granulation method for controlled release of propranolol HCl. The results of granules evaluation suggests that all the granules exhibits good flow properties, as the angle of repose values were less than 30°. A good packing ability of the granules was indicated by carr's compressibility index and hausner ratio, as the calculated values for carr's index were between 7.2 and 12.26 and hausner ratio values were between 1.07 and 1.13 were shown in Table 04.

Fourier transform infrared spectroscopy analysis

It is observed that the propranolol HCl shown peaks at 3282 cm^{-1} due to –NH structure, 2974 cm^{-1} due to aliphatic –CH structure, 1587 cm^{-1} due to ketone, 1242 and 1268 cm^{-1} are due to amine functional groups, 1107 cm^{-1} due to –OH group, 770 and 791 cm^{-1} are due to aromatic functional groups. The similar peaks were also observed in the spectra of resinate and drug loaded tablets with slight modifications. Hence, it shows that the drug is stable in the formulations, were shown in Figure 03 and 04.

***In vitro* drug release study of propranolol HCl sustained release matrix tablet in 7.2 pH**

In vitro drug release of pure drug and resinate was 98.23 and 98.32% at the end of 1 hr and 2.5 hrs respectively as shown in table 3 and Figure 1. The formulations containing carragenan, F1 to F5 showed release of 98.87, 98.5,94.43,91.29 and 88.12 at the end of 10th hr as shown in Table 5. The crosslinked formulations F6 to F8 showed delayed release upto 18 hrs. The crosslinked tamarined seed polyose, T1 to T6 showed greater controlled release upto 24th hr as sown in Table 6 and Figure 2. To examine further the release mechanism of propranolol HCl from mucoadhesive tablets, the result were analyzed according to the equation

$$\mathbf{Mt/M\infty = ktn}$$

The obtained values of 'n' lie between 0.5 and 1.0 in optimized formulation for release of propranolol HCl indicates non-fickian release kinetics, which is indicative of drug release mechanism involves diffusion an chain relaxation, shown in Table 7. In light of above discussion it can be concluded that formulation F1 could be used to release

the venlafaxine HCl uni-directionally in buccal cavity for extended period of time without the risk of mucosal irritation.

CONCLUSION

It can be concluded from the study that, among the prepared formulations, with respect to drug content, swelling studies and in vitro drug release, the blend hydrogel tablets of sodium alginate and tamarind seed polyose prepared by wet granulation method were found better than sodium alginate and carrageenan tablets. Therefore, the blend hydrogel tablets of sodium alginate and tamarind seed polyose containing resinates were suitable for oral controlled release of propranolol HCl.

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Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Propranolol HCl	40	-	-	-	-	-	-	-
Drug resin complex		187	187	187	187	187	187	187
Carrageenan	120	60	80	100	120	120	120	120
Sodium Alginate	110	170	160	150	110	110	110	110
Lactose	225	71	78	78	78	78	78	78
Talc	3	3	3	3	3	3	3	3
Mgnisum Stearate	2	2	2	2	2	2	2	2
Glutaradehyde (10% w/w of polymer)	-	-	-	-	-	15min	30min	45min
Starch	qs	qs	qs	qs	qs	qs	qs	qs
Total weight(mg)	500	500	500	500	500	500	500	500

Table 1: FORMULA FOR THE PREPARATION OF SA-CAR TABLETS

Ingredients(mg)	B1	B2	B3	B4	B5	B6
Drug- resin complex	187	187	187	187	187	187
Tamarind seed polyose	125	150	175	300	-	126.5
Cross-linked Alginate	175	150	125	-	300	126.5
Lactose	8	8	8	8	8	8
Talc	3	3	3	3	3	3
Mg. Stearate	2	2	2	2	2	2
Starch	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight	500	500	500	500	500	500

TABLE 2: FORMULA FOR THE PREPARATION SA-TSP TABLETS

Sl. No	Time (hr)	propranolol HCl	resinate
		% drug released	% drug released
1	0	0.00	0.00
2	0.5	55.12	26.04
3	1	98.23	46.76
4	1.5	-	67.02
5	2	-	84.22
6	2.5	-	98.32

Table 3: IN VITRO RELEASE DATA OF PURE DRUG PROPRANOLOL HCL AND RESINATE

Formulation codes	Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Swelling ratio
F1	510	5.4	0.43	98.4	5.455
F2	512	5.5	0.24	97.5	4.916
F3	511	5.7	0.26	98.5	4.761
F4	507	5.8	0.22	97.3	4.589
F5	501	5.2	0.33	98.7	4.331
F6	500	5	0.17	99.6	3.434
F7	496	5.7	0.13	98.3	2.885
F8	512	5.3	0.17	98.2	2.232

Table 4: PHYSICOCHEMICAL PARAMETERS OF FORMULATION

Sl No	Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
1	0.0	0	0	0	0	0	0	0	0
2	0.5	12.5	5.98	4.76	3.75	3.67	2.6	1.7	1.6
3	1.0	29.86	19.56	15.14	12.34	12.18	8.03	6.77	6.44
4	1.5	41.88	30.70	26.76	21.16	20.6	16.37	14.86	13.75
5	2.0	57.43	43.73	35.45	31.8	31.07	24.76	22.87	19.87
6	3.0	76.9	60.5	55.34	50.68	46.24	41.06	33.45	25.94
7	4.0	88.81	73.75	68.96	63.38	56.63	50.57	41.47	34.66
8	5.0	95.24	82.09	77.30	73.09	66.54	60.77	50.56	42.68
9	6.0	98.87	89.2	83.27	79.76	74.53	68.08	58.84	50.56
10	7.0	-	93.8	88.87	85.34	81.26	75.35	65.33	57.43
11	8.0	-	96.06	91.65	87.4	85.33	80.4	71.11	64
12	9.0	-	97.4	92.87	89.27	86.84	83.6	76.15	67.75
13	10	-	98.5	94.43	91.29	88.12	85.67	80.2	72.56
14	12	-	-	-	-	-	89.85	84.53	78.45
15	14	-	-	-	-	-	93.26	88.43	82.55
16	16	-	-	-	-	-	96.06	90.44	84.54
17	18	-		-	--	-	97.63	91.28	84.88

Table 5: IN VITRO RELEASE DATA OF PROPRANOLOL HCL FROM F1-F8 FORMULATIONS

SI. No	Time (hr)	T1	T2	T3	T4	T5	T6
1	0.0	0	0	0	0	0	0
2	0.5	7.75	12.32	16.52	16.3	6.45	7.5
3	1.0	13.33	20.13	29.51	26.15	10.86	10.95
4	1.5	19.45	26.66	42.34	35.59	14.52	16.75
5	2.0.	25.35	32.5	51.75	43.4	20.91	21.72
6	3.120	36.61	44.20	67.88	57.02	31.74	32.06
7	4.0	45.9	55	72.46	66.35	39.85	41.63
8	5.0	55.9	62.3	75.67	71	48.03	51.27
9	6.0	63.55	67.25	76.85	76.54	54.78	58.31
10	7.0	68.64	71.56	79.6	80.94	59.12	63.54
11	8.0	73	74.99	80.31	84.67	64.65	67.88
12	9.0	73.6	77.14	82.01	87.2	67.22	70.45
13	10	75.9	78.35	84.44	89.35	69.5	72.54
14	12	77.1	80.02	85.75	92.64	70.72	73.89
15	14	78.85	81.70	87.0	94.56	73	75.34
16	16	80.4	82.6	88.5	96.36	73.82	76.64
17	18	81.65	84.44	89.2	96.78	74.12	78.5
18	24	84.73	87.92	91.48	97.5	77.14	80.06

Table 6: IN VITRO RELEASE DATA OF PROPRANOLOL HCL FROM T1-T6 FORMULATION

Discs	Zero order equation	Higuchi equation	Korsemeyer's equation	
	r^2	r^2	n	r^2
F1	0.8827	0.9795	0.5901	0.9943
F2	0.9034	0.9873	0.6806	0.9925
F3	0.9206	0.9902	0.6300	0.9952
F4	0.9622	0.9923	0.6182	0.9948
F5	0.9596	0.9905	0.5921	0.9851
F6	0.9522	0.9942	0.7102	0.9856
F7	0.9497	0.9948	0.7393	0.9957
F8	0.9877	0.9877	0.7523	0.9915
F9	0.9854	0.9964	0.7422	0.9886

Table 7: KINETIC VALUES OF PROPRANOLOL HCL RELEASE FROM SA-CAR TABLETS

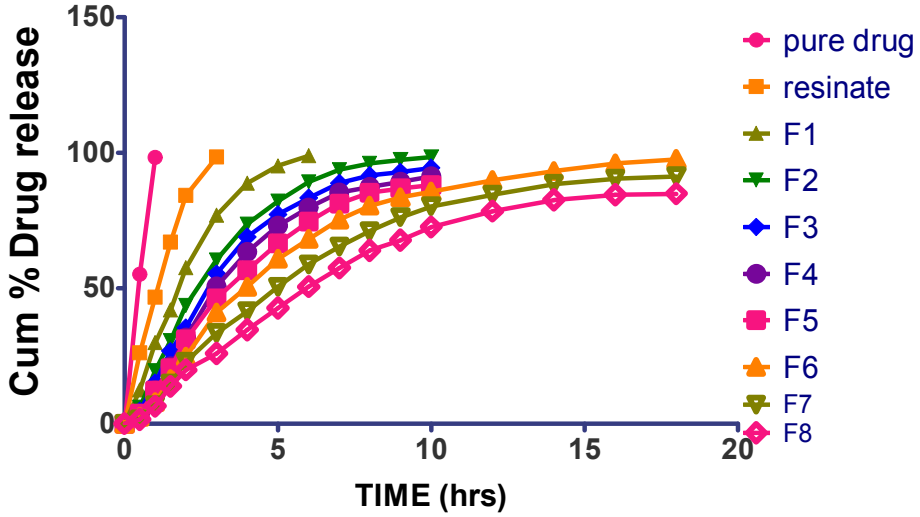


Figure 1: Drug release profiles of SA-TSP tablets.

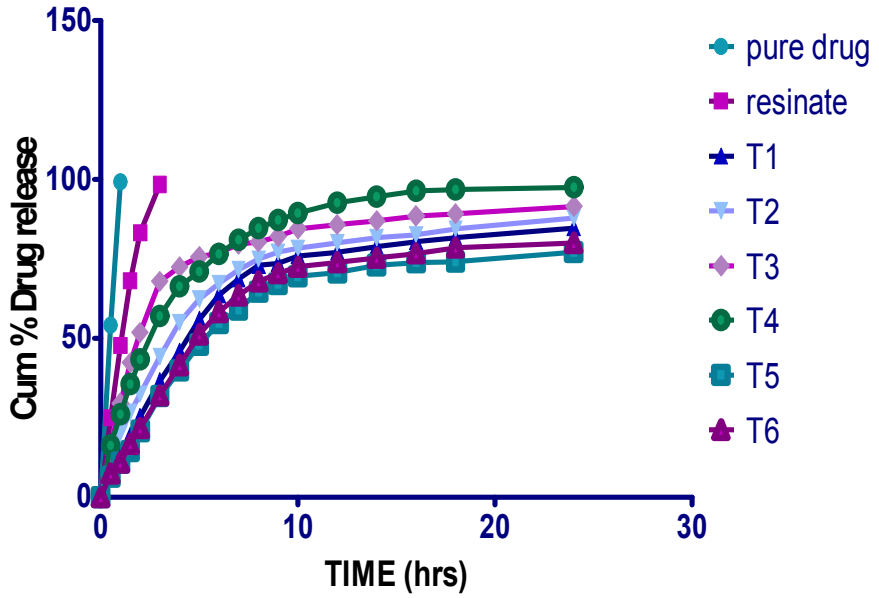
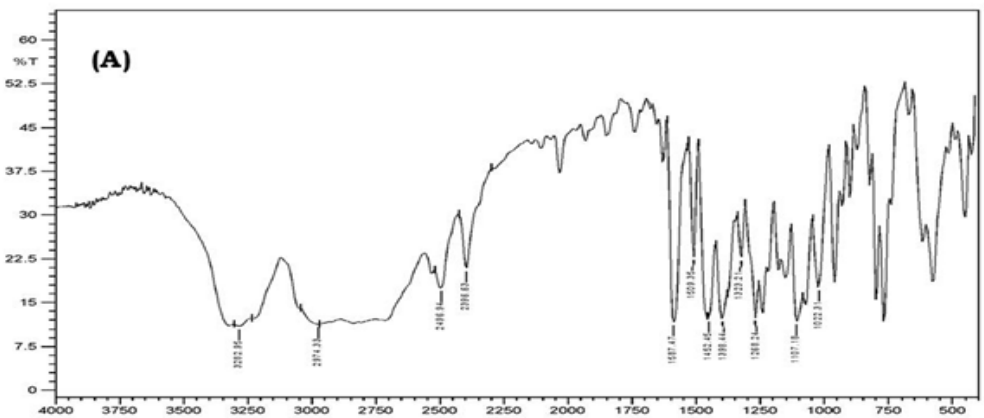


Figure 2: Drug release profiles of SA-TSP tablets.



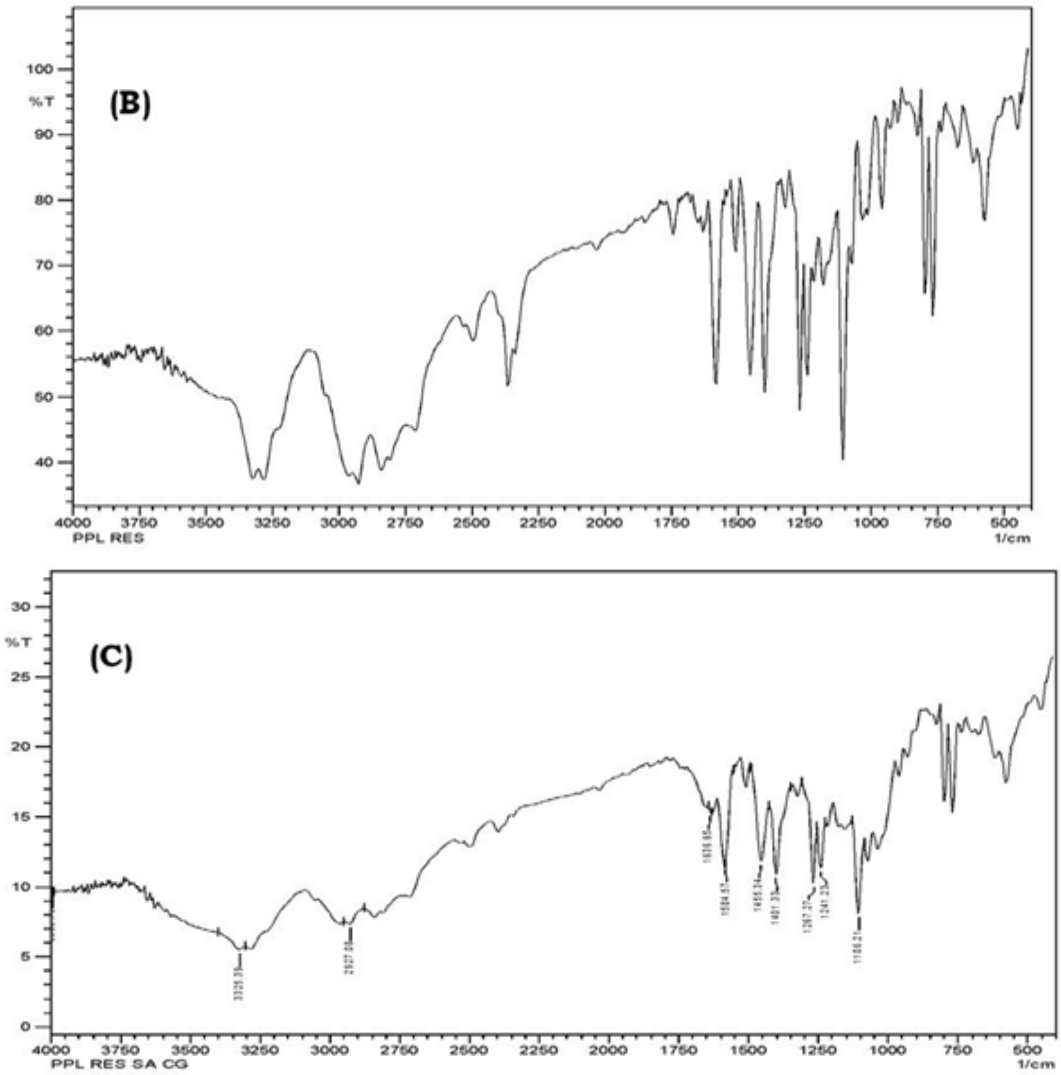
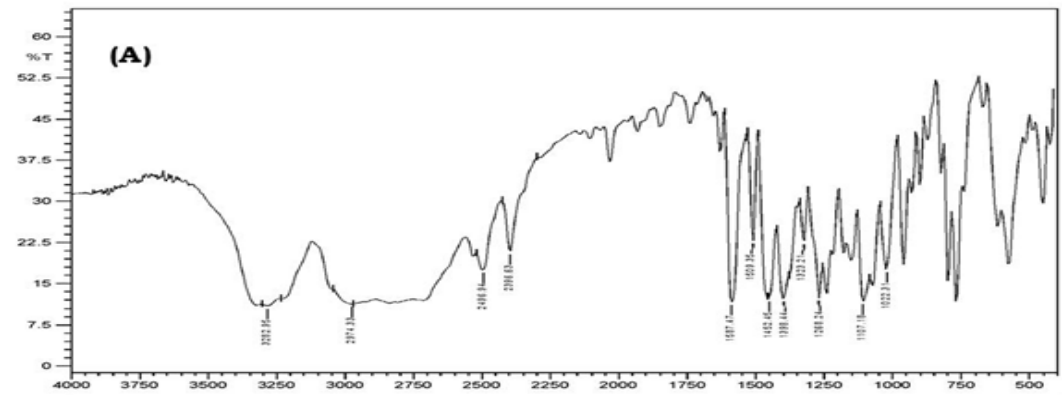


Figure 3: FTIR spectra of propranolol (A), resinate (B) and drug loaded F1 tablet (C).



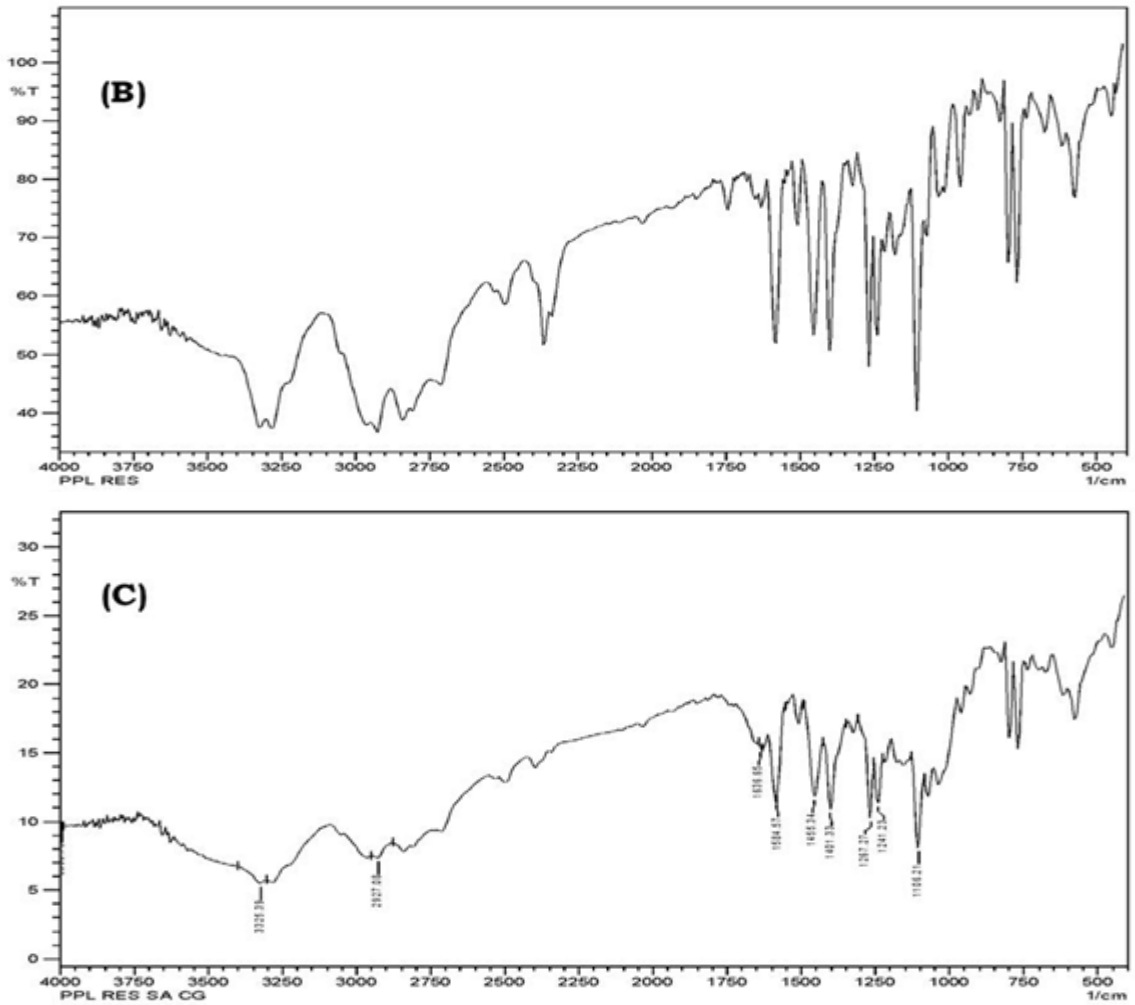


Figure 4: FTIR spectra of propranolol (A), resinate (B) and drug loaded T6 tablet (C).

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