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Research Article

DESIGN AND CHARACTERIZATION OF PULSATILE DRUG DELIVERY OF BUDESONIDE

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ABSTRACT

In the present study, an effort was made to develop the pulsatile Pulsatile drug delivery system of budesonide was designed with the intention of delivering the drug in the colon region for effective treatment of inflammatory bowel disease. A time delayed capsule was prepared by sealing the microspheres inside the insoluble hard gelatin capsule body with erodible hydrogel plug. The microspheres were prepared by emulsion solvent evaporation technique. Optimized microsphere formulations were selected based on dissolution studies. The entire device was enteric coated, so that the variability in gastric emptying time can be overcome and a colon-specific release can be achieved. Hydrogel plug (HPMCK4 and lactose in 1:1 ratio) having 4.5kg/cm^2 hardness and 100 mg weight was placed in the capsule opening and found that it was satisfactory to retard the drug release in small intestinal fluid and to eject out the plug in colonic fluid and releasing the microspheres into colonic fluid after a lag time criterion of 5 hours. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used. FTIR study confirmed that there was no interaction between drug and polymer. Among all the formulations Budesonide micropheres prepared with cellulose acetate in 1:2 ratio shown prolonged release for a period of 12 hours. The obtained results revealed the capability of the system in delaying drug release for a programmable period of time and for effective treatment of inflammatory bowel disease in the colon region.

Keywords: Budesonide, Eudragit L-100, Pulsatile, Microspheres, Solvent evaporation.

INTRODUCTION

Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount. These systems are beneficial for drugs having high first-pass effect; drugs administered for diseases that follow chronopharmacological behavior, drugs having specific absorption site in GIT, targeting to colon, and cases where night time dosing is required [1]. Budesonide is a second generation glucocorticoid exhibits high affinity to the corticosteroid receptors by decreasing the production of cytokines and interleukins [2]. Budesonide have half-life of 2-4 h with an oral bioavailibility of 10%. Budesonide is used in the long-term management of asthma and has important implications in the pharmacotherapy of inflammatory bowel disease, especially in the treatment of ulcerative colitis and Crohn's disease[3]. Inflammatory bowel diseases can be treated more effectively if drugs are targeted to the colon. Colonic drug delivery is also useful for better systemic absorption of drugs because of less hostile environment prevailing in the colon compared to stomach and small intestine. In normal oral controlled release formulations, it was found that less than 5% of the drug was available beyond the ileum and cecum, and therefore, colonic delivery still needs to be optimized by a more reliable targeted system. Budesonide undergoes approximately 85% first pass metabolism [4].To overcome these

drawbacks, the present study was undertaken to investigate the colon targeted drug delivery system of budesonide through pulsatile technique. Due to the distal location of the colon in the gastrointestinal tract, Pulsatile drug delivery should prevent drug release in the stomach and small intestine and produce an gradual onset of drug release upon entry into the colon [5]. Hence in the present study, Pulsatile drug delivery system of budesonide was designed with the intention of delivering the drug in the colon region for effective treatment of inflammatory bowel disease.

MATERIALS AND METHODS

Budesonide was a gratis sample obtained from Aurobindo Pharma limited; Hyderabad. Eudragit S-100, Eudragit L-100 were obtained from Himedia; Mumbai. HPMC K4, Carbapol, Na CMC and Methyl Cellulose were purchased from SD fine chemicals, Mumbai. All reagents used were of analytical-reagent grade, Mumbai. All reagents used were of analytical-reagent grade.

Preparation of Cross-Linked Gelatin Capsules

Approximately 100 number size 0 hard gelatine capsules were taken. Bodies were separated from cap, 25 ml of 15% (v/v) formaldehyde was taken into desiccators and a pinch of potassium permanganate was added to it, to generate formalin vapours. The wire mesh containing the empty bodies of capsule was then exposed to formaldehyde vapours. The caps were not exposed leaving them water-soluble. The desiccators were tightly closed. The reaction was carried out for 12 h after which the bodies were removed and dried at 50^0C for 30 min to ensure completion of reaction between gelatine and formaldehyde vapours. The bodies were then dried at room temperature to facilitate removal of residual formaldehyde[6]. These capsule bodies were capped with untreated caps and stored in a polythene bag.

Preparation of Hydrogel Plug

Plug for sealing the capsule body was prepared by compressing equal amount of equal amount of HPMC K100: lactose, carbapol: lactose, Na CMC: lactose, and Methyl Cellulose: lactose using 7 mm punches and dies on rotary tablet press keeping varying thickness and hardness values of tablet plug [7] .

Preparation of microspheres

All the microspheres formulations were prepared by emulsion solvent evaporation technique[8] and the composition was shown in table 1. The effect of various formulation and processing factors on microspheres characteristics were investigated by changing polymer: drug ratio. Weighed amount of Budesonide and polymer in 1:1 ratio were dissolved in 10ml of acetone. The homogeneous drug and polymer organic solution was then slowly added in a thin stream to 100ml of liquid paraffin containing 1% surfactant (span 80) with constant stirring for 1h. The resulting microspheres were separated by filtration and washed with petroleum ether. The microspheres finally air dried over a period of 12 hrs and stored in a desiccator. Incase of 1:1.5and 1:2 core:coat ratios, the corresponding polymer get varied respectively.

Designing of Pulsincap

The Pulsincap was designed by filling the microspheres equivalent to 9 mg of Budesonide into the formaldehyde treated bodies by hand filling. The capsules containing the microspheres were then plugged with optimized hydrogel plug. The joint of the capsule body and cap was sealed with a small amount of the 5% ethyl cellulose ethanolic solution[9]. The sealed capsules were completely coated by dip coating method with 5% cellulose acetate pthalate in 5:5 (v/v) mixture of acetone: ethanol plasticized with n-dibutylphthalate (0.75%), to prevent variable gastric emptying. Coating was repeated until an 8–12% increase in weight is obtained. % weight gain of the capsules before and after coating was determined[10].

Physicochemical Characterization of Hydrogel Plug

Hydrogel Plugs were studied for hardness, friability, weight variation and lag time .[10]

Drug content uniformity

Then encapsulated microspheres equivalent to 9 mg of Budesonide were taken into mortar and grounded with the help of pestle. The grounded power mixture was dissolved in 6.8 pH buffer , filtered and estimated spectrophotometrically at 304 nm[11] .

In vitro release profile of pulsatile capsule

Drug release studies of pulsincaps were carried out using a USP XXIII dissolution rate test apparatus (Apparatus 2, 100 rpm, 37 °C) for 2 hr in 0.1 M HCl (900 ml) as the average gastric emptying time is about 2 hr. Then the dissolution medium was replaced with pH-7.4 phosphate buffer (900 ml) for 3hr as the average small intestinal transit time is about 3 hr. After 5 hr, the dissolution medium was replaced with pH 6.8 phosphate buffer (900 ml) and tested for subsequent hours. Nine hundred

milliliters of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5°C. Five milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 304 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times [12].

IR spectral studies

The IR Spectra for the formulation, pure drugs and excipients were recorded on JASCO FT-Infra Red Spectrophotometer using KBr pellet technique[13] at the resolution rate of 4 cm^{-1}. Spectrum was integrated in transmittance mode at the wave number range 360 to 4370 cm^{-1} .

RESULTS AND DISCUSSION

Pulsincap dosage form was a capsule which consists of a water insoluble body and a water soluble cap. The microspheres was sealed within the capsule body by means of a hydrogel plug. When the pulsing cap was swallowed, the water soluble cap dissolves in the gastric juice and the exposed hydrogel plug begins to swell. At predetermined time after ingestion, the swollen plug was ejected out and the encapsulated drug formulation was then released into the colon, where it is dissolved and then absorbed into blood stream. In the present study, capsule bodies which were hardened with formaldehyde treatment for 12 hrs were used for the preparation of pulsincaps. It was sealed with unhardened cap of the capsule. The microspheres were prepared by emulsion solvent evaporation technique .The method employed gave discrete, spherical, non-sticky and free flowing microspheres. As aggregates these microspheres were also non-sticky and free flowing. The formation of a stable emulsion in the early stages is important if discrete microspheres are to be isolated. An optimal concentration of emulsifier is required to produce the finest stable dispersion. Below optimal concentration the dispersed globules/droplets tend to fuse and produce larger globules because of insufficient lowering in interfacial tension, while above the optimal concentration no significant decrease in particle size is observed, because a high amount of emulsifying agent increases the viscosity of the dispersion medium. The optimal concentration of surfactant was found to be 1.0%. Microscopic examination of the formulations revealed that the microspheres were spherical and appeared as aggregates or discrete particles.

All the formulations offered good flow properties. The particle size of the microspheres ranged between 132.55 and 168.47 µm. The use of the surfactant permits the remarkable reduction in the size of the microspheres as the result of decrease in the interfacial tension. All formulations had a narrow particle size distribution. The mean particle size of microspheres was influenced by the type of polymer proportion in the formulation. The mean size increased with increasing polymer concentration. It would appear that increasing polymer concentration produced a significant increase in viscosity of the internal phase, thus leading to an increase of emulsion droplet size and finally a higher microspheres size. Microspheres were developed with 1:1, 1:1.5, 1:2, ratios of core : coat to determine the affect of coating material concentration on the release rate of Budesonide. These microspheres were characterized for Drug Content and % Encapsulation Efficiency. The results are given in Table 2. The technique also showed good entrapment efficiency. Hydrogel Plugs were evaluated for hardness, friability, weight variation and lag time and the results were shown in Table 3. The formulations fitted with the various hydrogel plugs HP1,HP2, HP3, HP4 shown 0.45% , 6.36 % , 15.26 % and 19.74 % of drug release respectively at the end of 5th hour . It was observed that 100 mg hydrogel plug (HPMC K4: lactose in 1:1 ratio) having 4.5kg/cm^2 hardness was satisfactory to retard the drug release in small intestinal fluid and to eject out the plug in colonic fluid and releasing the microspheres into colonic fluid. This suggested that the lag time could also be adjusted and influenced by the plug composition.

During dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2 hrs in pH 1.2, but dissolved in intestinal pH, leaving the soluble cap of capsule, which also dissolved in pH 7.4, then the exposed polymer plug absorbed the surrounding fluid, swelled and released the drug through the swollen microspheres. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body; releasing the microspheres into simulated colonic fluid (pH 6.8 phosphate buffer). From the *In-vitro* release studies of device, it was observed that with all formulation, there was absolutely no drug release in simulated gastric fluid (acidic pH 1.2) for 2 hours and in simulated intestinal fluid (pH 7.4 phosphate buffer). Burst effect was found in colonic medium (pH 6.8 phosphate buffer).

In-vitro release profiles in colonic medium were found to have very good sustaining efficacy. Pulsin caps loaded with Budesonide microspheres prepared with Eudragit S-100 in 1:1,1:1.5 and 1:2 ratios shown sustained drug release for a period of 9 hours,10 hours and 11 hours(after 5th hour) respectively and are shown in figure 1. Pulsin caps loaded with Budesonide microspheres prepared with Eudragit L-100 in 1:1,1:1.5 and 1:2 ratios shown sustained drug release for a period of 9.5 hours,11 hours and 12 hours (after 5th hour) respectively and are shown in figure 2.The correlation coefficient values for dissolution kinetics data was shown in the Table 4. These values clearly indicated that the drug release followed zero order kinetics and the mechanism of drug release was governed by peppas - korsmeyer model. The exponential coefficient (n) values were found to be in between 0.7199 to 0.9576 indicating non fickian diffusion mechanisam.

The FTIR spectrum of Budesonide pure drug (Figure 3) showed characteristic peaks at wave numbers were 2353.72cm-1, 1688.17cm-1, 1648.64cm-1 ,622.49cm-1 and 575.18cm-1denoting stretching vibration of C=C stretching, N-H bending, C-O stretching, C-Cl Stretching and C-br Stretching respectively.The FTIR spectrum(Figure 4) of optimized formulation (F6) showed characteristic peaks at wave numbers were 2353.32cm-1, 1683.83cm-1, 1648.27cm-1 , 622.72 cm-1 and 577.88cm-1 denoting stretching vibration of C=C stretching, N-H bending, C-O stretching, C-Cl Stretching and C-br Stretching respectively. From the figures it was observed that similar peaks were also reported in optimized formulation. There was no change or shifting of characteristic peaks in drug loaded microspheres suggested that there was no significant drug polymer interaction which indicates the stable nature of the drug in optimized formulation.

CONCLUSION

Among all the formulations Pulsin caps loaded with Budesonide microspheres prepared with Eudragit L-100 in 1:2 ratio shown prolonged release for a period of 12 hours. The obtained results showed the capability of the system in delaying drug release for a programmable period of time and the possibility of exploiting such delay to attain colon targeting for effective treatment of inflammatory bowel disease.

Polymer employed			
Eudragit S-100		Eudragit L100	
Formulation Code	Core: Coat	Formulation Code	Core: Coat
F-1	1:1	F-4	1:1
F-2	1:1.5	F-5	1:1.5
F-3	1:2	F-6	1:2

Table 2: Evaluation data of Budesonide microspheres

Formulation	Angle of Repose	Bulk Density (g/cm³)	Carr's Index	Hausner's Ratio	Average Particle Size (µm)	% Drug Content	% Encapsulation Efficiency
F-1	27.64	0.867±0.08	15.86±0.04	1.20±0.03	132.55±0.07	44.96±0.02	89.92±0.09
F-2	25.73	0.886±0.04	14.18±0.02	1.20±0.06	146.36±0.05	37.94±0.04	94.85±0.06
F-3	23.44	0.897±0.03	13.13±0.06	1.18±0.04	168.47±0.06	31.82±0.05	96.42±0.04
F-4	27.64	0.514±0.02	15.87±0.06	1.188±0.06	139.44±0.06	46.56±0.05	93.12±0.06
F-5	26.93	0.519±0.05	15.49±0.07	1.183±0.08	156.47±0.09	37.66±0.09	92.90±0.05
F-6	26.75	0.531±0.08	15.31±0.05	1.181±0.09	168.39±0.05	31.25±0.06	94.39±0.04

Table 3: Evaluation characteristics of hydrogel plugs prepared with various natural polymers

Hydrogel Plug Code	Composition (1:1)	Weight (mg)	Thickness (mm)	Hardness (kg/cm2)	Lag time (hours)
HP1	HPMC K 4 : Lactose	100±1.2	3.44± 0.10	4.7±0.03	5±0.01
HP2	Carbopol : Lactose	99 ±1.1	3.42±0.12	4.6±0.01	4.5±0.02
HP3	Na CMC : Lactose	100±1.2	3.41±0.08	4.3±0.04	4.1±0.02
HP4	Methyl Cellulose : Lactose	99 ±1.1	3.43±0.09	4.1±0.02	3.0±0.01

Table 4: In-vitro disssolution kinetics parameters of Budesonide microspheres

Formulation	Correlation coefficient				Release kinetics			Diffusion Exponent value(n)
	Zero order	First order	Higuchi	Peppas	K_o (mg/hr)	T_{50} (hr)	T_{90} (hr)	
F1	0.9984	0.7672	0.9586	0.9786	1.063	4.23	7.5	0.7199
F2	0.9896	0.8434	0.9570	0.9972	0.930	4.8	8.6	0.7605
F3	0.9933	0.7522	0.9501	0.9970	0.848	5.3	9.6	0.7908
F4	0.9918	0.8208	0.9518	0.9961	0.918	4.9	8.8	0. 7555
F5	0.9951	0.8098	0.9444	0.9964	0.818	5.5	9.9	0.7976
F6	0.9986	0.7925	0.9354	0.9995	0.762	5.9	10.6	0.9576

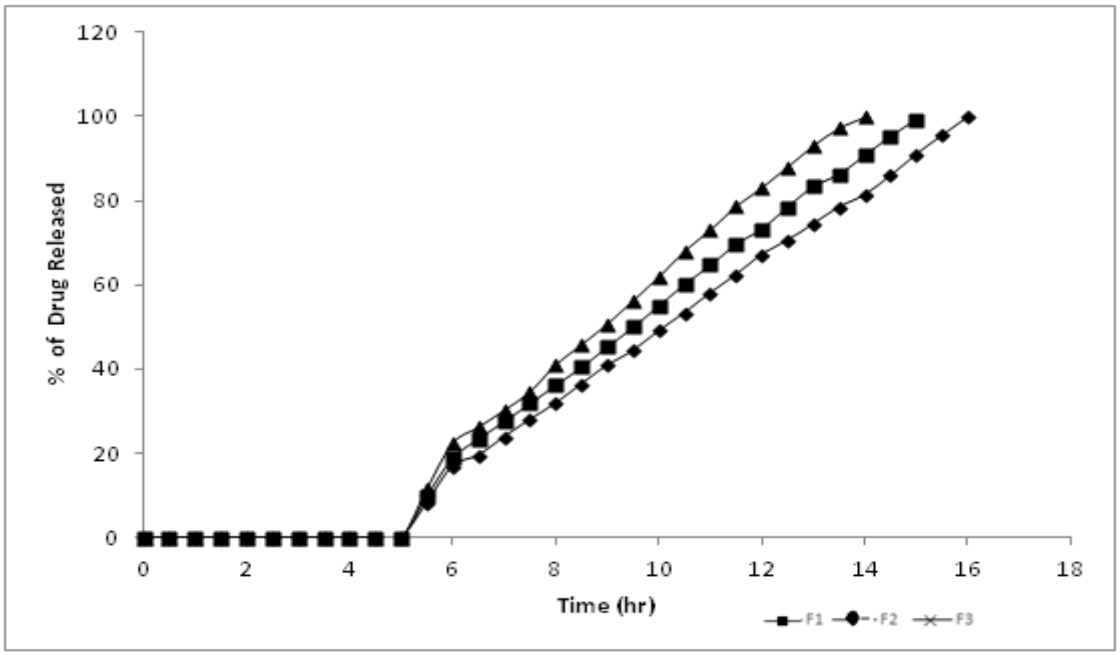

Fig. 1: Comparative *In-vitro* drug release profiles plot of Budesonide microspheres prepared with Eudragit S-100 in different ratios

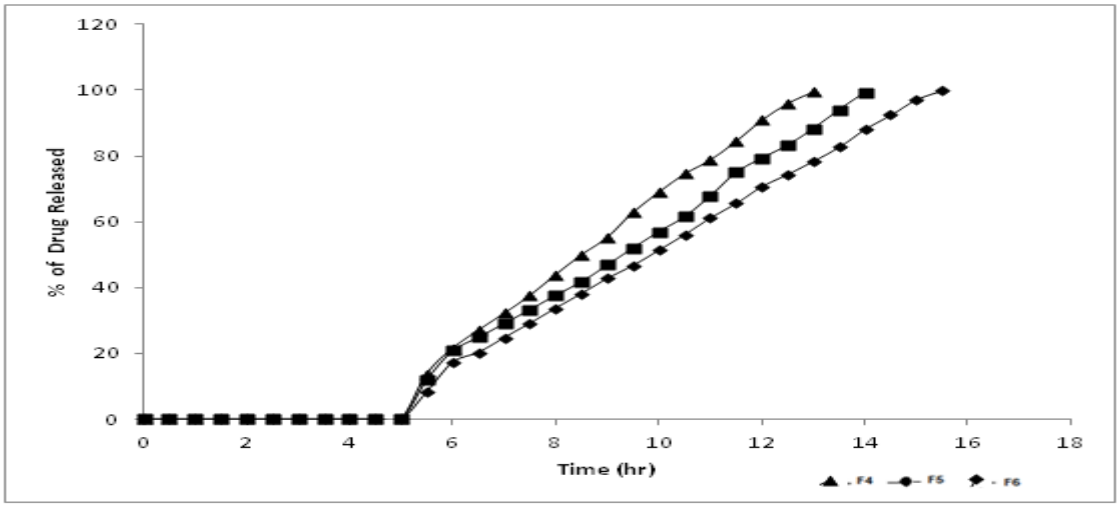

Fig. 2: Comparative *In-vitro* drug release profiles plot of Budesonide microspheres prepared with Eudragit L-100 in different ratios

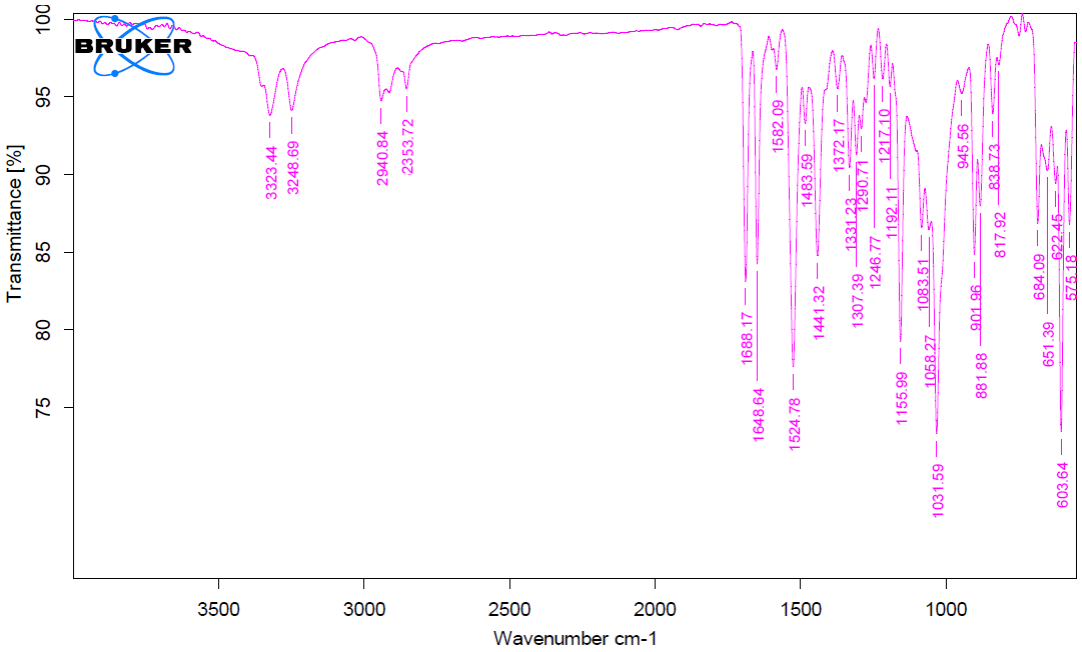

Fig. 3: FTIR spectrum of pure Budesonide

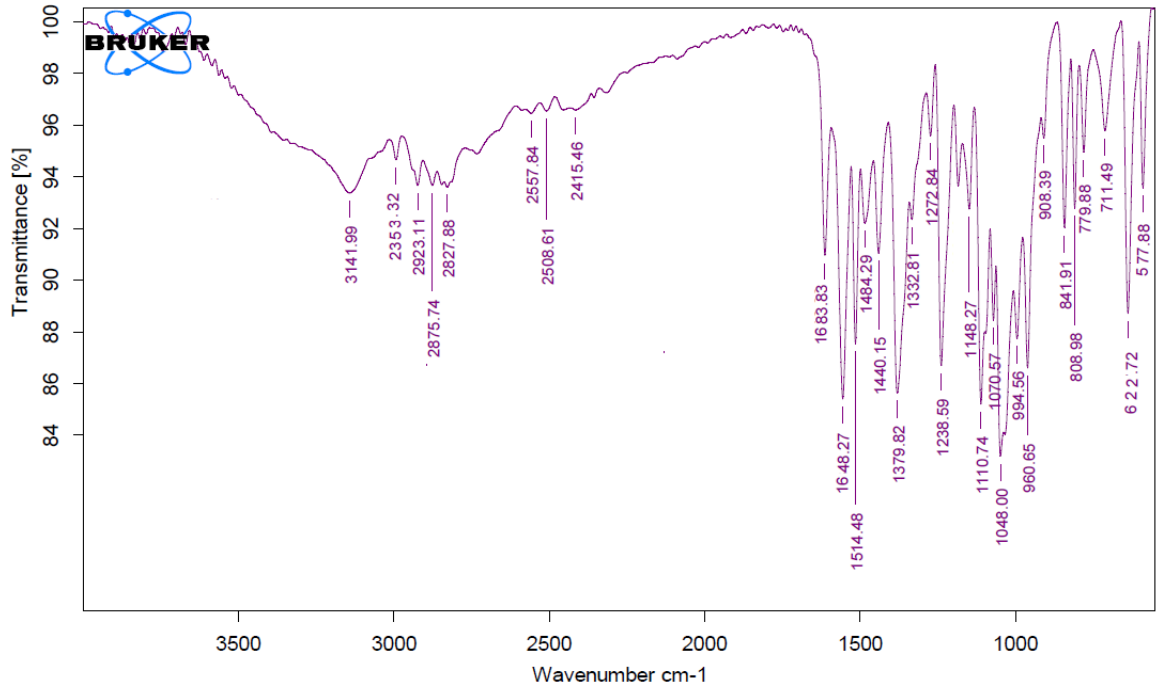

Fig. 4: FTIR spectrum of optimized formulation

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