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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF *ARAUCARIA BIDWILLI* GUM-BASED SUSTAIN RELEASE MATRIX TABLETS OF DICLOFENAE SODIUM

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ABSTRACT

A gel forming Polysaccharide gum obtained form the bark of *Araucaria bidwilli* was employed as a matrix sustained release tablet formulation of Diclofenac sodium (a non steroidal anti inflammatory agent). The effect of *Araucaria bidwilli* gum (Natural) and Synthetic polymer Hydroxypropyl methyl cellulose (HPMC K4 M) on the release of Diclofenac sodium was studied. The FT-IR spectroscopic studies of drug, gum and mixture indicated no chemical interaction. Six formulations were prepared by wet granulation method containing *Araucaria bidwilli* gum powder concentration 10% 20% & 30% w\w and 10% 20% &30% w\w of HPMC K4 M with sufficient volume of granulating agent Polyvinyl pyrrolene (PVP K 30), Avicel pH101 as diluents, Magnesium stearate and Aerosil is used lubricant and glidant respectively.This study was carried out to find out the difference between synthetic and natural gum and whether synthetic gum can be replaced by natural gums. Physical and technological studies of granules and tablets were compliance with Pharmacopoial standards.The drug release increased with *Araucaria bidwilli* gum when compared to synthetics polymer concentration .The value of release exponent were found to be almost straight line and regression coefficient value between 0.938 and 0.998.This implies that the release mechanism is diffusion. Formulation F3 (contained 30% w\w *Araucaria bidwilli* gum) met the desired requirements for a sustained release dosage form.

Keywords : Diclofenac sodium, *Araucaria bidwilli*, HPMC K4 M, Wet granulation, Sustained release

INTRODUCTION:

Apart from drugs and biologically active compounds, the plants also play an important role in pharmaceutical preparation like tablets,capsules,lotion,suspension,syrup and ointment etc[1].The most common excipients of plant origin include acacia, tragacanth, sodium alginate, starch and cellulose,which have wide variety of application in pharmaceutical dosage form. Recent trend towards the use of the plant and nontoxic products demands the replacement of synthetic additives with natural one. *Araucaria bidwilli* gum provide appropriate solution to the current problem. In view of the easy availability of the plant and the high demand on the gum through out the world, the gum obtained from *Araucaria bidwilli* was investigated for its application as a release modifier. *Araucaria bidwilli* (Araucariaceae) is a large evergreen tree, native of Australia[2-3]. Various experimental reports indicared diclofenac sodium as a good candidate for sustained release SR formulation [4-5]. The present study was undertaken to find out the potential of gum from *Araucaria bidwilli* to act as a release modifier in SR matrix tablet formulation.

MATERIALS AND METHODS:

Materials:

Diclofenac sodium was obtained as a gift sample from Dr.Reddy's Laboratories, Hyderabad,India. *Araucaria bidwilli* bark gum was collected from places in and around Ooty (Tamilnadu) .The plant was originally authenticated by Department of pharmacognosy. A herbarium sample of this plant is preserved at the Department of pharmacognosy, JSS college of pharmacy Ooty. Hydroxy propyl methyl cellulose (HPMC K4-M), Polyvinyl pyrrolene (PVP K30) ,Microcrystalline cellulose (Avicel pH 101), Magnesium stearate and Aerosil were procured from SD Fine chemicals,Mumbai,India.

Isolation of gum:

The crude gums were soaked in a distilled water over night until it was dissolved completely in water to form colloidal solution .This viscous solution obtained was passed through the muslin. The mucilage was precipitated out by addition of acetone. The coagulated mass was dried in oven at 40^0C

for 2 hours, made into fine powder, passed though sieve number 100 and stored for further use in desiccators [6-7].

Identification of gum:

In freshly prepared coralline soda, the sample was mounted and covered with coverslip. After few seconds it was irrigated with 25% Sodium carbonate solution. The polysaccharide gum power was stained pink colour.

Physicochemical properties of gum:

The physicochemical properties such as solubility, loss on drying and total ash content were determined according to Indian pharmacopoeial procedure [8] using air dried powder of gum. The pH of the gum was determined using digital pH meter [9]. The viscosity of 1% gum solution was determined at 25^0C using Oswald's viscometer after 24 hours of hydration.

Compatibility studies:

FT-IR spectra matching approach was used for detection of any possible chemical interaction between the drug and gum. The individual and physical mixture (1:1) of drug and gum powder was prepared and mixed with suitable quantity of potassium bromide. About 50 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 15 tons pressure. It was scanned from 4000 - 400 cm^{-1} in a Perkin Elmer FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and matching was done to detect any appearance or disappearance of peak.

Placebo tablet formulation:

Tablets were prepared using Avicel pH101 (quantity varied with concentration of gum), 10 % PVP K-30 as a binder and 2% Magnesium stearate as lubricant. *Araucaria bidwilli* powder gum was used as a release modifier in the concentration range of 10-30 % for preparation of granules.

Granulation:

Wet granulation technique used for the preparation of granules. All the excipient passed through to 80 mesh. Required quantity of Diclofenac sodium, Avicel pH101 and *Araucaria bidwilli* powder gum (120#) were mixed thoroughly and add sufficient quantity of granulation agent (PVP K 30 in water was added slowly) to obtained a damp mass suitable for granulation. The dump mass was passed through 8 mesh and granules were allowed to dry at 40 ^{0}C for 3-4 hours then shifted through 22 mesh.

Preformulation studies of granules:

Preformulation work is an important aspect of formulation ,which is monitored by requisite parameters, such as angle of repose, percentage compressibility, percentage drug content and percentage of fine etc. Performulation work was carried out on granules prepared using *Araucaria bidwilli* gum the result obtained were compared with those of HPMC K4 M [10-11] . The sample were graded as excellent, good ,fair or meager if the angel of repose was found to be is the range of 30-32,32-35,35-37 or 37-45 respectively by fixed funnel method. Carrs index (percentage compressibility), percentage drug content were calculated using standard formulae [12-13].

Tabletting:

The granules were homogenised with 0.5% Aerosil and lubricated with 2% Magnesium stearate .The tablet of average weights 200 mg were prepared on 10 stations rotary compression machine(Rimek,Ahamedabad ,India) using 8 mm diameter standard concave punch set. The batch size prepared was of 250 tablets. The compressed tablets were stored in a closed container for 15 days, no significant evidence of chemical change was observed. The tablets formulation using different concentration of *Araucaria bidwilli* gum and HPMC K4 M were given in Table 1**.** (For each one tablet) as F1,F2&F3 denoting natural gum and H1,H2,&H3 as synthetic gum.

Tablets Evaluation:

The compressed tablets were evaluated for physical parameters such as average weight, content uniformity, hardness, friability using standard formulae [14-15]. Swelling index of the formulated sustained release matrix tablets of *Araucaria bidwilli* gum was determined. A single tablet (Initial weight W_1) was placed in 6.8 pH buffer in a petri dish and the different time intervals the tablets was withdrawn. Excess buffer on the surface of the tablets was blotted with filter paper and reweighed (W_2).Swelling index was calculated using the formula [16-17].

Swelling index (%) = $[(W_1-W_2)100]/W_1$

In vitro drug releases studies of compressed tablet were carried out in USP XXIII tablet dissolution test apparatus-II (Electrolab) employing a paddle stirrer rotating at 50 rpm, 900 ml pH 6.8 phosphate buffer was used as a dissolution medium. The temperature of the dissolution medium was maintained at 37 $\pm 0.5^0$C throughout the experiment[18-19].One tablet was used in each test,5 ml of sample of dissolution medium was withdrawn. The sample were filtered through 0.45 µm membrane filter at specified intervals of time for period of 8 hours and was immediately replaced with fresh medium. Te sample was analysed for drug release by measuring the absorbance at 274 nm using UV-visible spectrophotometer(Techcom 2310 model) after suitable dilution.The content of drug and cumulative percentage drug release was calculated using an equation obtained from standard curve.

Kinetic modeling of drug release:

The dissolution profile of all the batches was fitted to various models such as Zero order, First order [20]Higuchi [21]and Korsmeyer peppas [22-23] to ascertain the kinetic modeling of drug release.

Accelerated Stability Studies:

Stability study was carried out to observe the effect of temperature and relative humidity on optimized formulation (F3), by keeping room temperature (28^{o}C) and at 40 ± 2^{0}C , in airtight container for three month, at RH 75±5 %. Physical evaluation and *invitro* drug release was carried out after every one month.

RESULTS AND DISCUSSION:

Many natural gums are found to possess high viscosity which can be useful as release modifier in the preparation of sustained release(SR) formulation. Where as high viscosity nature could be helpful in the formulation of gel layer around the matrix system through which it can act as release modifier. A pharmaceutical technologist should be very careful in optimizing the concentration of gum in the formulation based on the dosage form requirement.

In our preliminary studies, we observed that the natural gum gave positive result with polysaccharides test. Gum obtained from the *Araucaria bidwilli* bark was an amorphous free flowing powder with a light brown colour. It exhibited good solubility in water and gave viscous solution on standing. It has pH between 6-7 with acceptable limit loss on drying (LOD) and total ash content as shown in Table 2. In this present work Fig 1,2 &3 shows the IR spectra of Diclofenac sodium, *Araucaria bidwilli* gum and physical mixture of Diclofenac sodium and *Araucaria bidwilli* gum were performed. All the characteristic absorption bands of the pure drug and *Araucaria bidwilli* gum in the spectra of the formulation, without any shift in their position. It clearly suggests that the drug and the gum *Araucaria bidwilli* have not undergone any chemical change hence there was no interaction between Diclofenac and *Araucaria bidwilli* gum. The prepared granules are evaluated for angle of repose, percentage compressibility, percentage drug content and percentage of fine results are tabulated in Table 3 .The flow property of granules was determined by angle of repose and it was found that values were between 23-26^{0}C.It was found that natural gum and synthetic granules exhibited excellent flow properties, as there is no significant difference between percentage drug content and percentage fine.

The percentage compressibility (Carrs index) of *Araucaria bidwilli* gum granules comparatively less than that of HPMC K4 M granules. The values of carrs index between 11-15 indicant that the granules prepared using natural gum exhibit excellent flow property. Then the granules were compressed to tablets.

The evaluation of tablet formulation using natural gum and synthetic were based on quality control parameters which include average weight of the tablet (weight variation) hardness, percentage friability, uniformity content and swelling index. The results are indicated in Table 4, all the batches of tablets prepared fulfilled the official (IP) requirement for uniformity of weight. Hardness of the tablets in all the batches was found to be in the range of 5-5.5.kg /m^2 and was satisfactory. The percentage friability of tablets prepared using natural gum ranged between 0.4-0.7 %, which is almost equal to that of synthetic polymer used. The percent weight loss in the friability test from all formulation was found to be with in pharmacopoeial limit. All the tablets prepared were found to contain the medicament with 100 ± 5% of labeled claim.

Higher swelling index was found for tablets of F3 batch containing 30% of *Araucaria bidwilli* gum .Thus, the concentration of natural gum had major influence on swelling process and matrix integrity. Hence from the above result, it can be concluded the linear relationship between swelling process and concentration of natural gum ratio is as shown Figure 4.

Figure 5 and Figure 6 The *invitro* dissolution profile of using natural gum and synthetic polymer tablets formulated. Dissolution study showed that the drug releases from the tablets containing 10 to 20 %w/w of natural gum and 10 to 20% w/w of synthetic polymer was more than 50% release after 8 hours. The tablets at 30% w/w gum shown more optimum result as release modifier. The drug releases from the tablets decreases with the increases in gum concentration.

The result of dissolution data from dissolution profile fitted to various drug release kinetic equation of zero order, first order, Higuchi plot and Korsmeyer peppas having 'R^{2}', 'n' and 'k'. 'R^{2}' is value of correlation coefficient 'k' is a release rate constant and 'n' is the diffusional release exponent.

The different release mechanism as n= 0.5 (Fikian diffusion), 0.5 < n < 1 (Anomalous transport), n=1 (case II transport i.e. Zero order release) and n>1 (super case II transport).

The correlation coefficient 'R^{2}' values were calculated using the linear regression analysis to find out the best fitted model and in order to have an about the Kinetic mechanism of drug release. The Higuchi model and

Korsmeyer peppas model found to be best fitted in all six formulation (F1, F2, F3, H1, H2 & H3).

The correlation coefficient values between 0.938 to 0.998 followed by first order kinetic drug release equation and the value of 'n' was found to range from 0.300 to 0.605 shown in Table 5.Which indicate that the release mechanism shifted in the direction of anomalous transport (except H1&H2) and diffusion mechanism with erosion. The result of *invitro* dissolution studies of formulation F3 (30%w/w of *Araucaria bidwilli* gum) was found to be ideal for the formulation of SR matrix tablets , at it provides desired sustaining effect. Stability studies(40 ± 2^0C /RH 75±5 %)revealed that there was no significant change in hardness, friability, drug content and dissolution profile of selected batch for 6 months indicate that *Araucaria bidwilli* was stable in matrix SR table of Diclofenac sodium.

Table 1: Composition Diclofenac sodium sustained release matrix tablets

Ingredients (mg/tablets)	F1	F2	F3	H1	H2	H3
Diclofenac Sodium	100	100	100	100	100	100
Araucaria bidwilli	20	40	60	-	-	-
HPMC K4-M	-	-	-	20	40	60
Avicel pH 101	55	35	15	55	35	15
PVP K-30 (20% W/W in water)	20	20	20	20	20	20
Magnesium stearate	04	04	04	04	04	04
Aerosil	01	01	01	01	01	01
Total weight	200	200	200	200	200	200

Table 2: Physicochemical properties of *Araucaria bidwilli* gum powder

Parameters	Values
Solubility	Freely soluble in water
pH	6-7
Loss on drying	8% w/w
Total ash content	2.5 %w/w
Viscosity (1% w/w)	53.40 cps

Table 3: Preformulation studies of prepared granules (wet granulation)

Parameters	F1	F2	F3	H1	H2	H3
Angle of repose	23.50	24.69	25.46	24.44	23.49	23.48
Carss index	12	13.1	13.1	19.1	22.00	18.00
% Drug content	98.65	99.87	98.54	97.85	96.32	99.64
% Fine	15.41	13.53	14.60	13.43	14.08	14.22

Table 4: Physical properties of Diclofenac sodium sustained release matrix tablets

Parameters	F1	F2	F3	H1	H2	H3
Average weight	199.45	202.00	204.23	196.88	201. 91	203. 09
Hardness (Kg/m^2)	05.10±1	05.20±1.5	05.50±1.4	05.40±1.1	05.50±1.2	05.50±1.1
Friability (%)	0.50	0.57	0.47	0.46	0.78	0.34
Content uniformity(%)	99.76±0.6	98.04±0.7	99.03±0.5	97.56±0.3	99.42±0.4	100.35±0.4

Table 5: Kinetic values obtained from *in vitro* release profile for matrix tablets of Diclofenac sodium (Higuchi's and Korsmeyer peppa's models) regressions coefficient and release exponent values

Polymer	Batch code	Pappa's plot		Higuchi's	
		' R^2'	'n'	' R^2'	'n'
AB gum	F1	0.997	0.559	0.998	0.576
	F2	0.994	0.549	0.997	0.552
	F3	0.992	0.598	0.990	0.584
HPMC	H1	0.941	0.361	0.938	0.345
	H2	0.985	0.300	0.994	0.426
	H3	0.984	0.605	0.969	0.593

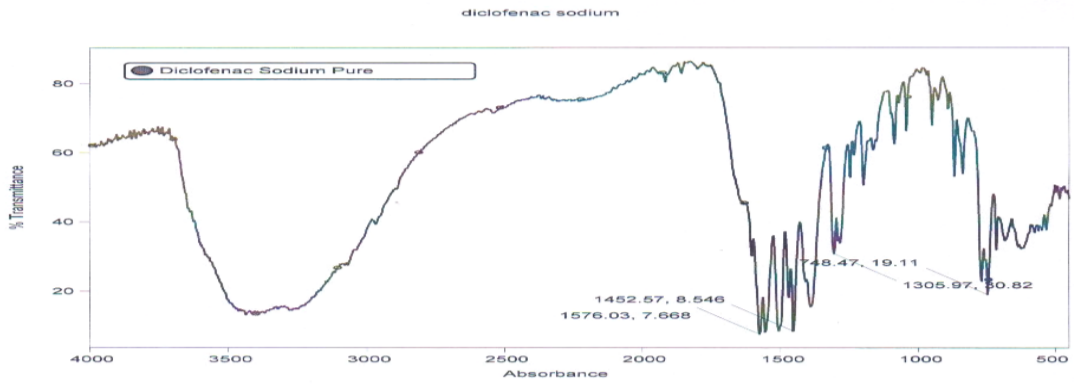

Figure 1: FT-IR Spectrum of Diclofenac sodium

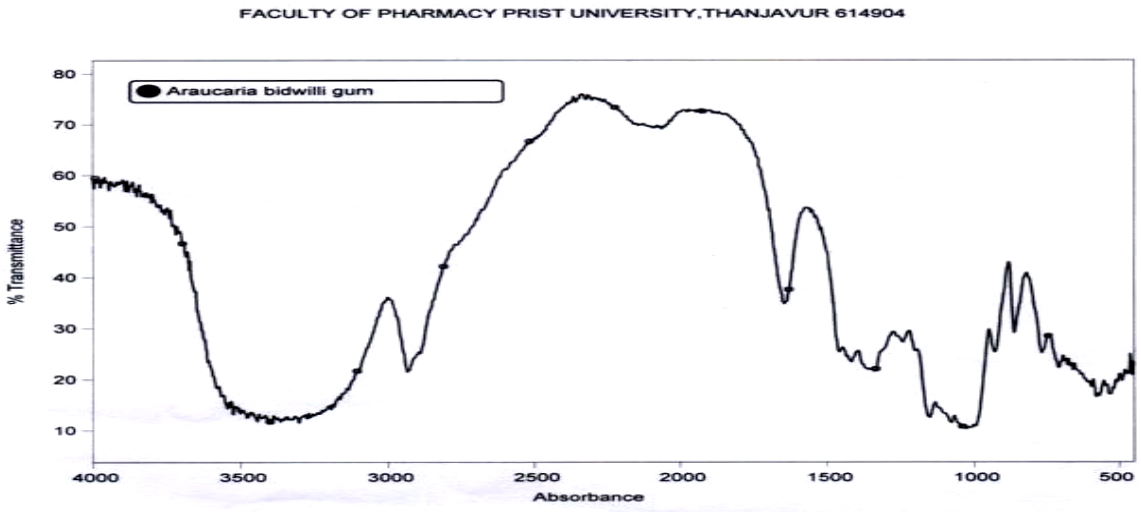

Figure 2: FT-IR Spectrum of *Araucaria bidwilli* gum

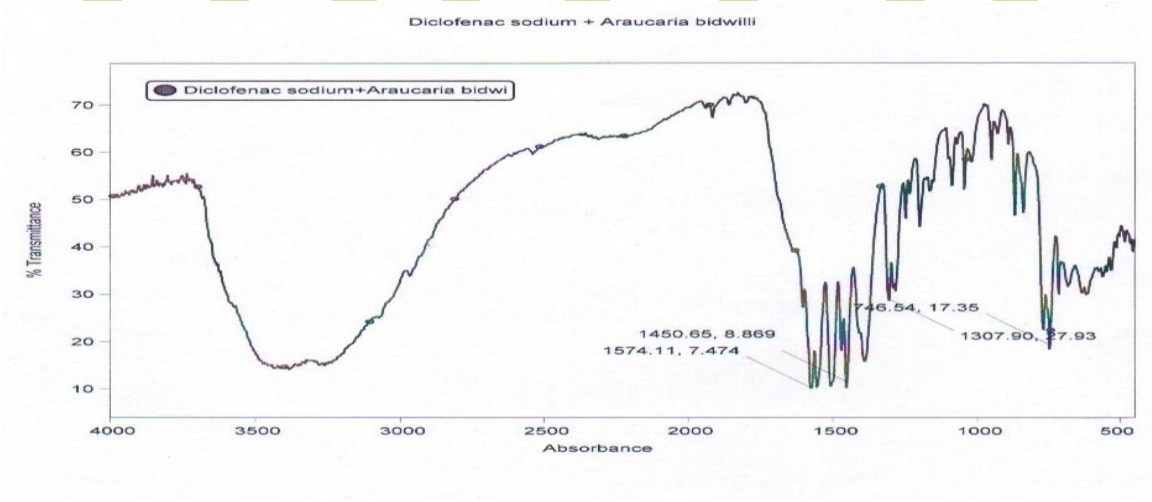

Figure 3: FT-IR Spectrum of powder sample of Diclofenac sodium with *Araucaria bidwilli* gum

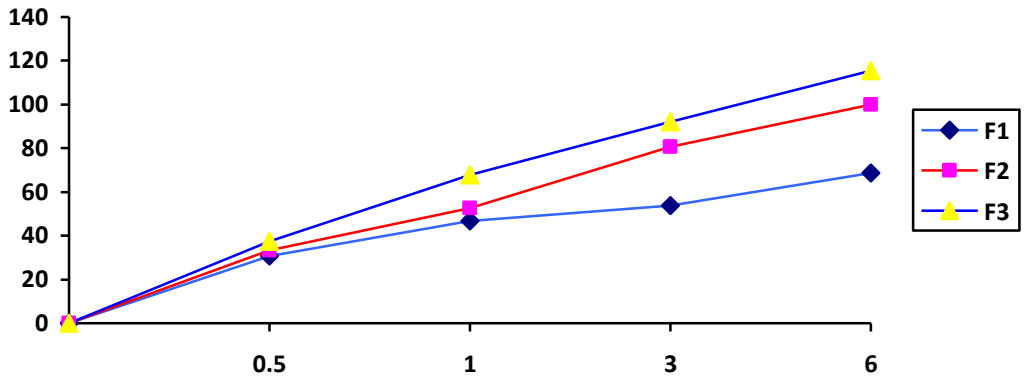

Figure 4 : Swelling index of *Araucaria bidwilli* gum tablets (Formulation F1,F2&F3)

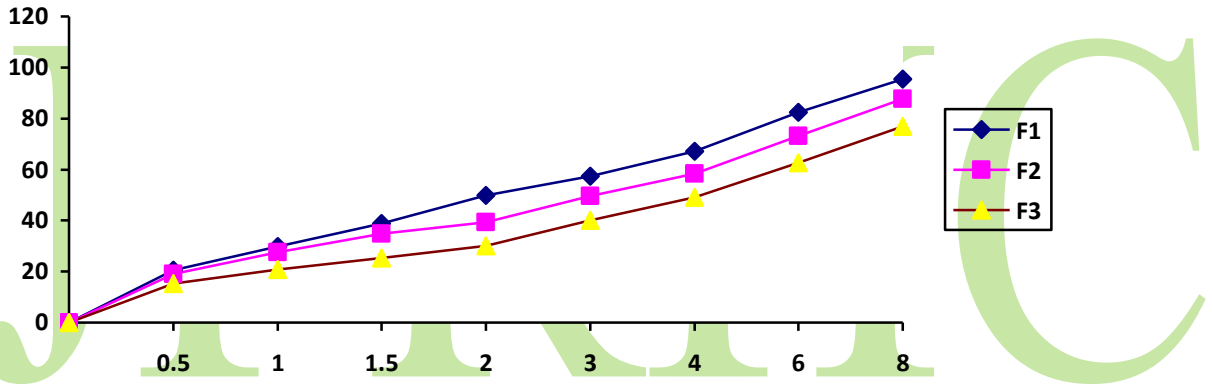

Figure 5: *In vitro* release profile of Diclofenac sodium from matrices containing different percentages of *Araucaria bidwilli* gum

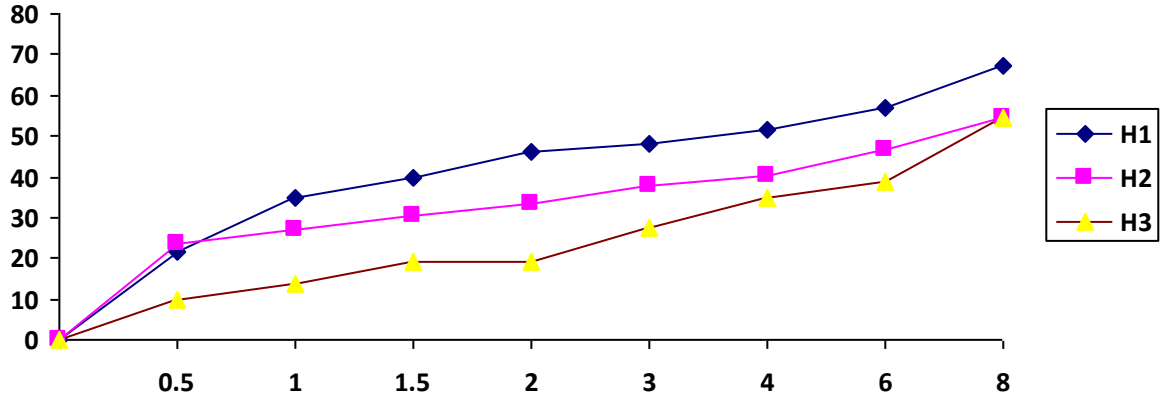

Figure 6: *In vitro* release profile of Diclofenac sodium from matrices containing different percentages of HPMC K4-M polymer.

CONCLUSION:

The present study revealed that *Araucaria bidwilli* gum appears to be suitable for use as a release modifier in the manufacture of once daily sustained release matrix tablets because of its good swelling index, good flow and suitability for matrix formulations. It could be concluded that *Araucaria bidwilli* gum can be used as an effective matrix former in the release of diclofenac sodium for sustained period of time.

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