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Design, optimization and comparative *IN VITRO* evaluation of sustain release matrix tablet using *ARAUCARIA HETEROPHYLLA* gum

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ABSTRACT

The present study deals with the formulation of oral sustained-release tablets using natural gum of *Araucaria heterophylla*, and the results were compared with existing polymer. The gum was isolated from the bark exudates of *Araucaria heterophylla* tree. Sustain release matrix tablets of aceclofenac as a model drug were prepared with the proportions 15%, 20%, 25% and 30% of *Araucaria heterophylla* gum by direct compression method. The results were compared with sustain release matrix tablets formulated from similar proportions of Guar gum and HPMC K4M. The tablets were evaluated for their physical characteristics. The formulation with 30% concentration of the gum showed a release of 91.68±0.72% whereas the formulation with 30% guar gum showed drug release of 91.26±0.41% after 8 hrs, while HPMC at 30% concentration gave a drug release of 86.26±0.61after 8 hrs. The other parameters were satisfactory and were within the Pharmacopoeial limits. The stability studies carried out under accelerated conditions as per ICH guidelines infer that the gum is chemically stable, compatible and maintain its physical and *in vitro* characteristics throughout the shelf life of the formulations.

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INTRODUCTION

Increasing attention has been given to the application of natural gums of various sources as pharmaceutical excipients. As they are explored for controlled release applications (Kamboj and Gupta, 2009). Matrix tablets made from the drug is expected to be released through the gel layer, thereby achieving a sustained release. (Mfoafo and Kwame, 2013). They are also desired for their chemical stability to disperse homogeneously throughout the matrix.

Araucaria heterophylla popularly called Christmas tree is a native of Pacific countries but spread throughout the world (Gayathri and Sundaraganapathy, 2019). The free-flowing nature of the gum makes it suitable to be used as an excipient for direct compression, thereby reducing the production time (Sunenegre *et al.*, 2008). *Araucaria heterophylla* gum was isolated, purified and characterized as per monograph (babu and Rajaram, 2012). The use of *Araucaria heterophylla* gum as a drug carrier is the main objective of the study. Matrix tablets containing different ratios of *Araucaria heterophylla* gum as release retardant were prepared and their *in vitro* release profiles were compared with for-

mulations made with similar proportions of established polymers, namely Guar gum and HPMCK4M. The drug release mechanism was interpreted using different kinetic models followed by stability studies. All these studies lead to consider the use of *Araucaria heterophylla* gum as a potential retardant in matrix sustain release tablets.

MATERIALS AND METHODS

Materials

Aceclofenac drug was obtained as a gift sample from Karpagam Pharma LLP, Coimbatore. *Araucaria heterophylla* gum was isolated from the bark exudates of the tree *Araucaria heterophylla* located in and around Coimbatore. The plant was originally authenticated from Botanical Survey of India, Coimbatore. All other chemicals used for the study were of analytical grade and were procured from SD fine chemicals, Mumbai, India.

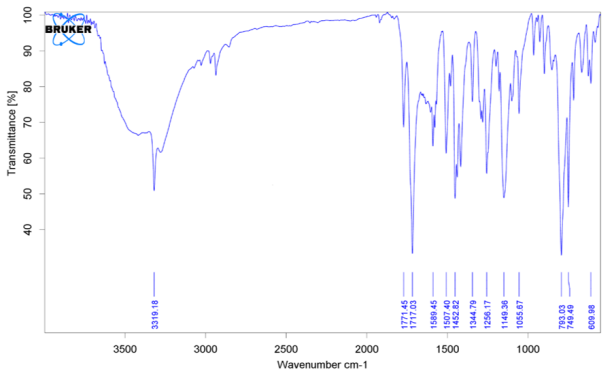

Figure 1: FT-IR spectrum of Drug

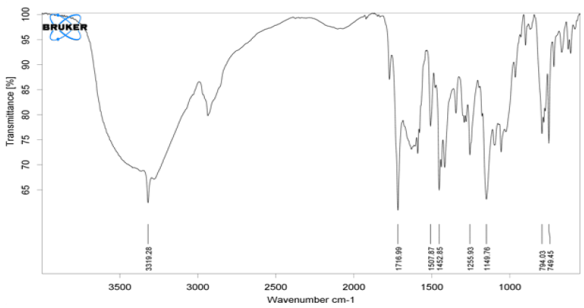

Figure 2: FT-IR spectrum of Araucaria *heterophylla* gum

Isolation and characterization of gum

The crude gum exuded from the incisions made on the bark of the tree was collected, soaked in purified water for 6 hrs and filtered with the muslin cloth. The filtered viscous solution was precipitated out by the addition of acetone and separated by decantation. The solid mass was then dried at 40°C in a hot air oven for 2hrs, made as fine powder, passed

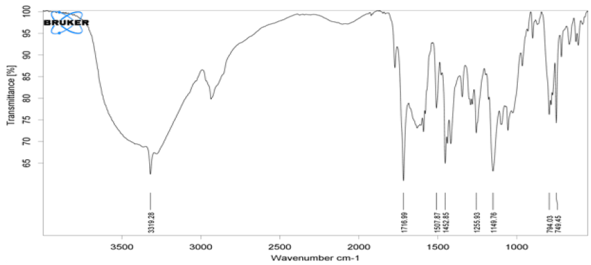

Figure 3: FT-IR spectrum of Drug and Araucaria *heterophylla* gum

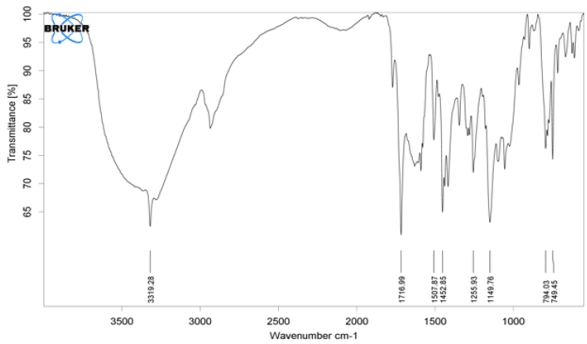

Figure 4: FT-IR spectrum of Drug and Guar gum

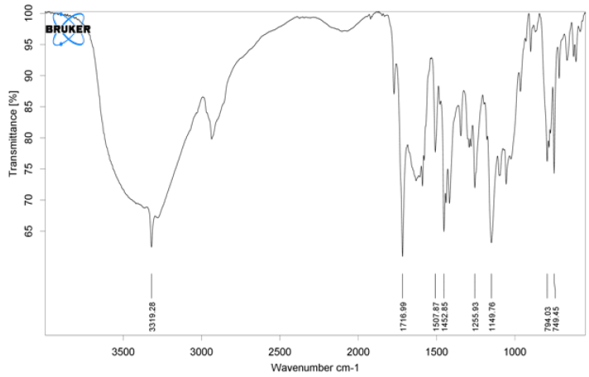

Figure 5: FT-IR spectrum of Drug and HPMC K4M

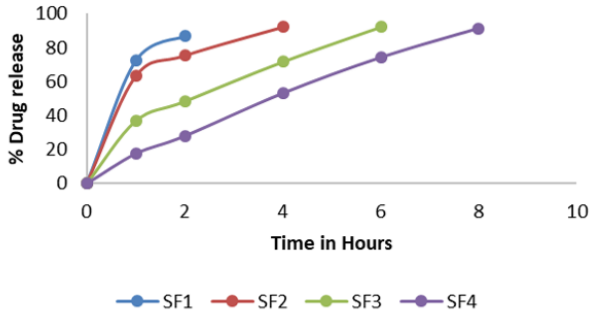

Figure 6: *In vitro* dissolution profileof SR tablets using Guar gum as matrix forming agent

through sieve number 80 and kept in dessicator.

The powdered gum of *Arauacaria heterophylla* was evaluated for preliminary Phytochemicals screening by chemical test for various phytoconstituents and Physicochemical characteristics like organoleptic, physical, rheological and micromeritic property (Gayathri and Sundaraganapathy, 2019).

Formulation and evaluation of Sustain release matrix tablet using *Araucaria heterophylla* gum, HPMC and Guar gum

Sustain release matrix tablet using *Araucaria heterophylla* gum as polymer at various concentrations and compared with the matrix tablets prepared using four different concentrations of HPMC K4M(synthetic) and guar gum(Natural polysaccharide) with Aceclofenac as a model drug (Chakraborty *et al.*, 2009).

The formulation blend using different polymer at various concentrations and excipients were prepared as per the composition mentioned in Table 1 and were subjected to compatibility studies by FT-IR spectroscopy to analyze the physical interaction of drug and polymer (Odeku, 2005). Preformulation studies such as the angle of repose, bulk density, tapped density, Hausner's ratio, and carr's index were performed for the compositions passed through sieve number 60 to determine flow characteristics to identify its suitability for direct compression.

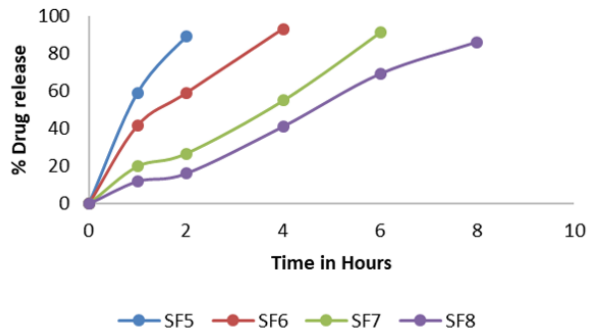

Figure 7: *Invitro* dissolution profile of SR tablets using HPMCK4M as matrix forming agent

Table 1 shows, Matrix tablets, each containing 100mg Aceclofenac were prepared by direct compression method. The composition of various formulation with 15,20,25and 30% concentration of polymers and excipients were blended and passed through sieve number 60 to get a uniform mass. The sustained release matrix tablets of each 200mg total tablet weight were compressed using 8mm flat-faced circular punches on an eight stationed rotary tablet press (Cadmach Machineries, Ahmedabad) at a constant compressional force (Mfoafo and Kwame,

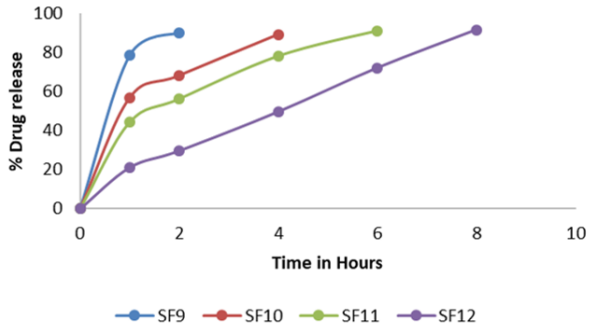

Figure 8: *Invitro* dissolution profile of SR tablets using Araucaria heterophylla gum as matrixforming agent

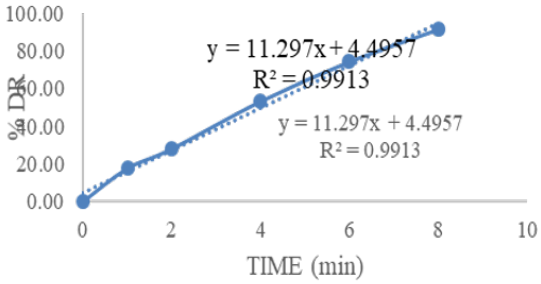

Figure 9: Zero order Kinetics –SF4

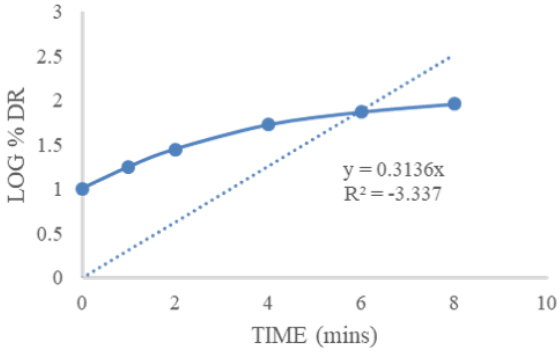

Figure 10: First order Kinetics –SF4

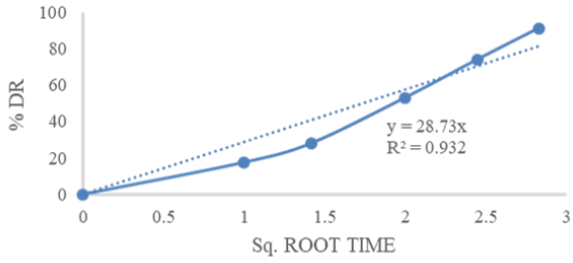

Figure 11: Higuchi Kinetics –SF 4

Table 1: Composition of formulations containing various concentrations of different polymers

Ingredients	Formulation Code											
	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9	SF10	SF11	SF12
Drug	100	100	100	100	100	100	100	100	100	100	100	100
Guar gum	30	40	50	60	—	—	—	—	—	—	—	—
HPMC	—	—	—	—	30	40	50	60	—	—	—	—
Gum	—	—	—	—	—	—	—	—	30	40	50	60
MCC	68	58	48	38	68	58	48	38	68	58	48	38
Colloidal Silicon Dioxide	2	2	2	2	2	2	2	2	2	2	2	2

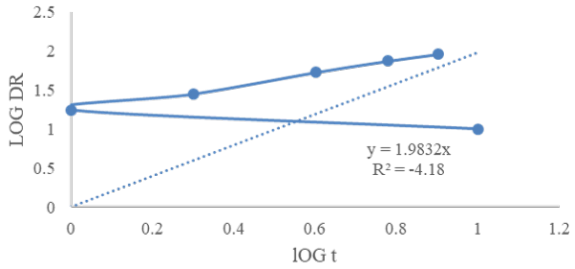

Figure 12: Korsemeyer Peppas kinetics – SF 4

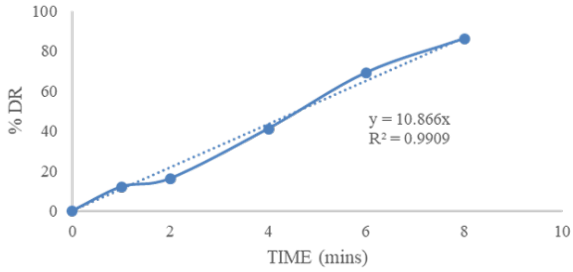

Figure 13: Zero order Kinetics – SF8

2013).

Evaluation of Sustain release tablets

The formulated tablets were studies for physical appearance, weight variation, hardness and drug content. Weight variation test was performed according to the official method and hardness was tested by using Monsanto hardness tester. The drug content was analyzed by measuring the absorbance of standard and sample at 275nm using UV/Visible spectrophotometer (Shimadzu 1800, Mumbai).

In vitro drug release study

In vitro drug release profile for all the 12 formulations, SF1 to SF12 were determined using USP XXIV type II paddle (Lab India DS 8000) dissolution apparatus using 900ml of Phosphate buffer 7.5 as the dissolution medium. The paddle was rotated at a speed of 100 RPM, and the temperature was maintained at 37± 0.5° C. Dissolution samples were withdrawn at a predetermined time intervals and replaced with equal volumes of fresh buffer. Samplings were done at an interval of 1hr up to 8 hrs and analyzed spectrophotometrically at 275 nm. The concentration of the drug in each sample was determined from the Beer- Lambert's plot of pure drug. The drug release was reported as an average of six determinations (Gayathri and Sundaraganapathy, 2019).

Kinetic analysis of release data

The release data obtained for the sustained release

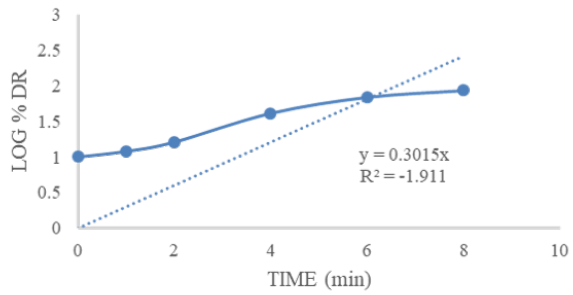

Figure 14: First Order Kinetics –SF 8

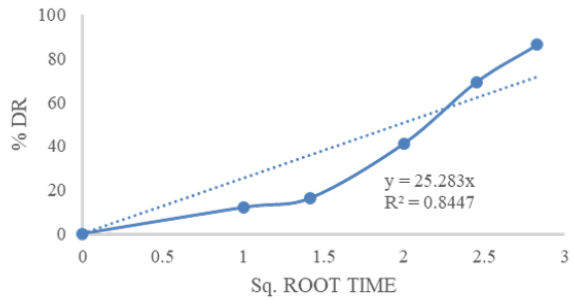

Figure 15: Higuchi Kinetics – SF8

formulation extended up to 8hr SF4, SF8 and SF12 were treated according to zero-order(R= k1t), first-order (R = k1t), Higuchi (R=K3$\sqrt{t}$), and Korsmeyer – Peppas (Log R= log k4+nlog t) equation, to find equation with the best fit (Prasanthi *et al.*, 2010).

Stability studies

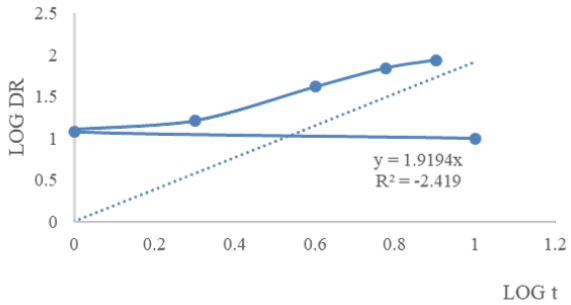

Figure 16: Korsemeyer Peppas Kinetics – SF8

Stability studies were performed for the formulation SF12 which gave sustain release for 8hrs, to confirm the integrity and stability of the new polymer in formulations under the accelerated condition as per ICH guidelines 40°C 75% RH for 180 days and observed for its physical and *In vitro* release characteristics (Ofori-Kwakye *et al.*, 2016).

RESULTS AND DISCUSSION

The percentage yield of the isolated and purified *Araucaria heterophylla* gum was found to yield 67.5±2% w/w of the gum by precipitation with acetone. The phytochemical evaluation showed the gum possesses the characteristics of polysaccharide and indicated the presence of carbohydrate and reducing sugars. Also the physicochemical property of the gum showed significant characteristics of excipient as a release retardant and the pH was found to be neutral with a swelling index of 13.9% and viscosity of 1.2cps for a concentration of 1%w/w (Gayathri and Sundaraganapathy, 2019). The values of micrometric, rheological properties clearly indicated the gum has necessary properties to be used as an excipient with good flow characteristics and the car's index above 5 indicates its suitability for direct compression (Sunenegre *et al.*, 2008).

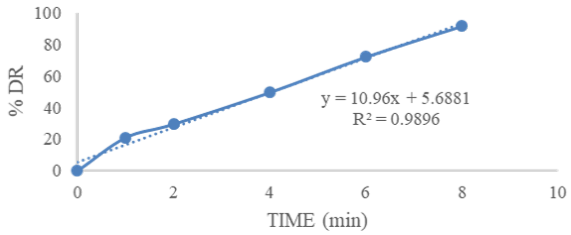

Figure 17: Zero Order Kinetics –SF12

The FT-IR spectrum of the drug and excipients reveals that there was no change in the characteristic peaks, as indicated in Figures 1, 2, 3, 4 and 5 which indicates no drug excipient interaction.

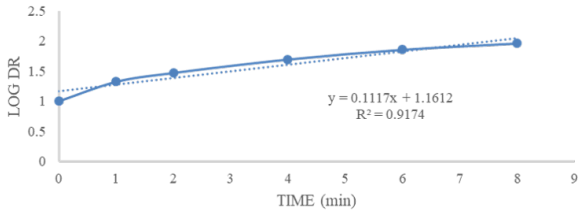

Figure 18: First order Kinetics – SF12

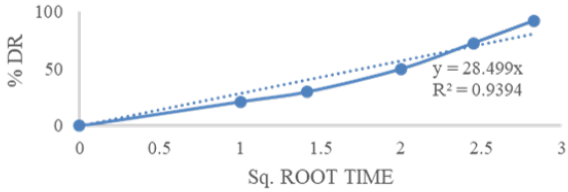

Figure 19: Higuchi Kinetics -SF12

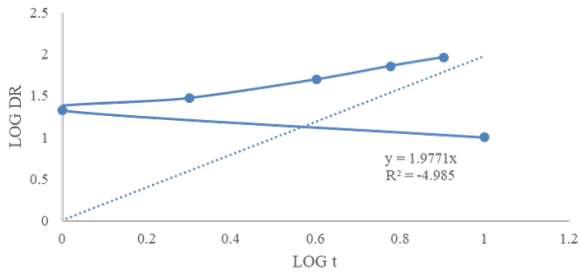

Figure 20: Korsemeyer Peppeas Kinetics- SF12

Twelve blends of the powders meant for compression were prepared using *Araucaria heterophylla* gum, Guar gum and HPMC K4M as retardant and preformulation analysis were done. Angle of repose of all the blends were from 26^{o} to 30^{o} indicating free flowing nature of the blend. All the blended formulations from SF1 to SF12 had hausner ratio and carr's index values of 1.156 to 1.262 and 13.82 to 20.78 respectively represented in Table 2. Thus having good interparticle porosity (Ofori-Kwakye *et al.*, 2010). Colloidal silicon dioxide is used to enhance free flow of the blended powders for direct compression. The versatility of MCC is an automatic choice as a direct compression excipient when it improves the compactability of the compression mix of the matrix tablet formulations (Thoorens *et al.*, 2014).

All the 12 formulation from SF1 to SF12 passed IP uniformity of test for weight variation. Hardness test values indicate tablets to have sufficient mechanical strength and abrasions during handling. The drug content in all the formulations was above 95% indicating proper flow of the blended powders and also uniform filling of the die shown in Table 3.

Table 2: Preformulation studies for Sustained release formulations

Parameter	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9	SF10	SF11	SF12
Bulk Density gm/cc	0.436 ±0.02	0.456 ±0.02	0.512 ±0.01	0.514 ±0.01	0.464 ±0.01	0.512 ±0.01	0.524 ±0.02	0.492 ±0.01	0.454 ±0.02	0.456 ±0.02	0.521 ±01	0.504 ±0.02
Tapped Density gm/cc	0.543 ±0.02	0.555 ±0.02	0.578 ±0.01	0.578 ±0.03	0.543 ±0.04	0.632 ±0.04	0.592 ±0.02	0.562 ±0.03	0.562 ±0.05	0.546 ±0.01	0.598 ±0.01	0.582 ±0.02
Hausner Ratio	1.245 ±0.01	1.217 ±0.05	1.10 ±0.01	1.124 ±0.02	1.170 ±0.01	1.234 ±0.01	1.129 ±0.02	1.142 ±0.01	1.237 ±0.01	1.197 ±0.05	1.147 ±0.04	1.154 ±0.05
Compressibility Index	19.70 ±0.02	17.83 ±0.01	11.41 ±0.01	11.07 ±0.04	14.54 ±0.02	18.98 ±0.04	11.45 ±0.02	12.45 ±0.04	19.21 ±0.03	16.48 ±0.04	12.87 ±0.01	13.40 ±0.04
Angle of repose (ɵ)	28°14′ ±0.122	27°32′ ±0.15	29°56′′ ±0.21	30°14′′ ±0.23	26°21′′ ±0.14	27°14′′ ±0.11	28°18′′ ±0.21	28°32′′ ±0.11	29°23′′ ±0.13	28°28′′ ±0.11	29°18′′ ±0.21	30°44′′ ±0.22

± SD standard deviation n=3

Table 3: Evaluation of Sustain release matrix tablets

S.No	Parameters	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9	SF10	SF11	SF12
1.	Weight Variation in %	1.6% ±0.02	1.8% ±0.12	1.2% ±0.22	1.1% ±0.11	1.2% ±0.23	1.2% ±0.11	2.3% ±0.12	2.2% ±0.11	2.5% ±0.22	1.3% ±0.13	1% ±0.14	1.2% ±0.23
2.	Hardness Kg/cm^2	6 ±0.23	6 ±0.22	6.5 ±0.13	6.5 ±0.11	6.2 ±0.15	6 ±0.11	6.9 ±0.54	6.2 ±0.21	6.5 ±0.33	6.5 ±0.12	6.7 ±0.21	6.6 ±0.22
3.	Drug Content %	98.52 ±0.03	98.32 ±0.12	98.68 ±0.23	96.5 ±0.12	98.4 ±0.25	94.8 ±0.21	99.26 ±0.01	92.21 ±0.01	95.87 ±0.03	95.32 ±0.15	97.52 ±0.23	98.32 ±0.12

± SD standard deviation n=3

Table 4 and Figures 6, 7 and 8 indicates the *in vitro* release profiles of all the 12 formulations SF1 to SF12. Formulation SF1 with 15% and SF2 with 20 % Guar gum could sustain the drug for only 2 and 4 hrs respectively. SF3 with 25% guar gum could extend the release up to 6 Hrs (92.2%) were as SF4 could prolong the release for 8 hrs which was found to be satisfactory for a sustained release matrix tablet. Formulation SF5 with a polymer concentration of 15% of HPMC K4M showed a release of 89.26% within 2hrs and SF6 with HPMC K4M concentration of 20% released 93.2% within 4 hrs. SF7 showed a release of 91.24% after 6 hours and SF8 releasing 86.26 % after 8 hours, indicating the concentration of the polymer was directly proportional to the sustainability of drug release.

Formulation SF9 with 15 % concentration *Araucaria heterophylla* gum showed a drug release of 90.21 % in 2hrs and SF10 with 20% of gum gave 89.28 % release in 4 hrs and SF11 with 25% gum showed 91.21% drug release in 6 hrs. Formulation SF 12 with 30% of *Araucaria heterophylla* gum could sustain the release up to 8 hrs with 91.68 % drug getting released which indicated it was ideal for matrix sustain release tablets.

Cumulative % release decreases with increasing concentration of *Araucaria heterophylla* gum, and the reason could be attributed to the fact that the swelling of the gelled layer from the tablets containing natural polymer. The drug release data were investigated for zero order, first order, Higuchi and Korsmeyer Peppas kinetic models. Regression values indicate Table 5 and Figures 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20 the pattern of drug release form the matrix follows Higuchi models indicating the release was zero-order and diffusion control.

The stability study performed for the formulation

Table 4: In Vitro Dissolution Profile of Sustain Release Matrix Tablet

Time in Hrs	% Drug Release of Guargum				% Drug Release of HPMC				% Drug Release of Gum			
	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9	SF10	SF11	F12
1	72.4 ±0.51	63.28 ±0.87	36.84 ±0.63	17.62 ±0.71	59.26 ±0.33	41.62 ±0.32	20 ±0.39	12 ±0.43	78.69 ±0.41	56.8 ±0.53	44.28 ±0.35	21.08 ±0.54
2	86.78 ±0.72	75.41 ±0.57	48.37 ±0.65	28.02 ±0.91	89.26 ±0.62	58.98 ±0.87	26.8 ±0.29	16.2 ±0.71	90.21 ±0.52	68.22 ±0.62	56.28 ±0.28	29.68 ±0.36
4		92.21 ±0.45	71.61 ±0.53	53.13 ±0.61		93.21 ±0.62	55.0 ±0.43	41.2 ±0.68		89.28 ±0.28	78.26 ±0.62	49.68 ±0.45
6			92.08 ±0.73	74.18 ±0.35			91.2 ±0.33	69.26 ±0.52			91.21 ±0.35	72.16 ±0.67
8				91.26 ±0.41				86.26 ±0.61				91.68 ±0.72

± SD standard deviation n=6

Table 5: Release kinetics for the formulations SF4,SF8 and SF12

Formulation Code	Zero Order Model		First Order Model		Higuchi Model		Korsemeyer Peppa's Model	
	SLOPE	R2	Slope	R2	Slope	R2	Slope	R2
SF4	11.297	0.9913	0.3136	-3.337	28.73	0.932	1.9832	-4.18
SF8	10.866	0.9909	0.3015	-1.911	25.283	0.8447	1.9194	-2.419
SF12	10.96	0.9896	0.1117	0.9174	28.499	0.9394	1.9771	-4.985

Table 6: Stability Studies at 40°C/75 % RH (accelerated condition as per ICH)

S.No	Sample withdrawal	SF12	
		Physical Appearance	Drug content
1.	0 days	No Change	98.32 ± 0.12
2.	180 days	No Change	97.25 ± 0.23

± SD standard deviation n=3

Table 7: In vitro Dissolution results after accelerated stability test

Time in Hrs	SF12 % Drug Release	
	0 days	180 days
0	0.00	0.00
1	21.08±0.54	19.83±0.14
2	29.68±0.36	28.38±1.21
4	49.68±0.45	50.48±1.15
6	72.163±0.67	74.13±1.37
8	91.68±0.72	90.27±1.12

± SD standard deviation n=6

containing gum SF12 for 180 days shown in Tables 6 and 7 indicates that the drug, polymer and excipient are stable and maintain their characters throughout the shelf life. The data clearly reveal that formulation SF12 posses the necessary retardant characters to sustain the release up to 8 hours.

CONCLUSION

Results have shown that *Araucaria heterophylla* gum powder have the requisite physicochemical properties to be used as a direct compression excipient. The gum exhibited swelling and could sustain drug release. It can be explored as a potential hydrophilic carrier in the design of oral controlled drug delivery systems.

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