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Formulation and evaluation of paracetamol suspension by using natural suspending agent extracted from *Pedalium murex* leaves

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Abstract
The present work was aimed to formulate and evaluate a new, cheap and effective natural suspending agent that can be used as an effective alternative for traditional suspending agent. The study procedure involved extraction of suspending agent from the *Pedalium murex* leaves, determination of swelling index, phytochemical testing, Micromeritic properties of mucilage like Bulk density, Tapped density, Carr's index, Angle of repose, Calibration of paracetamol, preparation of paracetamol suspensions and evaluated for P^H determination, determination of sedimentation volume, redispersibility, determination of flow rate, measurement of viscosity, effect of temperature, drug content, particle size determination and *In-vitro* dissolution studies. The study showed that the extraction of suspending agent from *Pedalium murex* leaves. The swelling index was found to be 60% in distilled water, 40% in 0.1N hydrochloric acid and 30% in phosphate buffer pH 7.4. The photochemical test showed contains carbohydrates. As the concentration of suspending agent increases therefore viscosity of suspension increases which ultimately reduces the sedimentation of suspension.

Keywords: *Pedalium murex*, paracetamol, swelling index, phytochemical testing, Micromeritic properties, sedimentation volume

Introduction
Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that are encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Several oral pharmaceuticals, numerous food and beverage products, and bulking agents have unpleasant, bitter tasting components. So, any pharmaceutical formulation with a pleasing taste would definitely be preferred over a competitor's product and would translate into better compliance and therapeutic value for the patient and more business and profits for the company. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability [1]. Suspending agents also called thickening agents are used to stabilize suspensions are hydrophilic colloid i.e., substances that spontaneously from colloidal dispersions with water because of an affinity between the dispersed particles and the dispersion medium [2]. They help in lowering the sedimentation rate of particles in suspension [3, 4].

Rationale of suspending agent selection: Mucilage of *Pedalium murex* leaves can be used as Binding agent, Suspending agent, Thickening agent, Humidifying agent, Disintegrating agent, Gelling agent and Release controlling properties in medicines. In the present study, attempts shall be made to utilize dried powder of *Pedalium murex* leaves mucilage as suspending agent.

Aim
The present work was aimed to formulate and evaluation of paracetamol suspension by using a new, cheap and effective natural suspending agent from *Pedalium murex* leaves.

Objective: The main objective of this extraction of suspending agent from a *Pedalium murex* leaves. Formulation development was done by using this suspending agent in order to optimize the natural suspending agent of *Pedalium murex* leaves.

Materials and Methods

Materials

Paracetamol were obtained from Suvidhinath laboratories, Vadodara, *Pedalium murex* leaves mucilage was isolated product *(Pedalium murex* leaves were collected around the local areas). Glycerin, Sodium benzoate, Sodium saccharine, Sodium Chloride, Sodium metabisulphite and Peppermint oil were obtained from Loba Chemicals PVT. Ltd. Amaranth was obtained from Kemphasol, Bombay. Purified water was produced by Institutional supply.

Extraction of suspending agent from *Pedalium murex* leaves

Initially dried seeds of *Pedalium murex leaves* were crushed and reduced in size using mill. The powdered seeds were soaked in water in the ratio 1:5 for 24 hrs and boiled in water bath for 2hrs. The material was squeezed through muslin cloth to remove the marc from the filtrate. Mucilage was precipitated from water using ethanol. Precipitated mucilage was dried in a vacuum oven at temperature of 45 ºC & passed through sieve no.80. The powdered mucilage was stored in desiccator until further use [15, 17].

Evaluation of extracted powder

1. Determination of Swelling Index.
2. Phytochemical screening of mucilage.
3. Micromeritic properties of mucilage.

a) Bulk density.
b) Tapped density.
c) Carr's Compressibility Index.
d) Angle of repose.

1. Determination of Swelling Index

500 mg of isolated mucilage was taken in a Petri dish and then 10 ml of distilled water was added and the mixture was shaken and allowed to stand for 1 hour. After 1 hour the remaining water in Petri dish was discarded and the weight increase of the isolated mucilage was determined [7].

Swelling Index % (SI) = (W2 – W1/W2) x 100 ---------- (1).

W1= Weight of compact at time '0'
W2= Weight of compact t at time't'

2. Phytochemical screening of mucilage

Preliminary tests were performed to confirm the nature of mucilage obtained. The chemical tests that were conducted are: Molisch's test, Ninhydrin test, Wagner's test, Ruthenium red test, Iodine test, Shinoda test, Keller-Killaini test and Ferric chloride test [7].

3. Micromeritic properties of mucilage

a & b: Bulk density and Tapped density [8, 9]: Loose bulk density and Tapped bulk density was calculated by the following formulae

$$D_b = \frac{\text{Mass of powder}}{\text{Bulk volume of the powder}}$$

$$D_t = \frac{\text{Mass of powder}}{\text{Tapped volume of the powder}}$$

c. Carr's Compressibility Index

% Carr's Index can be calculated by using the following formula

$$Carr's\ index\ (\%) = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

d. Angle of repose

Angle of repose (θ) can be calculated from the following formula

$$\mathbf{Tan\theta = h/r \ \ OR \ \ \theta = \tan^{-1}\frac{h}{r}}$$

H = height of pile and r = radius of the base of pile

Table 1: Physical characterization of the extracted powder

S. No.	Angle of repose	Carr's index	Flow property
1.	25-30	5-12	Free flowing
2.	30-35	12-16	Good
3.	35-40	18-21	Fair
4.	40-55	23-35	Poor
5.	55-65	33-38	Very poor
6.	>65	>40	Extremely poor

Estimation of Paracetamol

Determination of λmax of Paracetamol in Phosphate buffer pH 5.8

Stock solution: Standard stock solution was prepared by dissolving 100 mg drug in pH5.8 and make up with pH 5.8 to get concentration of 100µg/ml.

Method development: From the above stock solution, 1 ml was transferred into a 10 ml volumetric flask and volume was adjusted to 10 ml that corresponded to 100µg/ml solution. From that solution different aliquots of 0.2, 0.4, 0.6, 0.8 and 1 ml were transferred to 10ml volumetric flask, volume was adjusted with pH 5.8 phosphate buffer, which gave a concentration of 2,4,6,8 and 10 µg/ml of the final standard. A standard curve was plotted by taking absorbance of secondary stock solutions in UV double beam spectrophotometer at 257nm.

Formulation development

Design: F_1, F_2, F_3, F_4, F_5 and F_6 were designed to optimize the ratios of paracetamol and banana peel mucilage and to study the effect of mucilage in ratios.

Chemicals used in formulation

Table 2: List of chemicals used in study and their manufacturers

S. No.	Chemicals	Manufacturer	Purpose
1.	Paracetamol	Suvidhinath laboratories, Vadodara	API
2.	*Pedalium murex* leaves mucilage	Isolated product	Suspending agent
3.	Glycerin	LOBA Chemicals PVT. ltd	Protect API from natural suspending agent
4.	Sodium Benzoate	LOBA Chemicals PVT. ltd	preservative
5.	Sodium saccharine	LOBA Chemicals PVT. ltd	Sweetening agent
6.	Sodium chloride	LOBA Chemicals PVT. ltd	Flocculating agent
7.	Peppermint oil	LOBA Chemicals PVT. ltd	Flavoring agent
8.	Amaranth	Kemphasol, Bombay	Coloring agent
9.	Purified water	Institutional supply	Solvent

API- Active Pharmaceutical Ingredient

Equipments used in formulation

Table 3: List of instruments used in study and their manufacturers

S. No.	Equipment	Manufacturer
1.	Electronic balance	Shimadzu, Mumbai.
2.	Mechanical sieve shaker	Darwin, Vijayawada
3.	Tap density tester	Delta, Vijayawada
4.	Dissolution apparatus USP2	Lab India DS 8000, Mumbai
5.	Hot air oven	KEMI, Ernakulam, Kerala
6.	U.V Spectrophotometer	Shimadzu, Mumbai.
7.	P^H meter	Darwin, Vijayawada
8.	Ostwald viscometer	Darwin, Vijayawada
9.	Brookfield's viscometer	Asian Scientific Instruments, Hyderabad
10.	Microscope	Magnus Analytics, New Delhi

Formulation of suspension

Formulation Suspension was prepared as per formula given in table 2. Extracted *Pedalium murex* leaves powder was taken in mortar to which sodium benzoate & sodium chloride was added and triturated for some time along with water to make paste. In beaker paracetmol was mixed well with glycerin. This mixture was further added to the above paste and triturated for 20 min. Then colouring agent i.e. Amaranth and flavouring agent i.e. Peppermint oil were added mixed well in suspension. Volume made up with water up to 10 ml and further homogenized of suspension.

Optimization of formulation ingredients in preparation

Table 4: Optimization of formulation ingredients

S. No.	Ingredients	F_1	F_2	F_3	F_4	F_5	F_6
1.	Paracetmol (g)	0.5	0.5	0.5	0.5	0.5	0.5
2.	*Pedalium murex* leaves mucilage (g)	0	0.05	0.1	0.2	0.3	0.4
3.	Glycerin (ml)	1	1	1	1	1	1
4.	Sodium Benzoate(g)	0.2	0.2	0.2	0.2	0.2	0.2
5.	Sodium chloride (g)	0.2	0.2	0.2	0.2	0.2	0.2
6.	Sodium saccharine (g)	0.03	0.03	0.03	0.03	0.03	0.03
7.	Peppermint oil (ml)	0.2	0.2	0.2	0.2	0.2	0.2
8.	Amaranth (g)	0.002	0.002	0.002	0.002	0.002	0.002
9.	Purified water (m1)	10	10	10	10	10	10

Characterization of formulated suspensions [8, 9]

i. pH determination of suspension

The pH of all developed formulations was measured using digital pH meter.

ii. Sedimentation volume

Sedimentation volume is determined by following equation,

$$F = Hu\ Ho$$

Where, Hu is ultimate or final height of sediment as suspension settles,
Ho is original height of suspension.

iii. Particle size measurement: Particle size determination is carried out by optical microscopy method using motic microscope. Suspension was spread on slide & observed under microscope. Diameters of 50 particles were measured.

iv. Degree of flocculation

Degree of flocculation (β) was determined using following equation.
Where, (Vu)floc is ultimate sedimentation volume in flocculated suspension and (Vu)defloc is ultimate sedimentation volume in deflocculated suspension.

$$\beta = (Vu)\ foc\ (Vu)floc$$

v. Flow rate (F): The time taken for 10ml sample of suspension to flow through a 10ml pipette was determined and the flow rate calculated using the following equation:

$$F = Volume\ of\ pipette\ (ml)/Flow\ time\ (sec)$$

vi. Redispersibility
Fixed volume of each suspension (50 ml) was kept in calibrated tubes which were stored at room temperature for various time intervals (5, 15, 25 days). At regular interval one tube was removed and shaken vigorously to redistribute the sediment and the presence of deposit if any was recorded.

vii. Drug content
5 ml of suspension (250mg/ml) was accurately measured and transferred into 100 ml volumetric flask. And volume made up with P^H 5.8. Further from above suspension 1 ml was withdrawn and added to 10 ml flask, volume made with P^H 5.8. Absorbance was measured using UV-Visible double beam spectrophotometer at λ max 257 nm. Drug content was calculated by comparing the absorbance with standard curve.

viii. Determination of viscosity
The viscosity of suspension samples was determined using the Brookfield viscometer at 100 rpm. All determinations were carried out in at least triplicates and results obtained were expressed as the mean values.

ix. Effect of temperature
Further, the effect of the temperature (30 °C to 60 °C) was investigated on the viscosity of the suspension of all formulations.

x. *In vitro* dissolution studies
Dissolution study of formulated suspensions was carried out in USP type II dissolution test apparatus in 500 ml of water for 30 min (37 ± 0.5 °C and 25rpm). USP type II dissolution test apparatus although mainly designed for tablets and capsules, this apparatus has also been used by several investigators to study the dissolution behaviour of suspensions. [31]
5 ml suspension was introduced carefully into the bottom of the apparatus. 5 ml aliquots were withdrawn at interval of 5 min for analysis and replenished by equivalent amount of blank. The aliquots were filtered through Whatman filter paper and further analyzed at respective wavelength by double beam UV visible spectrophotometer.
To study the drug release kinetics, the data obtained from *in vitro* drug release studies were plotted in various kinetic models such as a first order equation.

First order kinetics: To study the first order release kinetics the release data was fitted into the following equation.

$$DQ/d_t = K_1Q$$

Where Q is amount of drug unreleased
K_1 is first order release rate constant
t is release time
The graph is plotted percentage log% cumulative drug unreleased v/s time

Results and Discussion

Evaluation of extracted powder

Determination of swelling index

Results

Swelling index of *Pedalium murex* leaves mucilage was found to be 60% in distilled water, 40% in 0.1N hydrochloric acid and 30% in phosphate buffer pH 7.4 at end of 1hrs.

Discussion

Result shows that the swelling index was found to be increased with time. Swelling index was increased, because weight gain by mucilage was proportional to rate of hydration. The direct relationship was observed between swelling index and mucilage concentration. As the mucilage concentration increases swelling index increases.

Phytochemical screening of mucilage

Table 5: Phytochemical screening of mucilage

S. No.	Identification test	Name of the test	Observation
1.	Test for carbohydrates	Molisch's test	Positive
2.	Test for proteins	Ninhydrin test	Negative
3.	Test for alkaloids	Wagner's test	Negative
4.	Test for mucilage	Ruthenium red test	Positive
5.	Test for starch	Iodine test	Negative
6.	Test for flavonoids	Shinoda test	Negative
7.	Test for glycosides	Keller Killani test	Negative
8.	Test for tannins	Ferric chloride test	Negative

Discussion: phytochemical test carries out on *Pedalium murex* leaves mucilage confirmed the absence of alkaloids, glycosides, starch and tannins. Treatment of mucilage with ruthenium red showed red coloration confirms the obtained product as mucilage. A violet ring was formed at the junction of two liquids on reaction with Molisch's reagent indicates presence of carbohydrates. The results are shown in Table. 5.

Micromeritic properties of mucilage

Table 6: Micromeritic properties of mucilage

S. No.	Parameters	Valve
1.	Bulk density	0.46g\ml
2.	Tapped density	0.51g\ml
3.	Carr's compressibility index	9.80
4.	Angle of repose	13.65

Discussion: from the above table values of Angle of repose and Carr's compressibility index showed that mucilage powder has excellent flow properties. The results are shown in Table. 6.

Standard curve of paracetamol

Table 7: Series of concentrations and their absorbance

Concentration (µg/ml)	Absorbance
0	0
2	0.163
4	0.308
6	0.464
8	0.597
10	0.755

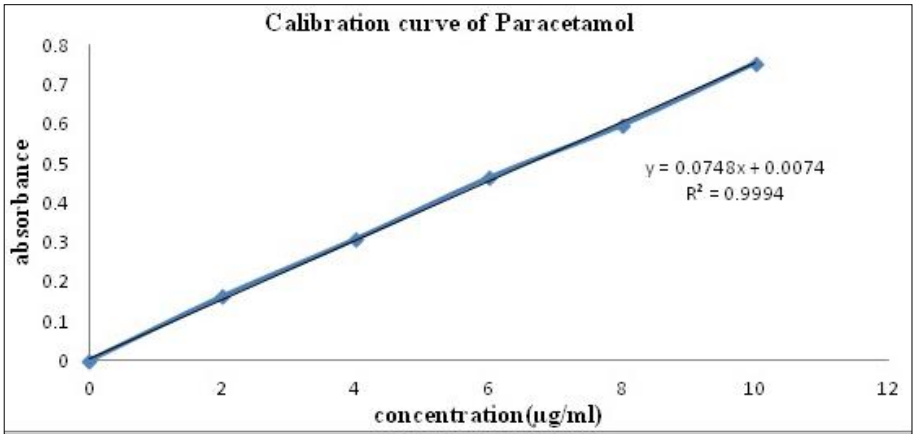

Fig 1: Calibration curve of Paracetamol

Discussion

Based on above results, it has been inferred that API shows linearity in concentration range of 2-10µg/ml. the regression coefficient of calibration curve was found to be 0.999. The linearity results were shown in Table. 7 and calibration curve were shown in Fig. 1.

Evaluation of formulated suspensions

i. pH

Table 8: pH values data for F_1, F_2, F_3, F_4, F_5 and F_6

pH	Formulations					
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**
0^{th} day	9.0	8.80	8.55	8.18	7.68	7.46
7^{th} day	8.94	8.73	8.48	8.02	7.58	7.28
14^{th} day	8.88	8.67	8.36	7.58	7.45	7.20
21^{st} day	8.82	8.58	8.20	7.28	7.31	7.10

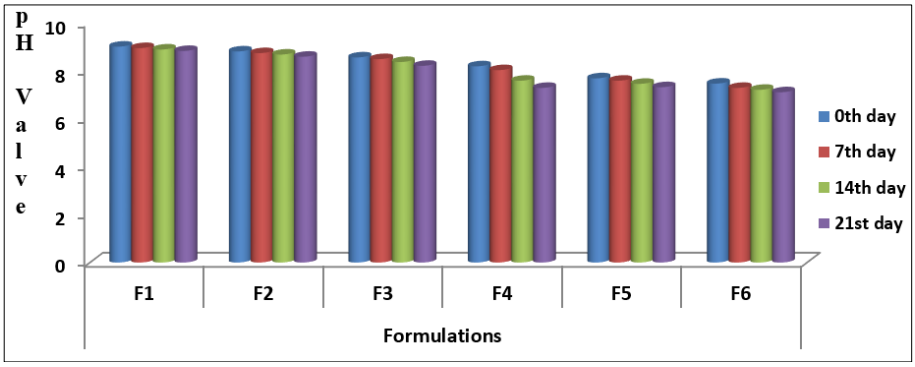

Fig 2: Comparative profiles of pH values of all formulations

Discussion

pH of all formulation was found to be in the range of 9.0 to 7.10 values shown in the table 8. comparative profiles of pH of all batches is given in Fig. 2. pH values of F_5 and F_6 formulations are near to 7 hence these formulations are considered as stable formulations.

ii. Sedimentation volume

Table 9: Sedimentation volume values % for F_1, F_2, F_3, F_4, F_5 and F_6

S. No.	Time (Mins)	F_1	F_2	F_3	F_4	F_5	F_6
1.	0	100	100	100	100	100	100
2.	5	24	90	96	97	99	99
3.	10	24	86	93	95	99	99
4.	15	24	80	91	93	98	98
5.	20	24	75	88	91	97	98
6.	25	24	69	86	89	96	98
7.	30	24	63	83	88	96	97

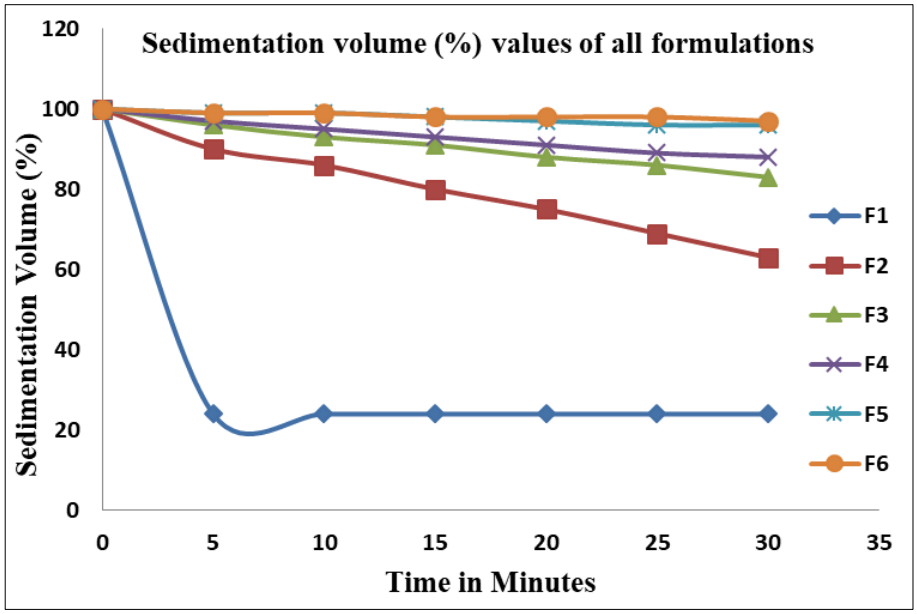

Fig 3: Comparative profiles of sedimentation volume of all formulations

Discussion

From the Table. 9 sedimentation volumes were found to be decreased at the end of 30mins. Result of values of Sedimentation Volume is reported in graphs shown in Fig.3. Batch F_6, was found to be stable and dispersed at the end of 30mins. The dispersed particle were sediment at faster rate in suspension containing lower concentration of suspending agent compared to containing higher amount.

Table 10: Evaluation of suspension for F_1, F_2, F_3, F_4, F_5 and F_6

Formula	Particle size (µm)	Degree of flocculation	Flow Rate	Re-dispersibility	Drug content (%)	Viscosity
F_1	68.2	0.24	3	15	98.09	0.55
F_2	71.2	0.75	1.0	8	98.8	0.90
F_3	65.8	0.83	0.97	6	97.96	1.00
F_4	66.5	0.88	0.84	5	98.36	1.10
F_5	64.5	0.96	0.73	4	98.97	1.20
F_6	67.2	0.97	0.61	4	99.12	1.45

Discussion

iii. Particle size (µm): Particle size of 50 particles of all formulated suspensions was determined and valves are reported. Which is acceptable and within limits. The results are shown in Table. 10.

iv. Degree of flocculation: Degree of flocculation was determined for all formulation suspensions using different concentration of *Pedalium murex* leaves mucilage. The values of degree of flocculation for all formulated suspension have been shown in Table. 10 were found to be increased at higher concentration of suspending agent, due to higher viscosity of suspension at higher concentration which ultimately reduces the sedimentation of suspension.

v. Flow rate: Flow rate was found to be decreased as concentration of suspending agent and viscosity of suspension increased found in the range of 3 to 0.61. The results are shown in Table. 10.

vi. Redispersibility: Since the suspension sediment on storage it must be readily dispersible so as to ensure a more uniform dosage administration of medicament after shaking. All the suspension was found to be easily redispersible after maximum 4 shakings after 25 days. Redispersibility was found to be faster for suspension with higher amount of suspending agent comparing to without suspending agent (Due to formation of hard cake). The results are shown in Table. 10.

vii. Drug content (%): Drug content for all formulations was found to be in the range of 98.09 to 99.12%. The results are shown in Table. 10.

viii. Viscosity (poise): Viscosity was found to be increased as concentration of suspending agent increased. It found in the range of 0.55 to 1.45.

ix. Effect of temperature: Viscosity was decreases with increase in temperature. The results are shown in Table. 10.

***x. In vitro* dissolution**

Table 11: Dissolution data for F_1, F_2, F_3, F_4, F_5 and F_6

S. No.	Time	F_1	F_2	F_3	F_4	F_5	F_6
1.	0	0	0	0	0	0	0
2.	5	60	58	58	56	58	58
3.	10	65	60	60	65	68	68
4.	15	66	68	68	73	78	76
5.	20	70	76	68	78	86	84
6.	25	82	86	80	80	90	92
7.	30	90	90	92	92	98	99

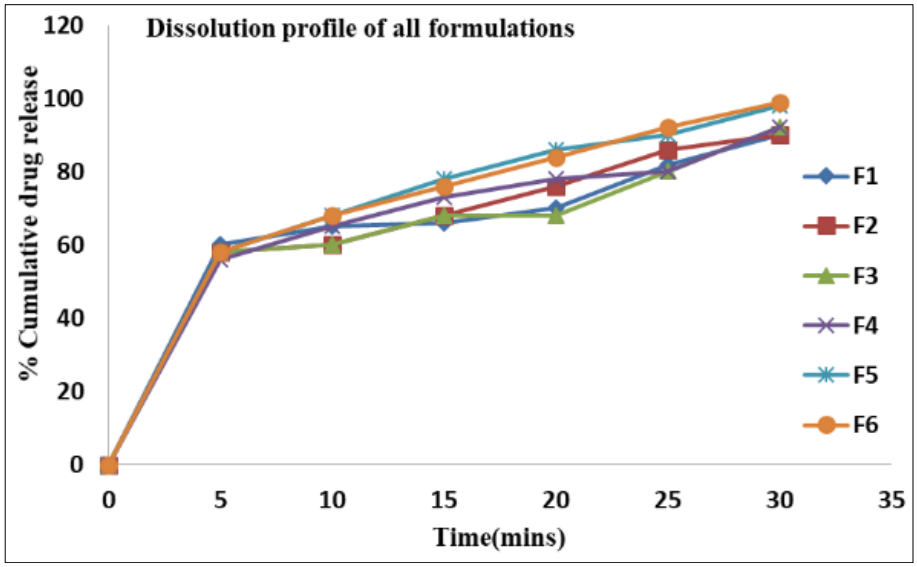

Fig 4: Comparative dissolution profile for F_1, F_2, F_3, F_4, F_5 and F_6

Discussion: Results shows that all formulations drug release was almost 90 to 99% at the end of 30 min. The results are shown in Table. 11 & the graph shown in the Fig. 4.

xi. Release order Kinetics

For most of the batches, the release kinetics of paracetamol suspensions appeared to follow first order release kinetics.

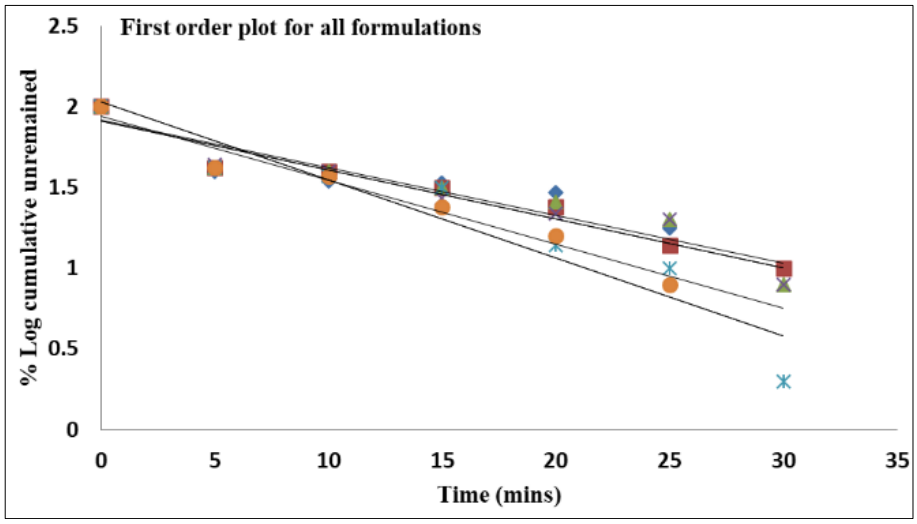

Fig 5: First order kinetics for dissolution profiles

Table 12: Regression co-efficient (R^2) values for F_1, F_2, F_3, F_4, F_5 and F_6

Formulation	F_1	F_2	F_3	F_4	F_5	F_6
R^2 Valve	0.90	0.94	0.86	0.91	0.90	0.963

Discussion

From the Table.12 & Fig 5 regression value was closer to unity in case of first order hence, release is apparently first order. As clearly indicated the release of the drug followed first order release kinetics and regression value indicates fair of linearity in the data. This shows that the release is dependent on the concentration of drug.

Conclusion

We can conclude that this formulation development was used to optimize the natural suspending agent of *Pedalium murex* leaves mucilage. The result generated in this study showed that all the evaluation values and were optimized formulation according to the pH, Sedimentation volume, Flow rate, Redispersibility, Drug content, Viscosity, Dissolution studies and First order kinetics. As the concentration of suspending agent increases viscosity of suspension increases this ultimately reduces the sedimentation volume of suspension.

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