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Research article

Evaluation & formulation of paracetamol matrix sustained release tablets using natural polymers

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Key words: Sustained release, matrix tablets, acacia, gelatin, and Tragacanth.

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Abstract

Objectives: To prepare tablets by direct compression method using natural gums such as acacia (F1, F2 and F3), gelatin (F4, F5 and F6) and tragacanth (F7, F8 and F9) at different concentrations. To assess the flow properties of the powder blend (polymers mixed with the drug). To evaluate physical properties of the polymer matrix based tablets for weight variation, hardness, friability, thickness, drug content uniformity, disintegration time, swelling index and in-vitro drug release. To perform stability studies for the optimized formula. **Method:** In the current investigation, an attempt was done to formulate sustained release matrix tablets using natural polymers, acacia, gelatin and tragacanth as release modifier. Paracetamol was used as a model drug. The different ratios used drug: Lactose: polymer were 100: 200: 50, 100: 150: 100 and 100: 100: 150 for acacia, gelatin and tragacanth respectively. Tablets were prepared by direct compression and evaluated by powder characterization, tablets physical properties, in-vitro release. The optimized formulation was subjected to stability studies for two months as per ICH guidelines. **Results:** Results showed good flowability and compressibility properties for all formulae. Physical properties of the tablets showed increase in polymer ratio there was decrease in friability but increase in hardness in all formulations. In-vitro release formulation F6 was optimized and selected for stability studies. Stability studies showed no significant changes in the formulation. **Conclusion:** The study concluded that uses of natural polymers especially acacia gum, are effective producing safe, cheap effective stable sustained release tablets.

Introduction

The basic goal of sustained release therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time, in order to reduce administration frequency and increase patient compliance [1] using natural, safe polymers such as acacia, gelatin and tragacanth. Chemical structures are shown in figure 1. The chemical structures of the natural polymers used as release modifier is beneficial in safety and cost effective [2].

Experimental

Preparation of PSR calibration curve

Process Standard Rotogravure (PSR) calibration curve was obtained from serial dilutions of PSR stock solution (x mg/mL) in 0.1N HCl: phosphate buffer (pH 7.4) [3]. The prepared samples were analyzed by Ultra Violet spectrophotometer (NMB-6200, USA) at 257 nm, Figure 2. The curve was obtained by plotting the absorbance determined as a mean of triplicate measurements against R^2 value. Microsoft Excel sheet 2007 was used to attain the best line regression analysis and the amount of PSR released with time in phosphate buffer was determined from the regression equation generated from the calibration curve. R^2 value indicates that PSR calibration curve obeys Beer's law within the range of concentrations used, as shown in table 1 and Figure 2 [4].

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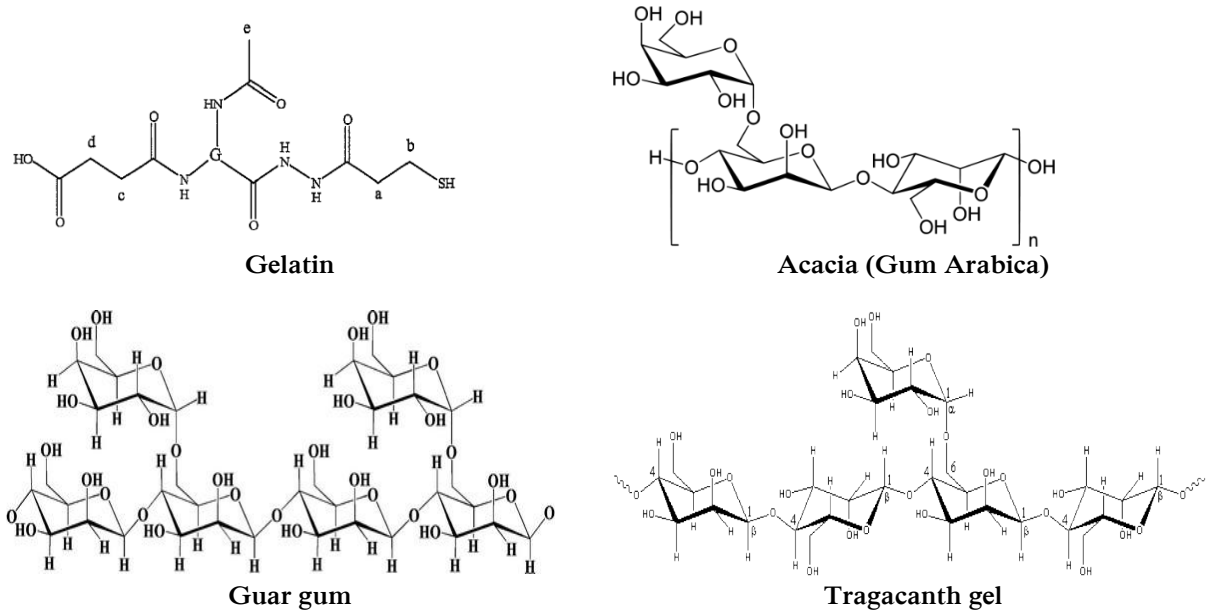


Figure 1. The chemical structures of the natural polymers used as release modifier is beneficial in safety and cost effective

Table 1. The absorbance of the PSR standard curve at 257 Nm in a different concentration

Concentration (mg / mL)	Absorbance (mAU)
0	0
0.002	0.15
0.004	0.29
0.006	0.44
0.008	0.59

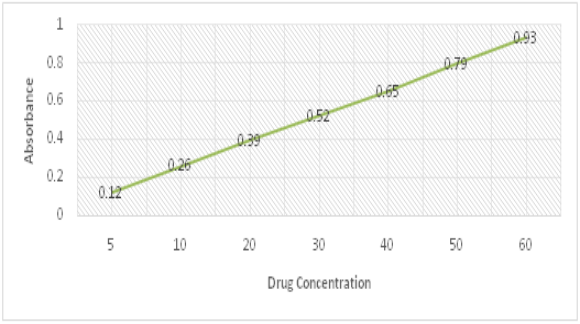


Figure 2. The Calibration curve of Paracetamol absorbance values in different concentrations at Buffer pH 7.4.

Table 2. The Equations of the measurements of flowability and density

Equation	Equation No.
Bulk density (pb) = Weight/Bulk volume	1
Tapped density (pt) = Weight/Tapped volume	2
Carr's Index = [(pt - pb)/pt] × 100	3
Hausner ratio = (pt/pb)	4
Compressibility Index= V 0 - V t /V 0 × 100 Where, V t is the tap volume and V 0 is the bulk volume.	5
Angle of repose (θ) = Tan-1(h/r)	6

Physical Characterization [5]

Measurement of flow ability and density

The loose bulk density and tapped bulk densities can be determined by using a density measuring apparatus, which is density meter DDM2909. An amount of the sample (5 g) is placed in a measuring cylinder and the volume (bulk volume) is measured after applying three taps. Tapped density is measured by transferring (20 g) of the material to a 100-ml graduated cylinder. The unsettled apparent volume is noted. The cylinder is tapped at a rate of 300 drops/min over a fixed drop distance of 14 ± 2 mm. After the first 500 drops, the volume of the material in the cylinder is measured. Further tapping (750 and then 1250 drops successively) is applied until the difference between two volumes following successive tapping is less than 2.0%. This final volume is taken as the tapped volume. Bulk/tapped densities, Carr's index (%), and Hausner ratio are calculated as in Equations 2 to 6.

Hausner ratio is the ratio of tapped density to bulk density, and varies from about 1.2 for a free-flowing powder to 1.6 for cohesive powders. The percentage compressibility, also called as Carr's index, is 100 times the ratio of the difference between tapped density and bulk density to the tapped density. Values of Carr's index of about 5 to 12% indicate free-flowing powder, 23 to 35% indicate poor flow, and >40% an extremely poor flow. Value of compressibility index below 15% indicates good flow properties, but values above 25% mean poor flow [6].

The increase in bulk density of a powder is related to its cohesiveness. Bulk density and tapped density relationship is another way to index flowability. Angle of

repose of the test materials can be assessed by the fixed funnel method and computed as in equation. Powders are classified as "light" or "heavy." Light powders have high bulk volume. Fines (up to 15%) increase angle of repose. Rough and irregular surface increases angle of repose. Lower the angle of repose better is the flow property. Angle of repose is commonly used to measure flow of powders, and is the maximum angle q between the plane of powder and horizontal surface. The value of q less than 30° usually indicates free-flowing material, up to 40° indicates reasonable flow potential, and above 50° indicates the power flows with great difficulty [7].

Measurement of Angle of Repose

Theory background

Angle of repose was determined to study the flowability of solid dispersion matrix particles comparing to the raw materials and their physical mixtures [8].

If the angle exceeds 50°, the material has unsatisfactory flow properties, whereas materials having values near the minimum (< 25°) will flow easily and properly. The cohesive and more irregular the particles, the higher is the angle of repose. The angle of repose was measured by passing approximately 10g of solid powders through a glass funnel of internal diameter 1.5 cm on the horizontal surface. The height (h) of the heap formed and the radius (r) of the cone base were determined, and then angle of repose (Φ) was calculated from Eq. 3

Φ = anti tan (h/r)……(Eq. 3)

Requirements: Funnels, Petri dishes, Rulers, Stands, Analytical balance

Method [9]

Sieve the material if gritty particles and clumps are included. Pour the sample in a regular way-through the funnel on to the slab. Mark the periphery of the base after completion of the formation of the cone (fixed height).Determine the mean diameter and mean radius. Calculate Θ. Θ = anti tan (h/r). Tabulate and discuss your results.

Determination of Powders Compressibility

A fixed weight of the samples (50mg) was gently poured into a graduated cylinder and the initial volume (Vo) of the powders was measured. Then the cylinder was tapped on density tester (Copley JV2000, U.K.) and the final volume (VF) was recorded after 200 taps. The data obtained were used to calculate powders' bulk density (Do) and tapped density (DF), to predict samples' porosity (p) and flowability depending on the value of percent compressibility (% C). Lower values of % C (<15) represent freely flowable powder [10]. Calculation was done according to the equations below:

(p) = (Vo-VF)/Vo X 100

% C = DF-Do/ DF X100

Determination of Powders Flowability

Theory background [11]

In order to find out the powders flowability we need to calculate the following:

Poured Density: (free settle density, initial density)

Do= M/ Vo, where Do is initial density, M is mass and Vo is initial volume.

Tapped Density: (final density)

DF= M/ VF, where DF is final density, M is mass and VF is final volume.

Porosity (p)

(p) = voids X 100,

Voids = (Vo-VF)/Vo

(p) = (Vo-VF)/Vo X 100

Hausner Ratio (HR) measurements:

HR = DF/Do

%Compressibility (% C) measurements:

% C = DF-D0/ DF X100

Methods

Sieve the samples if gritty particles and clumps are included. Weigh the measuring cylinder when it is empty first, and then pour the sample in a regular way through the funnel into the cylinder, then weigh it to determine the weight of the powder & record the initial volume. Tap the cylinder on a densitometer till constant volume achieved and record the final volume. Calculate the poured, tapped densities and porosity. Find out the flowability by calculating the % compressibility and Hausner ratio & compare between your formulas.

Preparation of paracetamol SR tablets

Sustained release tablets each containing 100 mg Paracetamol were prepared by direct compression technique using different polymers at various concentrations (50, 100, 150 mg) will be accurately weighed and passed through sieve no. 45. The content was mixed thoroughly in a mixer for 10 minutes. The lubricant and glidants were added to the above mixture and again mixed for 5 minutes. Then the mixture was directly compressed on a Rotary Tablet Machine (single punch) equipped with an 8 mm standard flat faced punch and die set. The compositions of different tablet formulations are shown in Table 3 [12].

Table 3. Composition of SR paracetamol formulations

Ingredient	Formulation Codes								
Weight in (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Paracetamol	100	100	100	100	100	100	100	100	100
Lactose	200	150	100	200	150	100	200	150	100
Acacia	50	100	150	…	…	…	…	…	…
Gelatin	…	…	…	50	100	150	…	…	…
Tragacanth	…	…	…	…	…	…	50	100	150
Lactose	200	150	100	200	150	100	200	150	100
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	351	351	351	351	351	351	351	351	351

Physicochemical Characterization

Thickness

Thickness of tablets was important for uniformity of tablet size. The thickness of the tablet was measured by using digital vernier caliper, twenty tablets from each batch were randomly selected and thickness was measured [13].

Weight variation

Twenty tablets were randomly selected from each batch individually weigh, the average weight and standard deviation of 20 tablet calculated.

Hardness

Hardness was measured using hardness tester, for each batch three tablet were tested.

Friability

Twenty tablets were weighed and placed in the Roche Friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dusted weight.

% loss= (initial wt. of tablets – final wt. of tablets /initial wt. of tablet) x 100 [14].

Drug Content Uniformity

From each batch of prepared tablets, ten tablets will be collected randomly and powdered. The powder equivalent to 10 mg of paracetamol will be transferred in to 10 ml of volumetric flask to this 5 ml of methanol was added and then the solution will be subjected to sonication for about 10 min. The solution was made up to the mark with methanol. The solution will be filtered and suitable dilutions will be prepared with pH 7.4 buffer. Same concentration of the standard solution was prepared.The drug content was estimated by recording the absorbance at 257 nm by using UV-Visible spectrophotometer [15].

Disintegration Test

The disintegration time is determined by using disintegration apparatus. Randomly select 6 tablets and Place them in the disintegration basket containing 900ml of phosphate buffer pH 7.8, maintaining the temperature at 37±2^{0}C as this is the required temperature per monograph to run disintegration test. Note the time taken for complete disintegrate in to small particles. Perform the test in triplicate and note down the average time taken by the tablets for disintegration [16].

Swelling Behavior of Sustained Release Matrix Tablets

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all formulation was studied. One tablet from each formulation was kept in a petri dish containing pH 7.4 phosphate buffer. At the end of 0.5 h and 1 h, the tablet was withdrawn, soaked with tissue paper, and weighed. Then for every 1 h, weights of the tablet were noted, and the process was continued till the end of 8 h. Percentage weight gain by the tablet was calculated by formula; [15,16].

S.I = {(Mt-Mo) / Mo} X 100
Where, S.I = swelling index, Mt = weight of tablet at time t (h) and Mo = weight of tablet at zero time

In vitro Paracetamol SR dissolution testing [13]

The in vitro dissolution study was carried out using USP dissolution apparatus Type II (Copley, UK). The dissolution medium was 900 ml of 0.1 N HCl. The dissolution vessel was maintained at 37±0.50^{0}C with 750ml , being stirred at 50 rpm during the first 2 hours, then 242 ml of 0.2 M Na_3PO_4(tri-sodium phosphate) was added, and adjusted to pH 7.4 by 6 N NaOH. Samples were filtered through filter paper (0.70 µm), and collected at predetermined time intervals for 12 h dissolution studies. Filtered solutions were centrifuged at 3000 rpm for 10 minutes, supernatants were filtered again through 0.45 µm membrane and measure paracetamol absorbance at 257 nm. Dissolution drug concentrations were determined via standard curves (Figures 3, 4, 5 and 6) in each medium and converted to percentage drug released. Average drug released and their standard deviations were calculated from three replications in all dissolution experiments. Paracetamol dissolution profiles are

presented as percent drug release versus time curves. The dissolution media used in the study was phosphate buffer (pH 7.4). Filtered samples were withdrawn at certain time intervals and replaced with equal volume of fresh medium. The quantity of PSR was assayed by Ultra Violet spectrophotometer (NMB-6200, USA) at 257nm [17].

Stability Study

The stability studies were carried out for the optimized satisfactory formulation as per ICH guidelines. The most satisfactory formulation sealed in aluminum packaging and kept in humidity chamber will be maintained at 30±2°C / 65±5% RH for two months. At the end of studies, samples will be analyzed for the drug content, in vitro dissolution sustained behavior.

Results & Discussion

Statistical treatment of data was done accordingly. The powder characterization was determined by calculating the flow properties of different formula blend (Table 4). While the physical characterization were evaluated and the data is summarized in the table 5. The Disintegration and dissolution of the polymers for all formula were summarized in table 7. Finally, the In vitro dissolution profiles of different formulations containing paracetamol sustained release matrix tablets, In vitro dissolution study was carried out in 0.1 N HCL (pH 1.2) for first 2 hr and then phosphate buffer (pH 6.8) for 10 hr of formulations (F1- F9) were plotted in figure 7.

Table 4. Flow properties of different formula blend

Formula code	Bulk density g/cm³	Tap density g/cm³	Hausner ratio	CI (%)	Angle of repose
F1	0.45±0.01	0.51±0.02	1.11 ±0.06	11.02±3.5	28.31±1.43
F2	0.45±0.01	0.52±0.02	1.124±0.04	13.09±1.34	27.95±1.07
F3	0.46±0.00	0.52±0.01	1.115±0.02	14.4±1.27	28.25±2.47
F4	0.44±0.03	0.54±0.03	1.095±0.04	12.00±0.7	27.45±0.07
F5	0.45±0.01	0.52±0.01	1.105±0.03	10.00±3.11	29.3±0.98
F6	0.45±0.00	0.52±0.01	1.1±0.00	12.45±3.74	27.75±1.48
F7	0.46±0.01	0.49±0.01	1.085±0.03	10.85±1.2	29.8±0.28
F8	0.45±0.01	0.53±0.03	1.15±0.00	14.1±0.56	27.1 ±1.69
F9	0.45±0.01	0.51±0.01	1.13±0.00	11.75±0.35	27.95±1.62

Table 5. Physical properties of the tablets

polymers	Formula code	Polym. Conc (w/w)	Average wt. of tablet (gm)	Thickness (mm)	Hardness (N)	Friability (%)
Acacia	F1	50	0.350 + 0.014	4.20	5.44 + 0.109	0.77 + o.o2
Gelatin	F2	50	0. 350 + 0.015	4.00	4.29 + o.o67	0.77 + o.11
Tragacanth	F3	50	0350 + 0.015	4.16	5.32 + o.218	0.81 + o.o3
Acacia	F4	100	0. 349 +0.018	4.20	5.55 + 0.147	0.68 + o.o1
Gelatin	F5	100	0. 350 +0.015	4.10	5.08 + o.o86	0.82 + o.86
Tragacanth	F6	100	0. 351 +0.015	4.10	5.62 + o.165	0.71 + o.o2
Acacia	F7	150	0. 350 +0.014	4.10	5.8 + 0.12	0.64 + o.03
Gelatin	F8	150	0. 350+0.014	4.20	5.6 + o.102	0.74 + o.03
Tragacanth	F9	150	0. 351 +0.014	4.00	5.72 + o.165	0.69 + o.o4

Table 7. Disintegration and dissolution for all formula

Polymers	Disintegration Time (Min.)	Dissolution (% C.R.)
Acacia	13.36 ±0.577	91.66 ± o.215
Gelatin	10.55 ±0.360	96.85 ± o.482
Tragacanth	10.46 ± 0.606	95.35 ± o.665
Acacia	15.56 ±0.750	78.58 ± o.665
Gelatin	13.38 ±0.175	83.92± o.58
Tragacanth	14.52±0.612	81.16± 2.394
Acacia	17.34±0.209	62.76± o.770
Gelatin	15.01+ 0.407	75.03± 0.150
Tragacanth	16.58±0.369	70.98± 1.128

Dissolution was performed at 7.4 pH for 10 hr.
S.D: standard deviation (n=3), (% C.R.)= cumulative release

Table 11. Percentage of drug released (After X H)

Code	Assay (%)	% of Drug Released (After X H)				
		(After 2 h)	(After 4 h)	(After 8 h)	(After 16 h)	(After 24 h)
F3	97.5+0.35	23	49	76	88	82
F2	99.1+0.39	16	27	30	62	96
F1	100.7+0.43	18	23	56	78	98
F4	98.33+0.50	12	22	32	67	88
F5	99.06+0.49	22	42	72	86	96
F6	99.05+0.33	40	66	78	89	97
F7	99.75+0.28	22	40	59	70	89
F8	100.89+0.44	20	34	50	60	92
F9	97.31+0.25	12	26	46	66	94

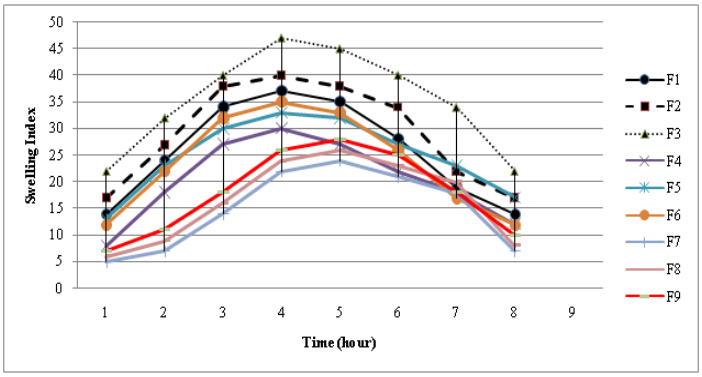


Figure 3. Swelling index profile of tablets containing acacia gum polymer.

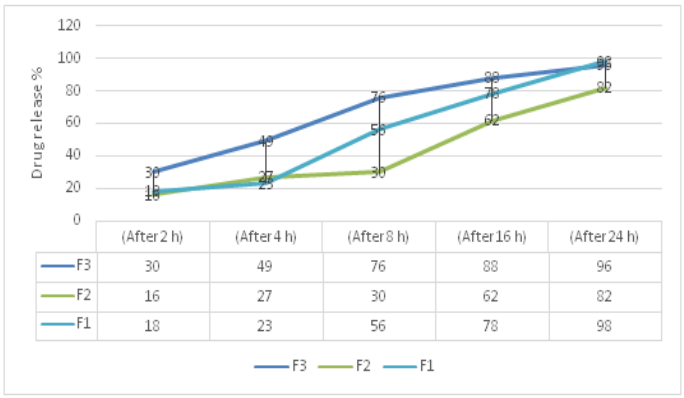


Figure 4. Drug release profile of PSR tablets containing acacia gum polymer.

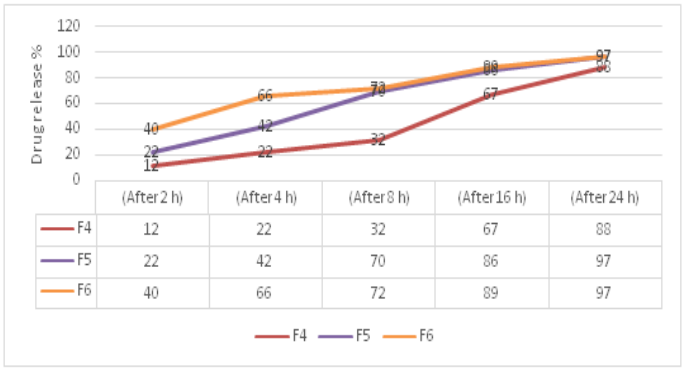


Figure 5. Drug release profile of PSR tablets containing gelatin polymer.

Powder Characterization

Evaluation of Physical Characterization

All powder blends and Tablets of all formulations were subjected to various powder characterization and physicochemical evaluation parameters such as flowability and compressibility and weight variation, thickness, diameter, hardness, friability, disintegration and drug content. The results of these studies were given in Table 4, 5, and 6.

As per the Tables 4, 5, and 6 the powder blend of all formulae are within acceptable limits of flowability and compressibility. Also, the formulated matrix tablets met the pharmacopoeial requirement of uniformity of weight and confirmed to the requirement of assay, as per USP. Hardness, percentage friability and thickness were all within acceptable limits [16,18].

It has been observed that an increase in the concentration of the polymers from 50, 100 to 150 mg effectively increase the binding characteristic of the tablets. Therefore, all the formulations showed increase in the hardness and disintegration time with decrease in the friability by as polymer concentration increases. That indicated that the binding capacity of the tablet is directly proportional to the concentration of polymers.

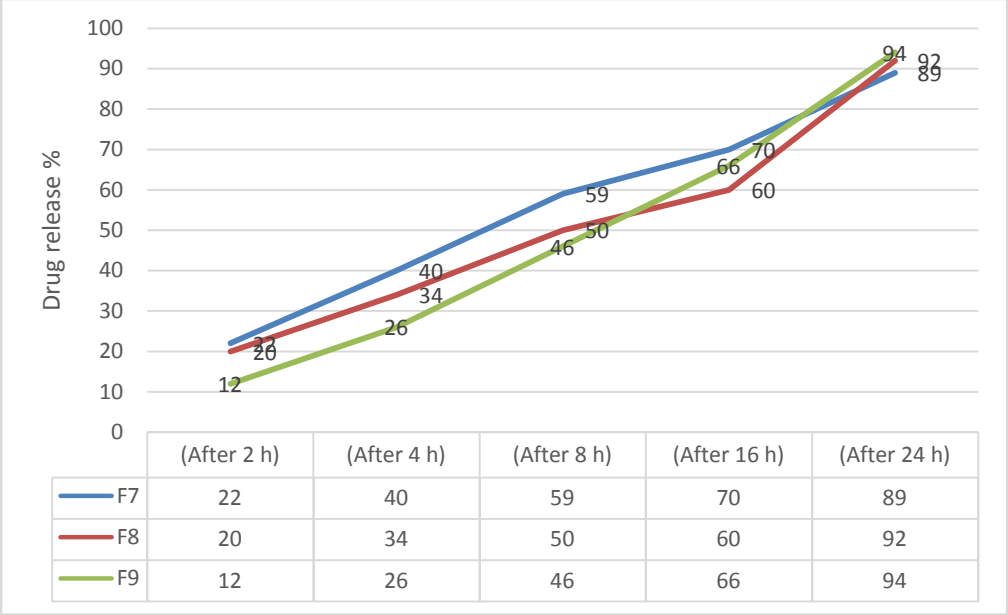
Figure 3 showed the swelling characteristics of gum acacia, gelatin and tagacanth respectively. The swelling index was calculated with respect to time. As time increases, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration up to certain limit. Later on, it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed between swelling index and polymer concentration, and as polymer concentration increases, swelling index was increased [19].

In Vitro Drug Dissolution Study

The results of dissolution studies showed that as the concentration of polymer increases in the release of drug also retarding. The t 50% of the formulation F1, F4 and F7 is within 4 hours where as for the formulation F2, F5

and F8 showed nearly six hours. The polymers in high concentration showed t 50% more than six hours. The formulations with high concentration F3, F6, F9 shows the sustained release of the drug up to 12 hrs which are found to be F3 (98.2%), F6 (86.4%), F9 (96.6%). Among the nine formulations F6 formulation showed good sustained activity. In vitro release study results revealed that the release of drug was retarded with the proportional increase of the polymer concentration. It was observed that the amount of polymer influences the drug release which is shown in Figure 3, 4, 5, 6 [20].

It has been observed that the cumulative percent drug release decreases with increasing concentration of polymer and swelling index. The reason attributed to this fact is slow erosion of the gelled layer from the tablets containing higher amount of natural polymer. This slow release is of the formation of a thick gel structure that delays drug release from tablet matrix [21].



	(After 2 h)	(After 4 h)	(After 8 h)	(After 16 h)	(After 24 h)
F7	22	40	59	70	89
F8	20	34	50	60	92
F9	12	26	46	66	94

Figure 6. Drug release profile of PSR tablets containing gelatin polymer.

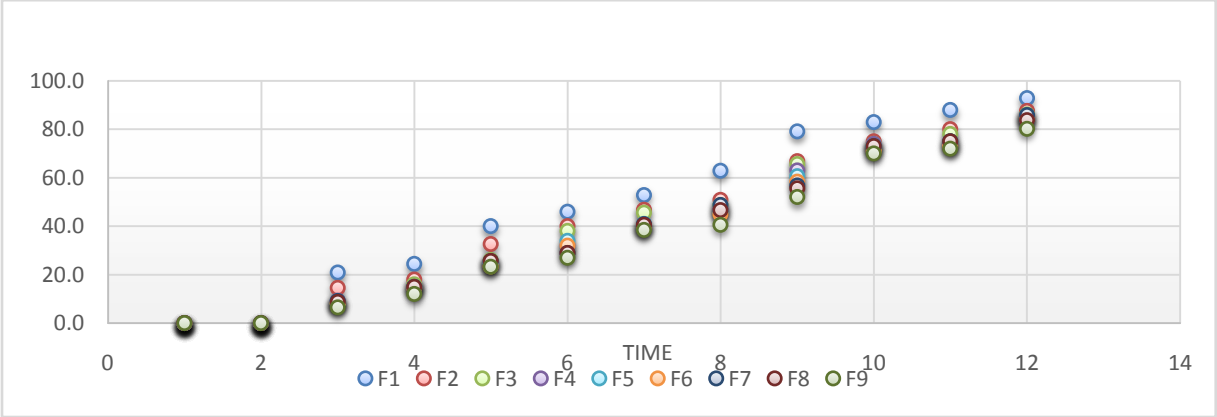


Figure 7. In vitro dissolution profiles of different formulations containing paracetamol sustained release matrix tablets, In vitro dissolution study was carried out in 0.1 N HCL (pH 1.2) for first 2hr and then phosphate buffer (pH 6.8) for 10 hr of formulations (F1- F9).

Conclusion

Natural polymers when used as release retardant exhibits uniform release over longer period of time. Hence, it can be concluded that, the acacia gum, which is a natural polymer, can be used as a drug release retardant in comparison to the other natural and synthetic established polymers in a particular concentration range. From the findings, obtained so far it can be concluded that Batch F3 of acacia in the concentration ratio of drug: polymer: lactose 100:150: 100 was promising concentration for oral sustained release matrix tablet of paracetamol [22].

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