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DEVELOPMENT AND EVALUATION OF PALIPERIDONE CAPSULE FOR SUSTAINED RELEASE ACTIVITY USING NATURAL POLYMER

Sachin Bhusari*, Tejal Chaudhari and Pravin Wakte

University Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431001, Maharashtra, India.

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***Corresponding Author**
Dr. Sachin Bhusari
University Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431001, Maharashtra, India.

ABSTRACT

The aim of present study was to formulate and evaluate a sustained release capsule of Paliperidone prepared by using natural polymers adopting wet granulation method. *Triumfetta rhomboidea* is natural polymer extracted from *Triumfetta rhomboidea* leaves powder by using ethanol. Paliperidone capsule were formulated by using *Triumfetta rhomboidea* polymer and other excipients to sustain the drug release. Extracted polymer was evaluated for its flow properties. All the prepared capsules were evaluated for weight variation, disintegration time, drug content uniformity and in vitro drug release characteristics. *Triumfetta rhomboidea* polymer showed excellent flow properties and all values were within the limit. FTIR studies suggested that drug and polymers were compatible and did not show any chemical interaction. weight variation and disintegration time were within the range of pharmacopoeia limit. The formulation F4 shows desired drug release and drug content and i.e. 94.36± 0.2 % and 92. 64 ± 0.3% respectively up to 12 h when compared with all other formulations. A lab scale method for extraction of *Triumfetta rhomboidea* polymer by ethanol precipitation method was developed. Through various evaluations, it was concluded that *Triumfetta rhomboidea* leaves polymer is an effective natural polymer and acts as a release rate modifier.

KEYWORDS: *Triumfetta rhomboidea,* Paliperidone, Natural polymer, Sustained release capsule, *In-vitro* drug release study.

INTRODUCTION

In the recent years, with the changing life style and busy schedule, people of all age groups are suffering from different types of psychological disorders and hence there is increased need for the psychotropic drugs.[1] Paliperidone is one of the atypical antipsychotics drug that helps to restore the balance of certain natural substances in brain.[2] Paliperidone is used to treat certain mental disorders such as schizophrenia.[3] This medication can decrease hallucinations and help to think more clearly and positively, feel less agitated and take a more active part in everyday life.[4]

Nowadays, Capsule is the most versatile of all pharmaceutical dosage forms. Capsules are solid dosage forms in which the medication contained within gelatine shells usually made of gelatin.[5] They can be divided into two main categories hard capsule and soft capsule. The majority of capsule formulation made up of hard gelatine capsule.[6] Advantages of hard gelatin capsule are rapid drug release possible, flexibility of formulation and sealed hard gelatin capsule are good barriers to atmospheric oxygen.[7]

Sustained release systems consist of any drug delivery system designed to release drug continuously and constantly over prolonged period of time to maintain plasma drugs concentration within therapeutic level.[8] Hydrophilic polymers are most suitable for retarding drug release and there is growing interest in using these polymers in sustained drug delivery system.[9]

Triumfetta rhomboidea (Malvaceae family) is also known as diamond burbark, Chinese bur, Burr Bush, Burrbark, Jhinpat[10] which is annual herb or perennial shrub that grows up to 200 cm tall; stem erect, up to 1 cm in diameter at the base; bark smooth, red-brown, scabrid, hairy or glabrous.[11] *Triumfetta rhomboidea* polymer is a natural hydrophilic polymer which is isolated from ethanol extract of leaves powder.

In the present study, we made an attempt to develop a stable formulation of oral immediate release Paliperidone hard gelatin capsule using natural polymer with optimum properties by wet granulation method.[12] To achieve this goal, various batches of hard gelatin capsule containing granules of Paliperidone using natural polymer were prepared and evaluated with respect to the various quality parameters both in process parameters for granules as well as natural polymer (percentage yield, angle of repose, bulk density, tapped density, carr's index,

Hausner's ratio) and parameters for finished products (disintegration time, drug content, dissolution studies).[13]

MATERIAL AND METHODS

Materials

The fresh leaves *Triumfetta rhomboidea* were collected from Buldhana region, Maharashtra. The active pharmaceutical ingredient (API) Paliperidone was gift sample acquired from Wockhardt Limited. Hydroxypropyl Methylcellulose (HPMC), Magnesium Stearate, Microcrystalline Cellulose (Avicel PH102) and Aerosil were obtained from TCI Chemicals, Mumbai. Acetone ethanol and isopropyl alcohol (IPA) were obtained from Rankem, India. Distilled water was used throughout the experiment.

Experimental Method

Isolation of polymer

Parts of the plant were collected, separated, washed and shade dried. Dried leaves were ground in a mixer followed by size reduction. Dissolving 500 gm of *Triumfetta rhomboidea* leaves powder in 2000ml double distilled water, boiled with stirring up, a slurry was formed. Further, it was kept to cool for 3 to 4 hours so as to separate the supernatant liquid. The clear solution at the top was decanted and the rest was centrifuged at 10,000 rpm for 5 minutes. The supernatant was separated and heated at 60ºC on water bath to concentrate the supernatant. The solution after heating was cooled to the room temperature and was then poured into twice the volume of acetone/ethanol with continuous stirring. The precipitates were formed and then the precipitated material was washed with distilled water and again dried at 50-60º under vacuum. The polymer was separated, dried in an oven at a temperature of less than 50^0C, collected, ground, passed through #80, weighed to calculate the yield and stored in desiccator till use.[14]

The extraction of *Triumfetta rhomboidea* leaves powder ethanol and acetone were performed in 1:2 (Supernatant aq. Part: organic solvent) ratio from these, the ethanol gave a better yield than acetone. On the basis of this result ethanol was taken for further study.[15]

Characterization of TR polymer

1. Taxonomical classification. The collected *Triumfetta rhomboidea* leaves were classified for its kingdom, class, order, family, genus, and species.

2. Physical evaluation: The polymer was evaluated for its colour, odour, appearance and taste as well as pH and swelling index.[16]

3. Phytochemical evaluation: The solution of 1% w/v extract was prepared using distilled water and evaluated for carbohydrates, alkaloid, glycosides, proteins, tannins, saponins and flavonoids.[17]

4. Flow Properties: Flow properties were evaluated by Angle of repose, Bulk density, Tapped density, Hausner's ratio, and Carr's index.

- ***Angle of Repose***

Angle of repose (α) was derived using funnel method. The powder polymer was poured through a funnel freely on to the surface that can be raised vertically until a maximum cone height (*h*) was obtained. The radius of the heap (*r*) was measured and angle of repose was calculated using the following equation:

$\alpha = \tan^{-1} (h/r)$

Where,

α = angle of repose,

h= height of the cone, and

r= radius of the cone base.

- ***Bulk density***

Bulk density is determined through measuring the bulk volume of known weighed quantity of powder using bulk density apparatus. Bulk density was calculated using the formula.

Bulk Density = Bulk Mass / Bulk Volume

- ***Tapped density***

Tapped density is calculated by measuring the tapped volume of known weighed quantity (m) of powder using bulk density apparatus and using the formula.

Tapped Density = Bulk Mass / Tapped Volume

- ***Carr's Index***

The Carr's index that determines % of compressibility of the powder. Based on the apparent bulk and the tapped density, the percentage compressibility of bulk was determined by the following formula.

Carr's index: = 100[(Tapped density - bulk density)/ Tapped density]

- ***Hausner's ratio***

  Hausner's ratio is an index of ease of powder flow; it is calculated by using following formula:

  Hausner's Ratio: = Tapped density / Bulk density

5. pH: pH of 1% w/v solution of *Triumfetta rhomboidea* leaves polymer was determined using pH meter.

6. Solubility Studies: Distilled water, hot water, Ethanol, 0.1N HCl, pH 6.8 Phosphate buffer solutions were used to determine the solubility of Paliperidone.

Drug-excipient compatibility studies by FT-IR

IR spectroscopy is one of the analytical techniques useful in chemical reactions which is conducted using an IR Spectrophotometer. The spectrum was recorded in the wavelength region of 4000–400 cm−1. The IR spectra of pure drug (Paliperidone) and physical mixture of pure drug with polymer were determined by FT-IR using KBr dispersion method. The procedure consisted of dispersing a sample and compressing into discs by applying a pressure of 5T for 5 min in a hydraulic press. The powder was placed in the light path and the spectrum was recorded.[18]

Table 1: Formulation of Paliperidone sustained release granules for capsule formulation.

Components (mg)	F1	F2	F3	F4	F5	F6	F7
Paliperidone	6	6	6	6	6	6	6
TR polymer	12	9.5	14.5	14.5	12	9.5	12
MCC	30	30	30	30	30	30	30
HPMC	10.5	20	20	10.5	29.5	20	10.5
Aerosil	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Mag. Stearate	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Total weight (mg/Cap)	59.5	66.55	71.5	76	78.5	69	71.5

Preparation of Paliperidone granules for capsule formulation

The sustained release granules of Paliperidone were prepared by using wet granulation method. The formulation was composed of various concentrations of microcrystalline cellulose, HPMC K100M and polymer mixed with other excipients in various percentage (Table no.1). All powders were passed through sieve. Drug was added to the mixture and a mass was prepared using isopropyl alcohol as granulating fluid. Then mass was passed

through 40 # sieve and granules were allowed to dry in oven at 50 °C for 30 min. Dried granules were passed through 24 # sieve and evaluated for several tests.[19]

Evaluation of granules

Flow properties of granules were evaluated by Angle of repose, Bulk density, Tapped density, Hausner's ratio, and Carr's index

Standard curve of paliperidone

5 mg of Paliperidone is dissolved in 5 ml of methanol to prepare the stock solution (1mg/ml). The prepared stock solution was subsequently diluted with methanol to get solution concentration of 1, 3, 6, 12, 15, 18 and 20µg/ml. The absorption of maximum Paliperidone was measured at 278 nm using UV–Visible spectrophotometer (Jasco-530) against the blank solution (methanol).[20]

Evaluation of Paliperidone capsule

1. Weight variation

Five capsules were selected randomly and the average weight was determined. Then the individual capsule was weighed and the individual weight was compared with the average weight.

2. Disintegration test

Introduce one capsule in each tube and suspend the apparatus in a beaker containing 60 ml of water at 37^0c. If hard capsules float on surface of water, the disc may be added. Operate the apparatus for 30 min, remove the assembly from the liquid and observe the residue remains on the screen of apparatus.

3. Drug content

Five capsules of each formulation were taken and the granules from capsules were removed. The quantity of powder equivalent to 10 mg of drug was transferred into 100 ml volumetric flask and dissolved with distilled water by keeping in a sonicator for 10-15 min, then it was filtered, suitable dilutions were made and absorbance was recorded by using UV spectrophotometer at 278 nm.

4. *In- vitro* drug release

Apparatus: Dissolution test apparatus -2; USP-32

Method: Paddle method

Dissolution medium: 0.1N HCl

Volume: 900 ml

Speed: 50 rpm

Procedure

The capsule was placed inside the dissolution vessel. 5ml of sample was withdrawn at time intervals of 2h, 4h, 6h, 8h, 10h, 12h. The volume of dissolution fluid was adjusted to 900 ml by replacing 5ml of dissolution medium after each sampling. The release studies were conducted with 6 capsules and the mean values were plotted versus time. Each sample was analysed at 278 nm using double beam UV and visible spectrophotometer against reagent blank. The drug concentration was calculated using standard calibration curve (fig. 3).

RESULTS AND DISCUSSION

Characterization of polymer

1.Taxonomical classification

Based on Taxonomical classification *Triumfetta rhomboidea* is classified under the Kingdom of Plantae, Class of Magnoliopsida, Order of Malvales, and family as Malvaceae. The detail classification is shown in Table 2.

Table 2: Taxonomical classification of *Triumfetta rhomboidea.*

Taxonomical hierarchy	
Kingdom	Plantae
Class	Magnoliopsida
Order	Malvales
Family	Malvaceae.
Genus	Triumfetta
Species	T. rhomboidei

2. Physical characterization of *Triumfetta rhomboidea polymer*

The extracted polymer powder appeared in slightly yellowish to brownish colour with no characteristic odour. The polymer is soluble in hot water producing viscous solution. Polymer also shows swelling index and pH, 3 and 5.64 respectively. *Triumfetta rhomboidea* leaves produced 9.28% of dried polymer in ethanol, All the values are depicted in Table 3.

Table 3: Physical characterization of *Triumfetta rhomboidea polymer.*

Physical properties	Observation
Appearance	Powder
Colour	Slightly yellowish to brown
Odour	No odour
Taste	Tasteless
Solubility	In hot water
Swelling index	3
pH	5.64
% yield	9.28

3. Phytochemical characterization of *Triumfetta rhomboidea polymer*

Phytochemical test for carbohydrates, alkaloid, glycosides, proteins, tannins, saponins and flavonoids were carried out using respective reagents. Results revealed that there was presence of carbohydrates, proteins, glycosides and flavonoids in *Triumfetta rhomboidea* polymer shown in table no.4.

Table 4: Phytochemical characterization of *Triumfetta rhomboidea polymer.*

Phytochemical test	Result obtained
Carbohydrates	+ve
Proteins	+ve
Alkaloids	-ve
Glycosides	+ve
Tannins	-ve
Flavonoids	+ve

4. Flow properties of *Triumfetta rhomboidea polymer*

Dried *Triumfetta rhomboidea* leaves polymer has an excellent flow property based on Angle of repose 27.14_± 0.357 Bulk density 0.45 ±0.016 g/cm3, and Tapped density 0.89± 0.013 g/cm3. Based on USP, Carr's index with value of 21.56 ± 0.09% and Hausner's ratio of 1.34± 0.003 noted values in excellent range of flowability. The polymer is now confirmed very suitable to be used in granules preparation. All these values are tabulated in Table 5.

Table 5: Flow properties of *Triumfetta rhomboidea polymer.*

Flow properties	Observation
Angle of repose	27.14_± 0.357
Bulk density	0.45 ±0.016 g/cm3
Tapped density	0.89± 0.013 g/cm3
Carr's index	21.56 ± 0.09%
Hausner's ratio	1.34± 0.003

Drug-excipient compatibility studies by FT-IR

Drug- excipient interactions plays an essential role in release of drug from the formulation. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The characteristic absorption peaks of Paliperidone were obtained. From the spectra of pure drug Paliperidone and the combination of drug with polymers, it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, thus indicating compatibility of the drug and polymer. IR spectra of the pure drug in combination with the polymers are shown in Figure No.1,2

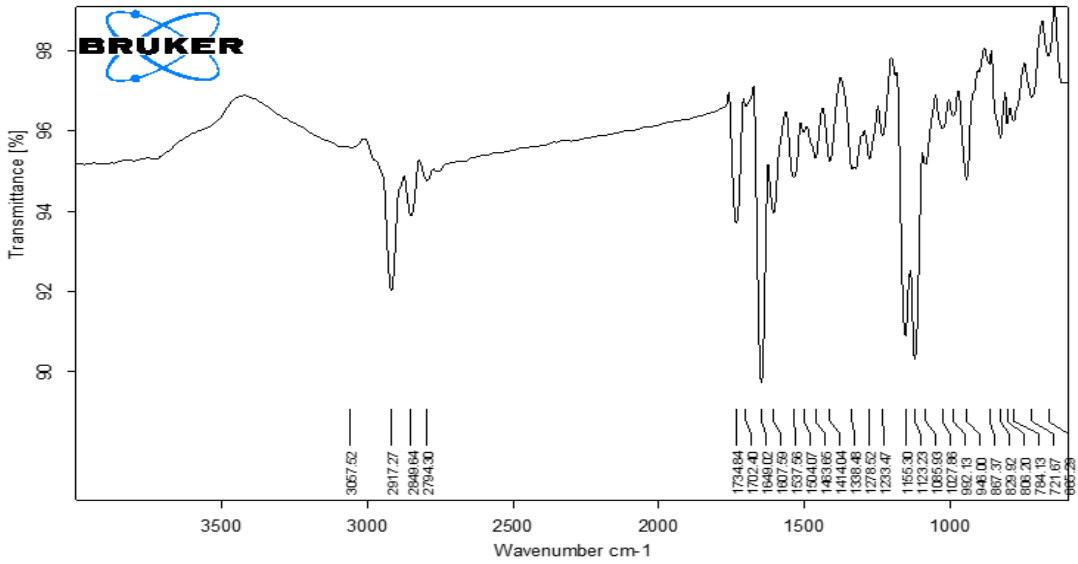

Fig. 1: FTIR spectra of Paliperidone (Pure drug).

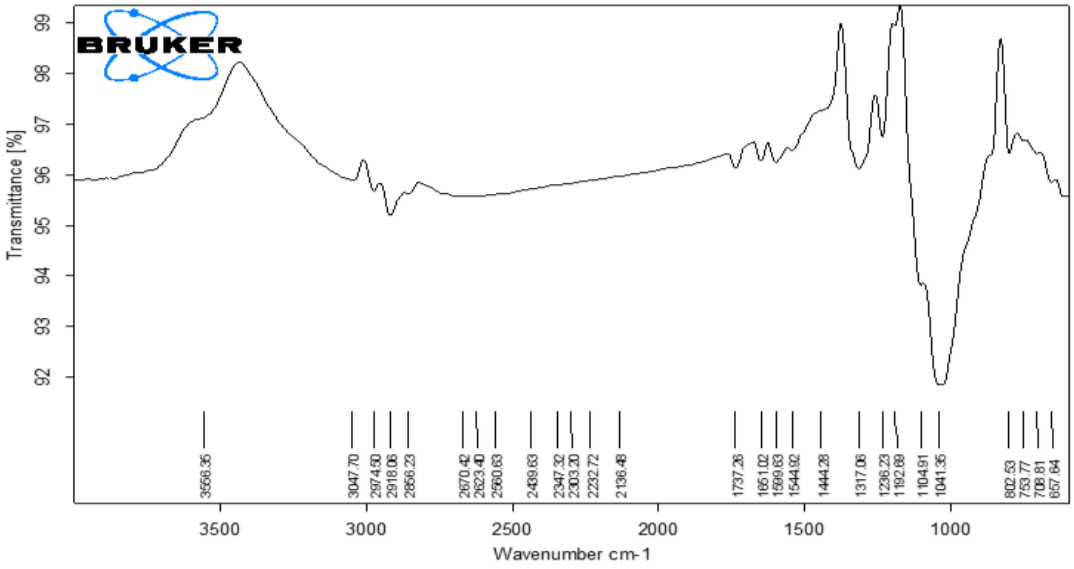

Fig. 2: FTIR spectra of physical mixture of Paliperidone with polymer.

Standard curve of paliperidone

The standard curve of Paliperidone was obtained by using different concentration of Paliperidone i.e. 1, 3, 6, 12, 15, 18 and 20 µg/ml with the selected wavelength (278nm). The blank solution used was methanol. The graphical presentation was determined by plotting absorbance against concentration (µg/ml) and we obtained a fine linear regression line with R value of 0.9976 as shown in Fig. 3. This standard line was adopted as a standard reference graph which was later used to calculate the concentration of drug released with corresponding absorbance value at particular instance during vitro dissolution studies.

Table 6: UV analysis of Paliperidone.

Concentration (µg/ml)	Absorbance (nm)
1	0.0512
3	0.1407
6	0.2734
12	0.5421
15	0.739
18	0.8612
20	0.9787

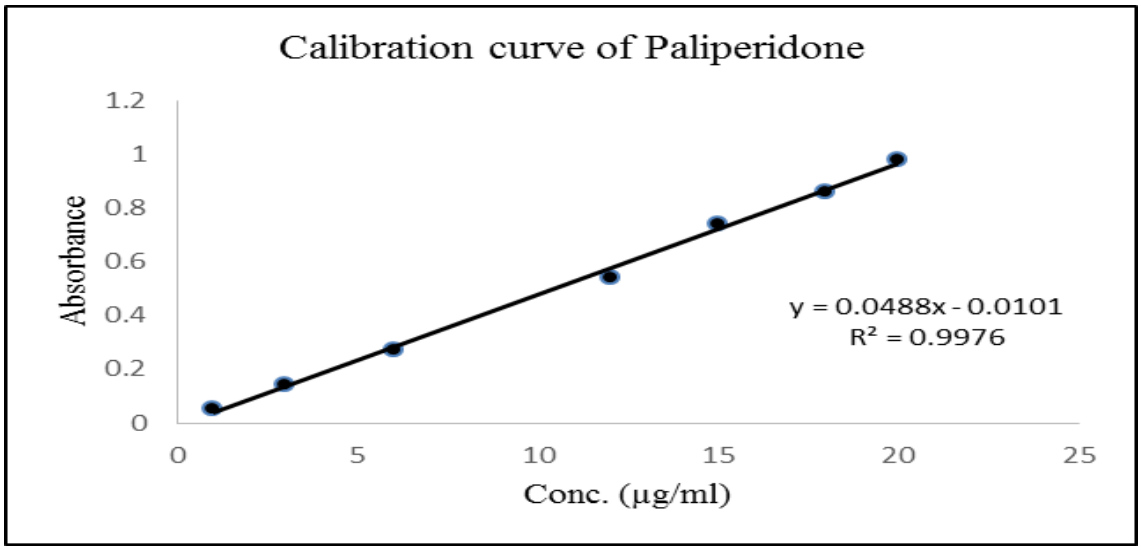

Fig. 3: Calibration curve of paliperidone.

Evaluation of powder granules

Flow properties of powder granules was evaluated by determining Angle of repose, Bulk density, Tapped density, Hausner's ratio, and Carr's index within an acceptable limit.

Table No.7 depicts the result of evaluation parameters of granules of all formulation. The bulk density & tapped density for all formulation varied in the range of 0.5149 to 0.5687 and

0.6159 to 0.6798 respectively. The Carr's index for all formulation was found to be in the range of 13.54 to 19.89. Hausner's ratio for all powder granules was found to be in the range of 1.15 to 1.24, also the angle of repose for powder granules of all formulation ranged between 27.02 and 31.95. Thus, all formulations showed good compressibility and good flow properties.

Table 7: Flow properties of granules.

Formulation	Angle of repose(θ)	Bulk density	Tapped density	Carr's index	Hausner's ration
F1	28.57	0.5687	0.6578	13.54	1.15
F2	31.95	0.5149	0.6428	19.89	1.24
F3	30.96	0.5264	0.6159	14.53	1.17
F4	27.02	0.5268	0.6237	15.53	1.18
F5	30.54	0.5364	0.6253	14.21	1.16
F6	27.92	0.5491	0.6798	19.22	1.23
F7	30.11	0.5184	0.6287	17.54	1.21

Evaluation of paliperidone capsule

The Paliperidone sustained release capsule was produced using wet granulation method. The capsules were evaluated for its physical parameters such as weight variation, disintegration time, drug content, (Table no. 8)

1. Weight variation

Five capsules were selected randomly and the average weight was determined. Then the individual capsule was weighed and the individual weight was compared with the average weight.

2. Disintegration time

The disintegration time for hard gelatin capsule was found to be in the range of 4.56 to 6.30 min, which was within the acceptable limits as per IP.

3. Drug content

The percentage drug content of all the formulations were found to be between 73.12 ± 0.5 to 92.64 ± 0.4, which was within the acceptable limits as per IP.

Table 8: Evaluation parameter of capsule.

Formulation	Weight variation	Disintegration time (min)	% Drug content
F1	131± 0.4	5.46	83.85 ± 0.3
F2	133 ± 0.2	6.23	73.12 ± 0.5
F3	139 ± 0.5	5.34	81.02 ± 0.4
F4	137 ± 0.4	4.56	92. 64 ± 0.3
F5	134 ± 0.3	5.52	88.69 ± 0.2
F6	136 ± 0.2	6.30	83.28 ± 0.4
F7	138 ± 0.3	5.24	76.65 ± 0.5

4. *In- vitro* Drug Release

In present study of dissolution profile as shown in Fig. 5, all the formulations have shown more than 70% of drugs being released within 12 h in 0.1 N HCL. From the observation, F1, F2, F3 has achieved drug release 83.65± 0.3 %, 73.62± 0.2% and 92.64± 0.4 % respectively within 12 h. whereas F4 was maximally able to achieve 94.36± 0.2% drug release. F5, F6, F7 has showed drug release 81.2± 0.3 %, 88.69± 0.3 % and 71.26± 0.5 respectively. This comparison can be used to conclude that formulation F4 contains maximum amount of polymer i.e. 14.5 % which is able to sustain the maximum drug release. The *in-vitro* drug release was tabulated in Table no 9.

Table 9: *in-vitro* drug release of F1-F7 formulation.

Time (h)	F1	F2	F3	F4	F5	F6	F7
0	0± 0.0	0± 0.0	0± 0.0	0± 0.0	0± 0.0	0± 0.0	0± 0.0
2	15.24± 0.5	20.59± 0.2	14.87 ± 0.3	22.15± 0.5	21.08± 0.3	24.59± 0.3	13.9± 0.4
4	22.45± 0.3	28.65± 0.4	23.78± 0.4	38.25± 0.3	30.56± 0.2	34.09± 0.2	23.84± 0.1
6	45.66± 0.2	48.22± 0.2	43.94± 0.4	49.21± 0.1	49.75± 0.4	50.12± 0.4	38.22± 0.3
8	60.48± 0.4	54.19± 0.3	60.57± 0.4	68.15± 0.4	62.15± 0.1	68.2± 0.1	51.86± 0.4
10	75.28± 0.3	69.38± 0.2	85.94± 0.4	89.54± 0.3	73.45± 0.2	80.15± 0.2	65.48± 0.1
12	83.65± 0.3	73.62± 0.2	92.64± 0.4	94.36± 0.2	81.2± 0.3	88.69± 0.3	71.26± 0.5

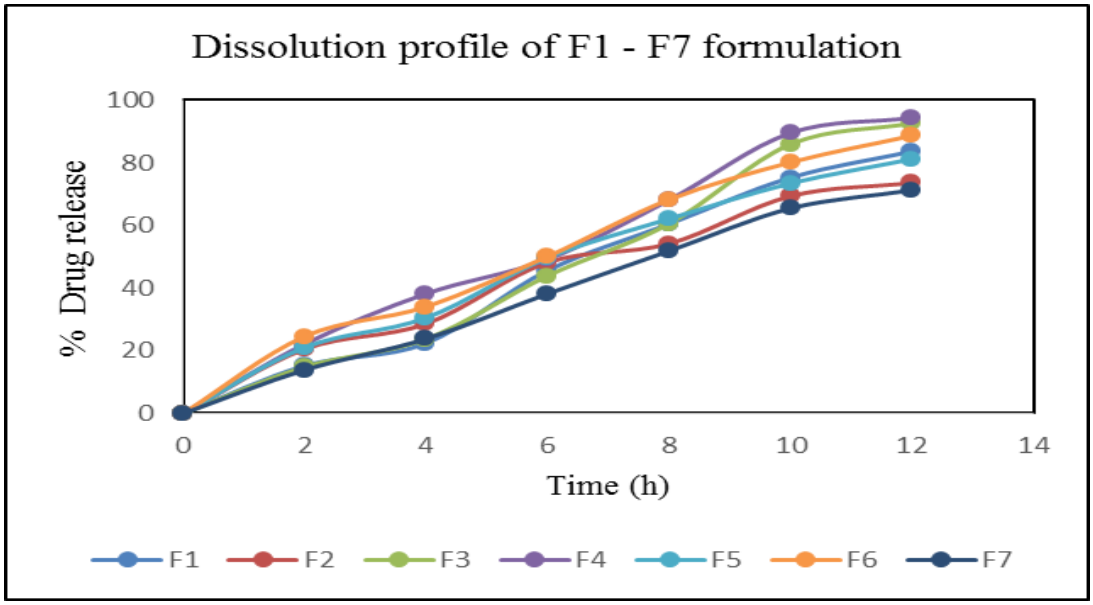

Fig. 4: *in-vitro* drug release of F1-F7 formulation.

CONCLUSION

A lab scale method for extraction of *Triumfetta rhomboidea* polymer by ethanol precipitation method was developed. The potential of *Triumfetta rhomboidea* polymer as a release rate modifier was established using Paliperidone to be a model drug. According to the formulations studied, the formulation F4 resulted in better dissolution profile i.e. 94.36± 0.2% up to 12 h. Through various evaluations, *Triumfetta rhomboidea* leaves polymer has been concluded as an effective natural polymer act as a release rate modifier.

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