Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Formulation and Optimization of Polyherbal Fast Dissolving Tablet of Curcumin, Quercetin and Rutin

Reshu Tiwari[1], Mohd. H. Siddiqui[2]*, Tarique Mahmood[3], Alvina Farooqui[2], Mukesh Tiwari[4], Farogh Ahsan[3]

[1]*School of Pharmacy, Singhania University, Pacherbari, Jhunjhunu, Rajasthan, India*
[2]*Department of Bioengineering, Faculty of Bioengineering, Integral University, Lucknow, Uttar Pradesh, India*
[3]*Department of Pharmacology, Faculty of Pharmacy Integral University, Lucknow, Uttar Pradesh, India*
[4]*Department of Pharmaceutics, Mahatma Gandhi Institute of Pharmacy, Lucknow, Uttar Pradesh, India*

ARTICLE INFO

Article history:
Received: 01 July, 2021
Revised: 11 October, 2021
Accepted: 20 October, 2021
Published: 30 November, 2021

Keywords:
Crospovidone, Curcumin, Direct compression method, Polyherbal combination, Polyherbal fast-dissolving tablets, Quercetin, Rutin.

DOI:
10.25004/IJPSDR.2021.130609

ABSTRACT

The current study was focused on the design, development, and evaluation of the fast-dissolving tablet of a polyherbal combination of curcumin, quercetin, and rutin. These herbal drugs are poorly water-soluble. The center of attention for this study is to provide quick onset of action, improved bioavailability, and increased patient compliance for administering a tablet. All parameters of Polyherbal Fast dissolving tablets were evaluated, and all were found within the official range. Drug content ranges between 90 to 105%. The formulation PHT24 containing a high concentration of Crosspovidone enhanced the drug release up to 94% within 5 minutes compared with the control. The optimized formula PHT24 showed favorable drug dissolve characteristics with better mouth feel and acceptable fast-dissolving properties. It was also observed that all formulations were acceptable with reasonable limits of the standard required for fast-dissolving tablets. The study also reveals that the Superdisintegrants used were effective in low or high concentrations. It was concluded that fast dissolving tablets with enhanced dissolution rates could be made using selected Superdisintegrants

Introduction

Flavonoids are naturally occurring substances having some beneficial effects on human health and are present in more than 1000 preparations available in the medicine market.[1] Many reviews have dealt with their structure, properties, and biosynthesis. These molecules show various biological effects, such as capillarity fragility protection,[1] inhibition of lipid peroxidation,[2] and anti-inflammatory activity by inhibiting the enzymes involved in arachidonate metabolism.[3,4] In particular, curcumin (Cm), rutin (Rt), and its metabolite quercetin (Qc) are flavonoids widely distributed in herbal drugs. Cm has a wide range of pharmacological applications such as anti-inflammation, anti-human immunodeficiency virus, antimicrobial, antioxidant, anti-parasitic, anti-mutagenic, and anti-cancer[5-9] with low or no intrinsic toxicity. Rt has significant scavenging properties on oxidizing species such as OH radicals, superoxide radicals, and peroxyl radicals. Therefore, it shows several pharmacological activities, including anti-allergic, anti-inflammatory, and vasoactive, antitumor, antibacterial, antiviral, and anti-protozoal properties.[10,11] Qc belongs to a sub-class of flavonoids known as flavonols, which find use in nutraceuticals or food supplements. Studies have shown that quercetin has antioxidant, anti-inflammatory, antibacterial, anti-coagulative, and anti-hypertensive properties.[12-17]

***Corresponding Author:** Mohd. H. Siddiqui

Address: Department of Bioengineering, Faculty of Bioengineering, Integral University, Lucknow, Uttar Pradesh, India

Email ✉**:** siddiquimohdharis@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Unfortunately, these flavonoids are slightly soluble in water and show a slow dissolution rate from solid oral forms, restricting their use in therapy. It is well known that the drug dissolution rate can be the critical limiting step in the bioavailability after oral administration and the therapeutic effect of the drug. In the case of low-solubility drugs, the drug absorption from the gastrointestinal tract is generally slow and irregular,[18] and any enhancement of the dissolution would improve its absorption and bioavailability. The possibility of improving the solubility of Cm, Rt, and Qc using the solid dispersions technique (SD) has been addressed previously. These studies demonstrated significant increases in the solubility and drug release of the drugs.

The present work aimed to prepare and examine the various parameters of a solid dosage form containing a polyherbal combination of Cm, Rt, and Qc SD.

Tablets are solid dosed medicinal forms developed by compressing a drug or a blend of a drug and excipients or formed special masses (powers, granules), intended for internal, external, sublingual, or parenteral use.[19] The main benefit of these medicinal forms is the high production rate, the wide range of possibilities for masking color and odor, and the potential for prolonging drug action, not to mention portability and ease of use.[20] The major disadvantage of these conventional solid dosage forms having to chew and swallowing difficulty (dysphagia). In pediatric patients and patients who have fear of choking, hand tremors, dysphasia in adolescents and schizophrenic patients, poor patient relaxation leads to reduced overall treatment effectiveness.[21,22] This problem has been overcome by the new technology known as fast dissolving tablet (FDTs) technology.

FDTs disintegrate into tiny particles or small size granules, melt in the mouth, and allow easy swallowing by patients. The disintegration time for acceptable FDTs differs from several seconds to one minute (USFDA 2003, Pharmaeuropa 1998). FDTs with good patient acceptance, compliance, and better biopharmaceutical properties, increased bioavailability and efficiency when compared with conventional oral doses.[23]

Superdisintegrants should make tablets strong and disperse the tablet in the mouth within 1 minute and enhance the dissolution properties, thereby increasing the drug bioavailability.[24] So, it was a significant challenge to develop FDTs with better mouthfeel and improved drug release.[25] The fast-dissolving drug delivery system is an equal line of expansion in a well-established market and it is very effective for surviving and extending the market value of the pharmaceutical industry.

Methods

Materials

Cm, Qc, and Rt were procured from Sissco Research Laboratories Pvt. Ltd. Mumbai, India. All other reagents were used of analytical grade and were supplied by local suppliers, Shubh scientific, Lucknow.

Method

Development of polyherbal fast dissolving tablets (PHFDTs)[26,27]

PHFDTs were prepared using the direct compression method with crospovidone as a super disintegrant with different concentrations of 15 and 30% w/w. All the ingredients were sieved through a 60-mesh sieve. A weighed quantity of each ingredient was taken, and the blend (powder blend) was uniformly mixed a dialated polyethylene pouch in a geometric ratio and compressed mixture into tablets of 800mg using flat-round punches on a single station rotary tablet machine (SS 304, Indosati, Haryana, India). The composition of each formulation is shown in Table 1.

Pre-compression Parameters

Flow Properties of Blend[28-31]

The powder blend was evaluated for various flow properties like the angle of repose, bulk and tapped density, Hausner's ratio, and Carr's index.

The Angle of Repose

The parameter of powder blend was carried out by applying the fixed funnel method. The weighed quantity of powder blend was passed through the funnel without any resistance and adjusted the funnel height properly that the funnel tip touched the heap's tip of the powder blend. Then measured the diameter and height of the powder heap.

$$\tan = \frac{h}{r}$$

where h = height of powder heap
r = radius of the powder heap

Bulk Density and Tapped Density

Powder blend weighing 5 g from each batch was taken into a measuring cylinder. Initially, the powder blend was agitated very lightly to break if any agglomerates are formed.

The initial volume was noted, and the measuring cylinder could tap onto a rigid surface obtained. Bulk density (BD) and Tapped bulk density (TBD) were calculated using the following formulas:

$$BD = \frac{\text{weight of the powder}}{\text{volume of the powder}}$$

$$TBD = \frac{\text{weight of the powder}}{\text{tapped volume of the powder}}$$

Compressibility Index and Hausner's Ratio

The following formula was used to determine the compressibility index of granules

$$\text{Carr's compressibility index (Carr's index)} = \frac{[(TBD\ \ BD)]}{TBD}$$

Table 1: Formula for various trial batches

Ingredients (mg)/ formulation code	*SD Complex*	*Cros povidone*	*Mannitol*	*Lactose*	*Magnesium stearate*	*Talc*	*Sodium saccharine*
PHT1	276	15	15	464	10	5	15
PHT2	276	30	15	449	10	5	15
PHT3	421	15	15	319	10	5	15
PHT4	421	30	15	304	10	5	15
PHT5	720	15	15	20	10	5	15
PHT6	720	30	15	5	10	5	15
PHT7	294	15	15	446	10	5	15
PHT8	294	30	15	431	10	5	15
PHT9	448	15	15	292	10	5	15
PHT10	448	30	15	277	10	5	15
PHT11	702	15	15	38	10	5	15
PHT12	702	30	15	23	10	5	15
PHT13	206	15	15	534	10	5	15
PHT14	206	30	15	519	10	5	15
PHT15	389	15	15	351	10	5	15
PHT16	389	30	15	336	10	5	15
PHT17	601	15	15	139	10	5	15
PHT18	601	30	15	124	10	5	15
PHT19	207	15	15	533	10	5	15
PHT20	207	30	15	518	10	5	15
PHT21	364	15	15	376	10	5	15
PHT22	364	30	15	361	10	5	15
PHT23	662	15	15	78	10	5	15
PHT24	662	30	15	63	10	5	15

Hausner's ratio was calculated by the following formula:

$$\text{Hausner} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Post Compression Parameters

Evaluation of Tablets

The tablets from all the batches were evaluated for different parameters as follows:

Appearance

Tablets were evaluated for organoleptic properties.[32]

Thickness

Three tablets were selected from each batch to determine the tablet thickness. The tablet thickness was measured by using a vernier caliper (Yamayo, India-150 mm), and an average value was calculated.[33,34]

Weight Variation

Twenty tablets were selected, and calculate the individual weight and average weight by using an electronic balance (AUX220 Uniblock 1987). A comparison study was done between individual weight and the average weight of the tablet.[32,34,35]

Hardness

From each batch, three tablets were selected hardness was checked by using Monsanto Hardness Tester.[32,34,35]

Friability

Pre-weighed eight (800 mg, each) tablets were put down in the USP type Roche Friabilator tester (HMK-1601 Tablet Friability Tester, AZONANO, India), and operated at 25 rpm for 4 minutes and reweighed, the tablet and calculate the percentage weight loss (friability); tablets should not lose more than 1% of their initial weight.[32,34]

Content of Active Ingredient

For this purpose, ten pre-weighed tablets were crushed with a pestle in a glass mortar. The fine powder of the crushed tablet was weighed to get 800 mg (equivalent to 50 mg of each pure drug) and transferred to a conical flask containing 100 mL of distilled water stirred for 45 minutes in an ultra sonicator. The solution was filtered and obtained filtrates were analyzed UV spectrophotometrically

(Pharmaspec UV-1700, Shimadzu) then determined the drug content for all batches.[32,36]

Wetting Time

A tissue paper was folded twice and put down in a petri dish containing 10 mL of water and a water-soluble dye then placed a tablet on the tissue paper surface and then allowed to wet completely. The time required for the complete wetting was measured.[34,37]

Water Absorption Ratio

Tissue paper was folded twice and put down in a small petri dish containing 6 ml of water and put the tablet on the tissue paper and allowed to wet completely. Then again weighed the wetted tablet.[34,38]

Water absorption ratio, R was measured by applying the following formula,

$$R = 100 = \frac{(WaWb)}{Wb}$$

Where Wa = tablet weight after water absorption
Wb = tablet weight before water absorption.

Dispersion Time

10 mL of water was filled in the Petri dish and put down the tablet at the center of the Petri dish and note down the complete disintegration of the tablet.[34,37]

Disintegration Time

The disintegration time of PHFDTs was measured in phosphate buffer (pH 6.8) at 37 ± 5°C in the USP Disintegration test apparatus (Single Basket Tablet Disintegration test apparatus, Ambala, India). Three trials for each batch were performed.[39]

In-vitro Dissolution

The *In vitro* dissolution study was performed on USP apparatus type I (basket type) (Esico international 1918/1916) by using 900 mL of phosphate buffer of pH 6.8 at 37 ± 5°C as dissolution medium at 50 rpm. Aliquot equal to 5 mL of dissolution medium was withdrawn at a specific interval and replaced with freshly prepared buffer medium to maintain the sink condition. The sample was filtered and determined the absorbance by double beam UV spectrophotometer (Pharmaspec UV-1700, Shimadzu) for Cm, Q, and Rt at 421 nm, 372 nm, and 359 nm, respectively.[40]

Stability Study

In any rational formulation and testing of drug dosage forms, the stability of active components should be determined for their acceptance or non-acceptance. For stability study, the selected formulations were packed in aluminum foils and then stored in a stability chamber at 40 ± 2°C/75% RH ± 5% for 6 months and further evaluated for their physical appearance, drug content, friability, hardness, and dispersion time at intervals of the 1st, 3rd, and 6th months.[41,42]

Results and Discussion

It was reported that Cm, Qc, and Rt are flavonoids and having various therapeutic activities.[43-45] In various studies, crospovidone has been used as super disintegrants at different for the preparation of FDTs.[46-48] Crospovidone quickly wicks saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth. Unlike other super disintegrants, which rely principally on swelling for disintegration, Crospovidone super disintegrants use a combination of swelling and wicking. When examined under a scanning electron microscope, crospovidone particles appear granular and highly porous. This unique, porous particle morphology facilitates the wicking of liquid into the tablet and particles to generate rapid disintegration.[49,50] Therefore, we have attempted to develop FDTs from the polyherbal combination of Cm, Qc, and Rt with crospovidone to investigate its potentials out to observe the release pattern of the drug from the complex.

PHFDTs were formulated by the direct compression method because it is the easiest and most profitable method. Lactose was used as a diluent to relate multidirectional advantages such as good aqueous solubility and wetting properties that help in the smooth breakdown of the tablet. Crospovidone is used as a super disintegrant that leads to quick breakdown and fast drug dissolution. Sodium saccharin was used as a sweetening agent in the tablet composition to improve patient compliance (palatability).

Pre-compression Parameters of Formulation Blend

Each combination of drugs and the ingredients used were prepared and evaluated by various parameters as described. Bulk density was found within the official range of 0.43 to 0.63 g/cm^3 and tapped density between 0.51 to 0.66 g/cm^3 as shown in Table 2. The compressibility index and Hausner's ratio were calculated by using these two densities. The compressibility index of the powder blend of all the formulations was found between 5.34 and 20.45, indicating good flowability. Hausner's ratio for all formulations was found less than 1.01, indicating good flowability. The compressibility flowability correlation data indicated an excellent flow property of powder blend, the range of angle of repose also confirmed the good flowability of the powder blend because it was found between 25.26 and 29.94.

Post Compression Parameters of Formulations

PHFDTs were prepared in twenty-four (24) formulations with two different concentrations of super disintegrant (Crospovidone) and lactose was used as diluents. The direct compression technique was used for the compression of the powder blend. Several post-compression parameters were performed for an individual batch of prepared PHFDTs. Tablets were found to have the same weight due

Table 2: Pre-compression parameters of Direct Compression method

Formulation code	*Angle of repose (°)*	*Bulk density (g/cm²)*	*Tapped density (g/cm²)*	*Hausner's ratio*	*Cars index (%)*
PHT1	29.78 ± 0.21	0.55 ± 0.03	0.63 ± 0.04	0.84 ± 0.06	12.24 ± 0.63
PHT2	28.45 ± 0.106	0.52 ± 0.01	0.61 ± 0.03	0.84 ± 0.04	13.28 ± 0.103
PHT3	27.38 ± 0.53	0.56 ± 0.02	0.59 ± 0.07	0.90 ± 0.12	19.43 ± 0.15
PHT4	25.52 ± 0.09	0.56 ± 0.01	0.59 ± 0.01	0.96 ± 0.02	10.10 ± 0.15
PHT5	27.74 ± 0.205	0.63 ± 0.01	0.62 ± 0.02	0.98 ± 0.03	5.34 ± 0.68
PHT6	29.04 ± 0.023	0.57 ± 0.01	0.58 ± 0.02	0.96 ± 0.04	6.94 ± 0.301
PHT7	25.41 ± 0.202	0.45 ± 0.02	0.51 ± 0.06	0.84 ± 0.104	18.39 ± 0.19
PHT8	27.005 ± 0.08	0.43 ± 0.03	0.54 ± 0.03	0.89 ± 0.05	7.63 ± 0.301
PHT9	27.08 ± 0.01	0.48 ± 0.01	0.54 ± 0.04	0.90 ± 0.07	5.75 ± 0.21
PHT10	26.34 ± 0.05	0.54 ± 0.04	0.56 ± 0.05	0.91 ± 0.08	13.07 ± 0.31
PHT11	27.81 ± 0.04	0.45 ± 0.03	0.54 ± 0.04	0.91 ± 0.07	8.18 ± 0.19
PHT12	26.44 ± 0.03	0.55 ± 0.03	0.58 ± 0.02	0.87 ± 0.03	15.98 ± 0.14
PHT13	26.88 ± 0.101	0.44 ± 0.04	0.58 ± 0.1	0.86 ± 0.13	7.95 ± 1.009
PHT14	26.18 ± 0.02	0.46 ± 0.04	0.56 ± 0.03	0.87 ± 0.05	13.57 ± 0.09
PHT15	27.18 ± 0.03	0.50 ± 0.04	0.58 ± 0.08	0.92 ± 0.12	6.17 ± 0.37
PHT16	27.74 ± 0.04	0.52 ± 0.04	0.59 ± 0.02	0.91 ± 0.04	12.94 ± 0.87
PHT17	28.32 ± 0.18	0.61 ± 0.03	0.66 ± 0.03	0.87 ± 0.04	8.09 ± 0.08
PHT18	29.94 ± 0.05	0.63 ± 0.03	0.63 ± 0.05	1.01 ± 0.07	7.22 ± 0.08
PHT19	25.72 ± 0.02	0.55 ± 0.104	0.53 ± 0.03	0.90 ± 0.06	9.82 ± 0.11
PHT20	25.64 ± 0.06	0.55 ± 0.06	0.60 ± 0.02	0.80 ± 0.02	17.69 ± 0.34
PHT21	25.35 ± 0.05	0.51 ± 0.04	0.58 ± 0.01	0.80 ± 0.02	19.55 ± 0.105
PHT22	26.27 ± 0.13	0.52 ± 0.12	0.54 ± 0.04	0.87 ± 0.07	13.00 ± 0.18
PHT23	25.32 ± 0.58	0.54 ± 0.04	0.61 ± 0.03	0.87 ± 0.05	7.25 ± 0.08
PHT24	25.26 ± 1.15	0.51 ± 0.11	0.64 ± 0.03	0.75 ± 0.03	20.45 ± 0.03

All values are expressed in mean ± SD, (n=3)

to the same die fill. The findings observed through the post-compression parameters such as weight variation, hardness, thickness, friability, wetting time, water absorption ratio and drug content are shown in Tables 3 to 5, and disintegration time and dispersion time are shown in Figs. 1 and 2.

Weight Variation

All the PHFDTs passed the weight variation test as the percentage weight variation was within the Pharmacopoeial limits. The weight of all the PHFDTs was presently found similar, with low standard deviation values indicating the uniform mixing of ingredients.

Thickness

The thickness of all formulations ranges between 5.87 to 6.58 mm.

Friability

The determined friability values are less than 1% and meet the official limits. The friability of the tablets was found between 0.54 to 0.75%, which indicates good mechanical resistance of tablets.

Hardness

The hardness was found between 2.76 to 3.43 kg/cm^2 for all the formulations, which show good mechanical strength and are capable of withstanding physical and mechanical stress while handling.

Dispersion Time

The Dispersion time of all the formulations was found between 9 to 115 sec, the wetting time and disintegration time of all the tablets were found to be within the prescribed limits and met the requirements of Dispersible tablets.

Disintegration Time

All tablets disintegrated quickly as per the prescribed range, especially when used at their required concentrations as reported in the literature. The Disintegration time of all batches was within the range of 4–62 seconds.

Table 3: Post-compression parameters of direct compression method

Formulation code	*Weight variation (mg)*	*Thickness (mm)*	*Hardness (kg/cm2)*	*Friability (%)*
PHT1	0.75 ± 0.07	6.28 ± 0.57	2.76 ± 0.05	0.54 ± 0.04
PHT2	0.74 ± 0.09	5.46 ± 0.78	2.86 ± 0.05	0.61 ± 0.02
PHT3	0.85 ± 0.12	5.32 ± 0.63	3.16 ± 0.05	0.72 ± 0.06
PHT4	0.75 ± 0.17	6.03 ± 0.55	2.86 ± 0.05	0.59 ± 0.02
PHT5	0.86 ± 0.08	6.13 ± 0.501	2.83 ± 0.05	0.61 ± 0.11
PHT6	0.87 ± 0.08	5.41 ± 0.74	3.23 ± 0.05	0.74 ± 0.13
PHT7	0.74 ± 0.06	5.01 ± 0.49	3.36 ± 0.58	0.71 ± 0.19
PHT8	0.89 ± 0.08	5.63 ± 0.05	3.43 ± 0.05	0.61 ± 0.1
PHT9	0.83 ± 0.14	6.13 ± 0.53	3.13 ± 0.05	0.79 ± 0.08
PHT10	0.73 ± 0.13	6.23 ± 0.52	3.26 ± 0.05	0.69 ± 0.06
PHT11	0.77 ± 0.06	5.93 ± 0.52	3.16 ± 0.05	0.76 ± 0.1
PHT12	0.71 ± 0.04	6.58 ± 0.41	3.23 ± 0.11	0.77 ± 0.26
PHT13	0.76 ± 0.09	5.41 ± 0.71	3.2 ± 0.1	0.85 ± 0.12
PHT14	0.88 ± 0.06	6.01 ± 0.96	3.33 ± 0.05	0.69 ± 0.12
PHT15	0.81 ± 0.05	5.86 ± 0.25	3.33 ± 0.11	0.64 ± 0.41
PHT16	0.75 ± 0.06	5.67 ± 0.52	3.23 ± 0.05	0.71 ± 0.07
PHT17	0.82 ± 0.07	6.13 ± 0.46	3.23 ± 0.11	0.74 ± 0.11
PHT18	0.81 ± 0.07	6.08 ± 0.82	3.43 ± 0.05	0.67 ± 0.11
PHT19	0.77 ± 0.102	6.03 ± 1.39	3.15 ± .06	0.70 ± 0.08
PHT20	0.79 ± 0.01	5.15 ± 0.56	3.4 ± 0.1	0.78 ± 0.13
PHT21	0.86 ± 0.07	6.09 ± 0.51	3.33 ± 0.05	0.77 ± 0.23
PHT22	0.82 ± 0.06	6.49 ± 0.57	2.83 ± 0.05	0.69 ± 0.1
PHT23	0.7 ± 0.01	5.49 ± 0.44	2.93 ± 0.15	0.58 ± 0.01
PHT24	0.86 ± 0.11	6.01 ± 0.52	2.83 ± 0.05	0.61 ± 0.13

All values are expressed in mean ± SD, (n=3)

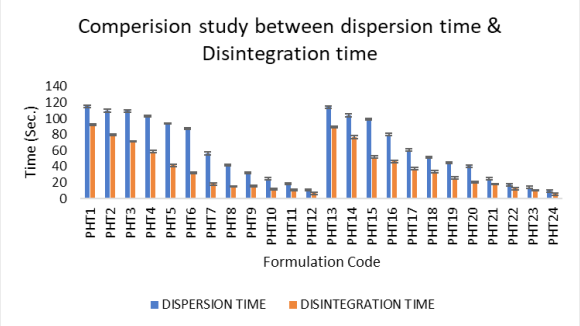

Fig. 1: Graph for the comparison study of dispersion time & disintegration time in each formulation. All the values were depicted as means of triplet ± SD for each parameter.

It was noticed that when crospovidone was used in high concentration than, the tablets disintegrated quickly within less time due to easy swelling ability.

Wetting Time and Water Absorption Ratio

The water absorption ratio of all formulations was found between 1.34 to 1.93%. This resulted in quick wetting of tablets of all formulations as reflected from wetting time ranging between 11–13 seconds.

Table6: Post-compression parameters of Direct Compression method formulation code

Drug Content

The percentage of drug contents of all the tablets were found between 95.41 % to 105.03 %, 95.33% to 105.51%, 95.22% to 105.66% of Cm, Qc, and Rt respectively, within the acceptable limits.

Drug Release Study

The dissolution studies were carried out in a phosphate buffer of pH 6.8, to simulate the gastric pH condition. These PHFDTs are drafted to enhance the disintegration property in the oral cavity and enhance the bioavailability of the drug.

A dissolution study of some of the formulations (PHT6, PHT12, PHT18, and PHT24) was carried out to observe the release pattern of the drug from the complex. The dissolution studies were carried out in a phosphate buffer

Table 4: Post-compression parameters of Direct Compression method

Formulation Code	*Wetting time (sec)*	*Water absorption ratio*
PHT1	131 ± 0.57	1.34 ± 0.01
PHT2	122 ± 1.52	1.39 ± 0.01
PHT3	117 ± 1.15	1.52 ± 0.27
PHT4	111 ± 1	1.48 ± 0.01
PHT5	102 ± 1.58	1.51 ± 0.03
PHT6	91 ± 1.15	1.57 ± 0.02
PHT7	78 ± 1.15	1.63 ± 0.023
PHT8	58 ± 0.57	1.72 ± 0.01
PHT9	50 ± 1.73	1.78 ± 0.02
PHT10	44 ± 1.15	1.72 ± 0.01
PHT11	31 ± 0.57	1.75 ± 0.02
PHT12	24 ± 1	1.82 ± 0.02
PHT13	129 ± 1.58	1.47 ± 0.03
PHT14	114 ± 1.15	1.54 ± 0.13
PHT15	109 ± 1.52	1.52 ± 0.05
PHT16	91 ± 1.52	1.53 ± 0.01
PHT17	63 ± 1.52	1.52 ± 0.02
PHT18	57 ± 1.15	1.64 ± 0.02
PHT19	51 ± 1.15	1.71 ± 0.01
PHT20	42 ± 0.57	1.71 ± 0.04
PHT21	31 ± 0.57	1.81 ± 0.02
PHT22	27 ± 1.52	1.81 ± 0.06
PHT23	24 ± 1.15	1.81 ± 0.02
PHT24	11 ± 1	1.93 ± 0.01

All values are expressed in mean ± SD, (n=3)

Table 5: Drug content of Cm, Qc, and Rt in PHFDTs

Formulation Code	*Curcumin*	*Quercetin*	*Rutin*
PHT1	95.41 ± 0.17	96.06 ± 0.09	95.22 ± 0.09
PHT 2	98.27 ± 0.24	95.33 ± 0.37	97.38 ± 0.49
PHT3	97.09 ± 0.14	98.16 ± 0.06	99.41 ± 0.27
PHT4	99.19 ± 0.05	99.45 ± 0.20	98.28 ± 0.13
PHT5	99.48 ± 0.34	100.51 ± 0.43	100.21 ± 0.31
PHT6	100.45 ± 0.54	99.93 ± 0.07	100.61 ± 0.24
PHT7	101.24 ± 0.15	102.72 ± 0.25	102.50 ± 0.65
PHT8	99.19 ± 0.04	102.56 ± 0.20	99.40 ± 0.12
PHT9	100.24 ± 0.33	100.78 ± 0.25	100.57 ± 0.76
PHT10	102.52 ± 0.06	100.73 ± 0.28	101.54 ± 0.58
PHT11	104.14 ± 0.13	103.48 ± 0.37	103.66 ± 0.78
PHT12	103.81 ± 0.59	105.33 ± 0.16	105.66 ± 0.34
PHT13	98.12 ± 0.12	98.31 ± 0.40	99.25 ± 0.26
PHT14	99.08 ± 0.13	99.45 ± 0.25	98.23 ± 0.09
PHT15	99.46 ± 0.34	99.32 ± 0.42	99.22 ± 0.02
PHT16	101.32 ± 0.48	97.15 ± 0.19	100.78 ± 0.11
PHT17	99.52 ± 0.32	100.98 ± 0.19	100.73 ± 0.78
PHT18	102.48 ± 0.45	101.74 ± 0.27	102.66 ± 0.72
PHT19	102.44 ± 0.46	99.57 ± 0.33	101.46 ± 0.53
PHT20	104.58 ± 0.27	102.77 ± 0.10	101.56 ± 0.03
PHT21	101.16 ± 0.18	100.54 ± 0.34	102.39 ± 0.33
PHT22	102.37 ± 0.37	102.60 ± 0.27	100.81 ± 0.85
PHT23	103.74 ± 0.12	103.38 ± 0.30	103.68 ± 0.77
PHT24	105.03 ± 0.82	105.51 ± 0.11	105.66 ± 0.88

All values are expressed in mean ± SD, (n=3)

of pH 6.8, to simulate the gastric pH condition. The result was presented in Figs. 2 to4. The cumulative percentage of the drug released from batch PHT24 shows the better drug release, indicating better bioavailability. These PHFDTs are drafted to enhance the disintegration property in the oral cavity and enhance the bioavailability of the drug. From the present findings, four batches of PHFDTs were prepared with different concentrations of super disintegrant. All the prepared batches were compared with a control batch consisting of super disintegrants. Figs. 2 to 4 represents the *in-vitro* drug release profile of the formulated batches. Noticeable differences in the dissolution profile of selected batches were observed. All selected compositions indicate an acceptable level of acceptance because more than 95% of the mark dose was dissolved within 15 minutes. These results show that the super disintegrant is used to prepare the FDTs to improve the rate of dissolution of PHC. The control batch could only provide about 58% of drug release within 1-hour.

Curcumin

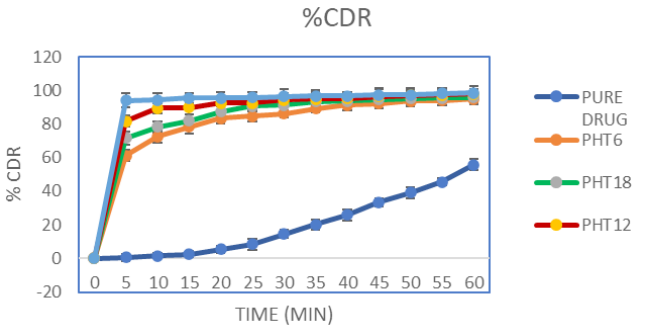

Fig. 2: Graph for the cumulative percentage drug release (%CDR) of Curcumin in phosphate buffer (pH 6.8). All the values were depicted as means of triplet ± SD.

QUERCETIN

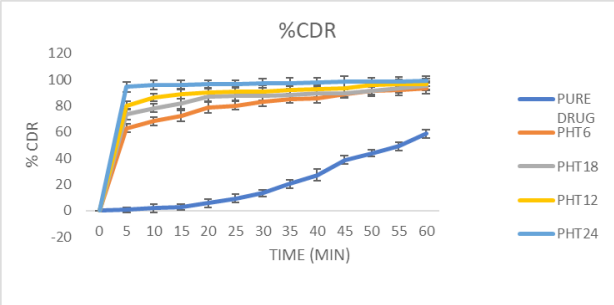

Fig. 3: Graph for the cumulative percentage drug release (%CDR) of Quercetin in phosphate buffer (pH 6.8). All the values were depicted as means of triplet ± SD.

RUTIN

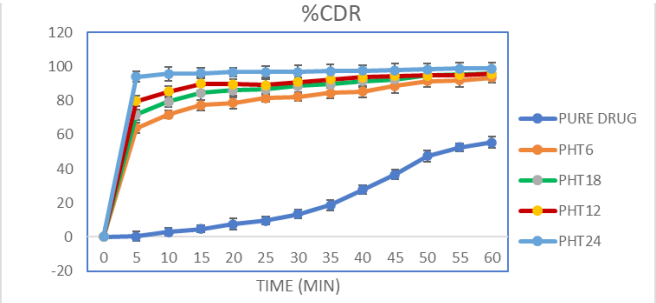

Fig. 4: Graph for the cumulative percentage drug release (%CDR) of Rutin in phosphate buffer (pH 6.8). All the values were depicted as means of triplet ± SD.

Table 6: Stability study (Post-Compression parameters of Direct Compression method formulation)

Time	*Formulation code*	*Colour*	*Odour*	*Hardness*	*Friability*	*Dispersion time*	*Drug content*		
							Curcumin	*Quercetin*	*Rutin*
0 MONTH	PHT6	NC	NC	3.233 ± 0.057	0.702 ± 0.13	87.333 ± 0.57	100.415 ± 0.50	99.931 ± 0.07	100.617 ± 0.22
	PHT12	NC	NC	3.233 ± 0.11	0.718 ± 0.23	11.001 ± 1.00	103.815 ± 0.57	105.331 ± 0.17	105.612 ± 0.23
	PHT18	NC	NC	3.233 ± 0.05	0.694 ± 0.11	51.667 ± 1.73	102.487 ± 0.44	101.397 ± 0.22	102.656 ± 0.37
	PHT24	NC	NC	2.833 ± 0.05	0.668 ± 0.13	9.333 ± 1.15	105.035 ± 0.84	105.509 ± 0.19	105.556 ± 0.18
3 MONTHS	PHT6	NC	NC	3.4 ± 0.1	0.721 ± 0.12	90.667 ± 0.57	99.794 ± 0.17	98.235 ± 0.08	99.438 ± 0.39
	PHT12	NC	NC	3.4 ± 0.1	0.743 ± 0.21	15.667 ± 0.57	103.355 ± 0.18	104.205 ± 0.09	104.322 ± 0.04
	PHT18	NC	NC	3.2 ± 0.1	0.728 ± 0.12	55.333 ± 1.52	101.709 ± 0.39	100.466 ± 0.21	100.567 ± 0.33
	PHT24	NC	NC	3.133 ± 0.57	0.704 ± 0.13	15.333 ± 1.52	104.479 ± 0.84	104.471 ± 0.16	104.095 ± 0.05
6 MONTHS	PHT6	NC	NC	3.467 ± 0.05	0.743 ± 0.14	94.667 ± 1.52	98.793 ± 0.16	97.372 ± 0.09	98.569 ± 0.29
	PHT12	NC	NC	3.567 ± 0.57	0.77 ± 0.21	18.667 ± 0.57	101.573 ± 0.18	102.418 ± 0.16	102.555 ± 0.27
	PHT18	NC	NC	3.433 ± 0.11	0.757 ± 0.11	61.333 ± 1.52	100.965 ± 0.42	99.342 ± 0.06	99.639 ± 0.32
	PHT24	NC	NC	3.2 ± 0.1	0.724 ± 0.12	18.667 ± 1.15	102.616 ± 0.22	104.454 ± 0.12	103.607 ± 0.34

All values are expressed in mean ± SD, (n=3)
NC = No Change

Stability Study

The results showed that no significant differences were observed in organoleptic properties, hardness, friability, dispersion time, and drug content uniformity before and after the storage period at room temperature and ambient humidity, but, when stored at a temperature of 40 ± 2 °C/75% RH ± 5% relative humidity. The hardness of PHFDTs were increased with time, increasing the dispersion time of the PHFDTs; the reason may be loss of moisture from tablets, but, in all cases, dispersion time is within the specified IP limit. This indicates that the formulation is satisfactorily stable.

Drug content was optimized for PHT6. PHT12, PHT18, and PHT24 batches and all the observed data were shown in Table No.6 As there are no significant changes were found during the study period. Thus, the prepared formulations were found to be stable.

From all the prepared formulations tablets of batch PHT24 containing high concentration o1 polymer and super disintegrant was found to be the finest as compared to other formulations because this formulation showed good hardness, low friability, and lowest wetting time (11 ± 1 sec.) and disintegration time (4 ± 1.15 sec.), which is an ideal characteristic of a dispersible tablet.

Therefore, in PHFDTs the effect of super disintegrant especially at the level of 15 and 30%, and in vitro drug dissolution rate was evaluated for performance comparison. These standards include the full focus of selected super disintegrants to be used in formulations. Tablets containing a high concentration of crospovidone may rapidly disintegrate into uniform fine particles, while tablets containing a low concentration of crospovidone showed very slow disintegration into uniform coarser particles. When crospovidone comes in contact with aqueous media gets swollen and burst immediately and release the drug in very short duration. The tablets showed not less than 95 % drug release in 15 minutes in phosphate buffer. The comparative dissolution profile of all Batches

(PHT6, PHT12, PHT18, PHT24) is given in Fig. 3–5. The In vitro drug release order was received as follows: PHT24 > PHT12> PHT18>PHT6

Conclusions

The present study showed potentials for fast absorption, enhanced bioavailability, effective therapy, and patient compliance.

The prepared PHFDTs blend mix showed good pre-compression properties and the results were within the limits. The PHFDTs, showed post-compression results complying with pharmacopoeial limits. The release of polyherbal combination from PHT24 PHFDTs was faster than pure drug and other formulations.

List of Abbreviations:

PHFDTs: Polyherbal fast dissolving tablet, Cm: Curcumin, Qc: quercetin, Rt: Rutin, FDTs: Fast dissolving tablet, SD: Solid dispersion, PHT: Polyherbal tablet, TBD: Tapped bulk density, BD: Bulk density, PHC: Polyherbal combination.

Acknowledgment

Author thanks the management of Singhania University, Rajasthan for enrollment in the esteemed institute for pursuing a doctoral degree. The author extends his heartful gratitude towards the Integral University for providing excellent workplace and research facility in the university. The university has provided a manuscript communication number for further communication IU/R&D/2021-MCN0001136.

References

1. Wadworth AN, Faulds D. Hydroxyethylrutosides. A review of its pharmacology, and therapeutic efficacy in venous insufficiency and related disorders. Drugs. 1992 Dec 1;44(6):1013-1032. Available from: DOI: 10.2165/00003495-199244060-00009
2. Ferrandiz ML, Alcaraz MJ. Anti-inflammatory activity and inhibition of arachidonic acid metabolism by flavonoids. Agents and actions. 1991 Mar;32(3):283-288.
3. Mascolo N, Pinto A, Capasso F. Flavonoids, leucocyte migration and eicosanoids. Journal of pharmacy and pharmacology. 1988 Apr;40(4):293-295. Available from: doi.org/10.1111/ j.2042-7158.1988.tb05250.x
4. Middleton Jr E, Kandaswami C. Effects of flavonoids on immune and inflammatory cell functions. Biochemical pharmacology. 1992 Mar 17;43(6):1167-1179. Available from: doi.org/10.1016/0006-2952(92)90489-90486
5. Bar-Sela G, Epelbaum R, Schaffer M. Curcumin as an anti-cancer agent: review of the gap between basic and clinical applications. Current medicinal chemistry. 2010 Jan 1;17(3):190-197. Available from: doi.org/10.2174/092986710790149738
6. Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Alternative medicine review. 2009 Jun 1;14(2).
7. Maheshwari RK, Singh AK, Gaddipati J, Srimal RC. Multiple biological activities of curcumin: a short review. Life sciences. 2006 Mar 27;78(18):2081-2087. Available from: doi.org/10.1016/j.lfs.2005.12.007
8. Strimpakos AS, Sharma RA. Curcumin: preventive and therapeutic properties in laboratory studies and clinical trials. Antioxidants & redox signaling. 2008 Mar 1;10(3):511-546. Available from: doi.org/10.1089/ars.2007.1769
9. Sharma RA, Steward WP, Gescher AJ. Pharmacokinetics and pharmacodynamics of curcumin. The molecular targets and therapeutic uses of curcumin in health and disease. 2007:453-470.
10. Mauludin R, Müller RH, Keck CM. Development of an oral rutin nanocrystal formulation. International journal of pharmaceutics. 2009 Mar 31;370(1-2):202-209. Available from: doi.org/10.1016/j.ijpharm.2008.11.029
11. Yang J, Guo J, Yuan J. In vitro antioxidant properties of rutin. LWT-Food Science and Technology. 2008 Jul 1;41(6):1060-1066. Available from: doi.org/10.1016/j.lwt.2007.06.010
12. Boots AW, Haenen GR, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. European journal of pharmacology. 2008 May 13;585(2-3):325-337. Available from: doi.org/10.1016/j.ejphar.2008.03.008
13. Laughton MJ, Halliwell B, Evans PJ, Robin J, Hoult S. Antioxidant and pro-oxidant actions of the plant phenolics quercetin, gossypol and myricetin: effects on lipid peroxidation, hydroxyl radical generation and bleomycin-dependent damage to DNA. Biochemical pharmacology. 1989 Sep 1;38(17):2859-2865. Available from: doi.org/10.1016/0006-2952(89)90442-5
14. Oršolić N, Knežević AH, Šver L, Terzić S, Bašić I. Immunomodulatory and antimetastatic action of propolis and related polyphenolic compounds. Journal of ethnopharmacology. 2004 Oct 1;94(2-3):307-315. Available from: doi.org/10.1016/j.jep.2004.06.006
15. Cushnie TT, Lamb AJ. Antimicrobial activity of flavonoids. International journal of antimicrobial agents. 2005 Nov 1;26(5):343-356. Available from: doi.org/10.1016/j.ijantimicag.2005.09.002
16. Bucki R, Pastore JJ, Giraud F, Sulpice JC, Janmey PA. Flavonoid inhibition of platelet procoagulant activity and phosphoinositide synthesis. Journal of Thrombosis and Haemostasis. 2003 Aug;1(8):1820-1828. Available from: doi.org/10.1046/j.1538-7836.2003.00294.x
17. Duarte J, Pérez-Palencia R, Vargas F, Angeles Ocete M, Pérez-Vizcaino F, Zarzuelo A, Tamargo J. Antihypertensive effects of the flavonoid quercetin in spontaneously hypertensive rats. British journal of pharmacology. 2001 May;133(1):117-124. Available from: doi.org/10.1038/sj.bjp.0704064
18. Fincher JH. Particle size of drugs and its relationship to absorption and activity. Journal of pharmaceutical sciences. 1968 Nov 1;57(11):1825-1835. Available from: doi.org/10.1002/jps.2600571102
19. Krasnyuk II, Koval'skii IV, Nikulina OI, Belyatskaya AV, Kharitonov YY, Grikh VV, Obidchenko YA, Vorob'ev AN. Preparation and investigation of tabletted medicinal formulations of a solid dispersion of rutin. Pharmaceutical Chemistry Journal. 2015 Oct 1;49(7):481-485. Available from: DOI 10.1007/s11094-015-1310-0
20. Bardakov AI, Litvin AA, Slivkin AI, Biopharmaceutical Approaches to the Development and Assessment of Ready pharmaceutical Formulations: a Textbook [in Russian], IPTs VGU, Voronezh.
21. Seager H. Drug-delivery products and the Zydis fast-dissolving dosage form. Journal of pharmacy and pharmacology. 1998 Apr;50(4):375-382. Available from: doi.org/10.1111/j.2042-7158.1998.tb06876.x
22. Habib W, Khankari R, Hontz J. Fast-dissolve drug delivery systems. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2000;17(1). Available from: DOI: 10.1615/CritRevTherDrugCarrierSyst.v17.i1.20
23. Indurwade NH, Rajyaguru TH, Nakhat PD. Novel approach- Fast dissolving tablets. Indian drugs. 2002; 39:405-409.
24. Swain RP, Nagamani R, Panda S. Formulation, in vitro characterization and stability studies of fast dispersing tablets of diclofenac sodium. J. Appl. Pharm. Sci. 2015 Jul;5:94-102. Available from: DOI: 10.7324/JAPS.2015.50715
25. Sohi H, Sultana Y, Khar RK. Taste masking technologies in oral pharmaceuticals: recent developments and approaches. Drug development and industrial pharmacy. 2004 Jan 1;30(5):429-448. Available from: doi.org/10.1081/DDC-120037477
26. Kagalkar AA, Nitave SA. Development & evaluation of herbal fast dissolving tablet of Bauhenia veriagata Linn. Indian Journal of Drugs. 2014;2(4):169-173.
27. Pawar H, Varkhade C, Jadhav P, Mehra K. Development and evaluation of orodispersible tablets using a natural polysaccharide

isolated from Cassia tora seeds. Integrative medicine research. 2014 Jun 1;3(2):91-98. Available from: doi.org/10.1016/j.imr.2014.03.002
28. Aulton ME. Pharmaceutics: The Science of Dosage Form Design. 2nd edition, Published by Churchill Livingstone, USA 1998; 223-253.
29. Martin A, Swarbrick J, Cammarata A. "Physical Pharmacy", 3rd Ed, Varghese Publishing Company, Bombay 1991; 492-520.
30. Augshurger LL, Vuppla MK. Hand Book of Pharmaceutical Granulation Technology, Drugs and the Pharmaceutical Sciences, 7-23.
31. Encyclopedia of Pharmaceutical Technology, IIIrd Edition, Vol.-I, 4078.
32. Government of India, Ministry of health and family welfare, Indian Pharmacopoeia. The controller of Publications Ghaziabad, 2007; Vol- II, 423-424.
33. Subrahmanyam C.V.S. "Text Book of Physical Pharmaceutics". 2nd edition. Delhi: Vallabh Prakashan. 2004; 210-228.
34. Shahi SR, Agrawal GR, Shinde NV, Shaikh SA, Shaikh SS, Somani VG, Shamkuvar PB, Kale MA. Formulation and in vitro evaluation of orodispersible tablets of etoricoxib with emphasis on comparative functionality evaluation of three classes of superdisintegrants. Rasayan J Chem. 2008;1(2):292-300.
35. Indian Pharmacopoeia the Controller Publication.Vol. II. Delhi; 1996; 256-257
36. British Pharmacopoeia- London, Vol-I and II, 2009; 1973-1977.
37. Furtado S, Deveswaran R, Bharath S, Basavaraj BV, Abraham S, Madhavan V. Development and characterization of orodispersible tablets of famotidine containing a subliming agent. Tropical journal of pharmaceutical research. 2008;7(4):1185-9. Available from: DOI: 10.4314/tjpr.v7i4.14705
38. Singh J, Singh R. Optimization and formulation of orodispersible tablets of meloxicam. Tropical Journal of Pharmaceutical Research. 2009;8(2). Available from: DOI: 10.4314/tjpr.v8i2.44524
39. Radke RS, Jadhav JK, Chajeed MR. Formulation and evaluation of orodispersible tablets of baclofen. Int J Chem Tech Res. 2009 Jul;1(3):517-21.
40. United States Pharmacopoeia 29' The Official Compendia of Standards. Asian. Rockville MD: United States Pharmacopoeial Convention Inc. 2006; 714-720.
41. Sharma D, Singh G, Kumar D, Singh M. Formulation development and evaluation of fast disintegrating tablets of salbutamol sulphate, cetirizine hydrochloride in combined pharmaceutical dosage form: a new era in novel drug delivery for pediatrics and geriatrics. Journal of drug delivery. 2015;2015. Available from: doi.org/10.1155/2015/640529
42. The guideline, I.H. Stability Testing: Requirements for New Dosage Forms Q1C. 1996.
43. Daugherty DJ, Marquez A, Calcutt NA, Schubert D. A novel curcumin derivative for the treatment of diabetic neuropathy. Neuropharmacology. 2018 Feb 1;129:26-35. Available from: doi.org/10.1016/j.neuropharm.2017.11.007
44. Ferreira PE, Lopes CR, Alves AM, Alves ÉP, Linden DR, Zanoni JN, Buttow NC. Diabetic neuropathy: an evaluation of the use of quercetin in the cecum of rats. World Journal of Gastroenterology: WJG. 2013 Oct 14;19(38):6416. Available from: doi: 10.3748/wjg.v19.i38.6416
45. Tian R, Yang W, Xue Q, Gao L, Huo J, Ren D, Chen X. Rutin ameliorates diabetic neuropathy by lowering plasma glucose and decreasing oxidative stress via Nrf2 signaling pathway in rats. European journal of pharmacology. 2016 Jan 15;771:84-92. Available from: doi.org/10.1016/j.ejphar.2015.12.021
46. Solanki SS, Paliwal P, Jain S, Sharma P, Sarkar B. Formulation and Evaluation of CurcuminLiquisolid Tablets. Current Research in Pharmaceutical Sciences. 2012 Dec 31:210-214.
47. Shetake RM, Nanjwade BK, Sarkar AB, Srichana T, Bellad KA. Development and Evaluation of Quercetin Dispersible Tablets.
48. Mahajan HS, Bhalkar KG. Development and Evaluation of Rutin-HPβCD Inclusion Complex Based Mouth Dissolving Tablets. International Journal of Pharmaceutical Sciences and Developmental Research. 2017 Jan 21;3(1):1-6. Available from: DOI: 10.17352/ijpsdr.000009
49. Setty CM, Prasad DV, Gupta VR, Sa B. Development of fast dispersible aceclofenac tablets: effect of functionality of superdisintegrants. Indian journal of pharmaceutical sciences. 2008 Mar;70(2):180. Available from: doi: 10.4103/0250-474X.41452
50. Mohanachandran PS, Sindhumol PG, Kiran TS. Superdisintegrants: an overview. International journal of pharmaceutical sciences review and research. 2011 Jan;6(1):105-109.

How to Cite this Article: Tiwari R, Siddiqui MH, Mahmood T, Farooqui A, Tiwari M, Ahsan F. Formulation and Optimization of Polyherbal Fast Dissolving Tablet of Curcumin, Quercetin and Rutin. Int. J. Pharm. Sci. Drug Res. 2021;13(6):661-670. DOI: 10.25004/IJPSDR.2021.130609