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Formulation and Evaluation of Dry Suspension of Tikhur

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Abstract

Curcuma angustifolia Roxb (Zingiberaceae) known as Tikhur, is a plant that is native to India. Rhizome of this plant is commonly used in traditional medicine to treat a variety of ailments such as fever, acidity, diarrhea, gastric ulcer, burning micturition etc. The objective of present study was to develop a stable reconstitutable dry suspension of tikhur. We prepared four different formulations of tikhur as dry suspensions. Geometric mixing methodology was followed to prepare the formulations. Tests performed to evaluate dry formulations included flow properties. Among all the developed formulations, P4 was the best having excellent flow property. There was no interaction between the drug and excipients used in the suspension which was confirmed from the compatibility studies. Reconstituted suspension was evaluated for its colour, taste, viscosity, pH, sedimentation volume, density, redispersibility, stability studies. During stability studies no significant changes were observed for 3 months. Thus, the formulation of reconstitutable suspension of tikhur was optimized and evaluated.

Keywords: Tikhur; Dry powder; Formulation; Optimization; Stability

Introduction

Tikhur (Curcuma angustifolia; family Zingiberaceae) is a rhizomatous herb [1]. It is one of over 80 species belonging to the Curcuma L. genus. It is traditionally used as a medicinal plant. This species is native to the Indian subcontinent. Tikhur is cultivated as medicinal crop in many parts of the India under moist deciduous sal and mixed forest of Chhattisgarh, Madhya Pradesh and Jharkhand [2,4]. Additionally, this species can be found in Nepal, Pakistan, Burma and Laos [5,6]. The leaves have a taste that resembles turmeric. Nutritional and therapeutic qualities are present in the rhizome [7]. The main active components of the rhizome are the non-volatile curcuminoids (curcumin, desmethoxycurcumin and bisdemethoxycurcumin) [8-11]. The starch obtained from the rhizome of tikhur is used for the treatment of cough and bronchitis, burning micturition, appetizer and stomach pains, and peptic ulcers. The starch is also used for the preparation of several foods such as barfi halwa, khoa-jalebi and Gulabjamun [14,15]. The starchy flour is used as a weaning food called shotti. The leaves of the plant yield a volatile oil, possessing antimicrobial and anti-inflammatory properties [12,13]. The route preferred for achieving systemic therapeutic effects is the oral route [16]. Besides solid dosage form such as tablets & capsules, liquid products such as suspensions and emulsions are also used. Suspension is defined as a coarse dispersion of finely subdivided insoluble solid drug suspended in a suitable liquid (usually aqueous) medium. It is a biphasic preparation of one or more solids. Basically it may be flocculated or deflocculated [17]. Dry suspension is a commercial dry mixture that requires addition of water and shaking at the time of dispensing [18]. The preparation of suspension requires a number of excipients or formulation additives so as to render it stable and present it in desired form with essential properties. The various excipients used in the formulation of suspension are: vehicles, wetting agents, suspending agents, flocculating agents, viscosity modifiers, and formulation additives

[19]. When swallowing is challenging, it is a better method of delivery than solid dosage forms like tablets or capsules. Due to its advantages over other routes of administration, including ease, patient compliance, and safety, oral administration is recommended [20]. A dry suspension can offer several advantages such as maintenance of the chemical stability of the active compounds until reconstitution at the start of treatment. The suspension can be easily administered to children of different ages by adapting the volume to swallow [21]. The purpose of this work was to prepare, optimize and evaluate the reconstitutable suspension of Tikhur. Consequently, the initial goal of this work is to formulate a dry powder suspension from which a stable reconstituted suspension can be prepared .Factorial designs are used in experiments where the effects of different factors or conditions on experimental results are to be elucidated. A factor is an assigned variable such as concentration, temperature, lubricating agent, drug treatment or diet. Our experiment is based on 2*2 factorial design in which two factors are to be studied at two levels.

Materials and Methods

Materials

HPMC, stearic acid and silicon dioxide were obtained as a gift samples from 'Reve Pharma' MIDC, Sinnar, Nashik. Sucrose and flavouring agent (cinnamon) were purchased from M/s. Dagdu Teli Chandwadkar Trading Co, Nashik. Sodium benzoate from Cookwell foods, Pune, Maharashtra, India. Tikhur powder was procured from Herbal dealer Sudhir Jain, Kenda Tal. Kota Dist. Bilaspur, Chhattisgarh. The tikhur had been prepared by the tribals by traditional methods.

Equipments: Digital pH meter (model EQ610), Sieve shaker machine (Sodexo HTM, Electro lab/EMS8), measuring balance (WENSAR), Bulk density apparatus, Brookfield viscometer (Viscolead adv.), Mortar-pestle, Stability chamber.

Compatibility study

Drug and excipients were mixed in 1:1 ratio (1g:1g) and stored in polybags at room temperature. Samples were analyzed after 24 hrs and at the end of 4 weeks storage [22].

Preparation of dry suspension of Tikhur

Different reconstitutable formulations of tikhur powder were prepared by following method. The granules of tikhur were powdered mixed with the required quantity of sugar. Sodium benzoate was mixed with colloidal silicon dioxide, stearic acid and hydroxy propyl methyl cellulose. Flavour was mixed with above ingredients. All the materials were mixed properly. After mixing, this powder blend was mixed continuously for 30 minutes. All the formulations of dry suspension were prepared in the same manner. All prepared formulations were filled into bottles (Table 1). Suspension was prepared by adding water q.s to make 50mL. Factorial design [23]. 2*2 factorial design was applied for preparing trial batches. Factor A-HPMC, was tested at 2 levels-1.25g and 0.75 g. Factor B-Colloidal silicon dioxide was tested at 2 levels-0.75 and 0.5 g. The responses measured were 1-Sedimentation volume and 2-Angle of repose.

Evaluation

Preformulation studies

The formulated batches for powdered dry suspension were evaluated for their bulk density, tapped density, Hausner's ratio, angle of repose, compressibility index according to the standard procedures [24,25].

Sieve analysis

The Sieve number # 20, # 40, #60, # 80, # 120 were placed in a series in increasing pore diameter (decreasing sieve)order. 50 g of powdered drug was weighed accurately and transferred on the sieve #20 which is kept on the top. The sieves were shaken for 15 min.Then the drug retained on each sieve was taken and weighed separately and expressed in terms of % [26].

Organoleptic evaluation

The formulated suspensions were analyzed for colour, odour and taste [27,28]. The taste of suspension was evaluated by panel method. A test was conducted on the four formulations. Six volunteers between the ages of 22-60 were selected. Each volunteer was given 5mL dose of formulated suspensions.

Evaluation of the reconstituted suspension

Physiochemical characteristics

To each dry suspension. These were evaluated according to the parameters given below relating to their physicochemical characteristics.

pH

pH of the suspension was determined using a calibrated digital pH meter at 25ºC [29].

Viscosity

Brookfield viscometer are used to determine the viscosity of the suspension. For this test 30mL of suspension was taken in a small beaker in such way that spindle L2 was completely immersed in suspension. Measurements were taken at 50 rpm and 25 ºC [30].

Sedimentation volume

Sedimentation volume (F) is a ratio of the final volume of sediment (Vu) to the original volume of sediment (Vo). 50 mL of each

suspension was transferred into 100 mL measuring cylinder and the volume of sediment formed was noted after 24 hrs [31].

Redispersibility

The test consisted of manually shaking the stoppered bottle after allowing the sedimentation experiment for 24 hrs. The formulation was assessed based on the time and work needed to turn the silt into a homogenous suspension. Good dispersion in a single inversion was considered as 100% redispersible. The percent ease of redispersibility dropped by 5% for each subsequent inversion required [32].

Density

The specific gravity bottle method was used to determine the density of the suspension formulation. The specific gravity bottle was weighed (W1) after being carefully cleaned and dried. The bottle was filled with suspension and weighed again (W2). The density of suspension was then determined from the weight of content [33,34].

Pourability

Suspension was reconstituted in water. Then it was filled in bottles and poured from the bottles to evaluate its pourability [30].

Stability studies

Dry powder and reconstituted suspension were subjected to stability studies according to the ICH guidelines. F4 formulation showing good flow property and sedimentation volume was selected for stability studies at RT and 40oC/75 RH in stability chamber for 3 months. It was evaluated for colour, pH, and viscosity at intermittent of intervals up to 3 months [35].

Results and Discussion

The formulation development of oral suspension of tikhur was done with different levels of HPMC IP as suspending agent and colloidal SiO2 as glidant & anticaking agent.

Compatibility study

Compatibility testing proved that the drug and excipients did not interact chemically and physically with each other (Table 2).

Sieve analysis

The particle size analysis is concludes that large amount (77.92%) of drug particle was retained on sieve 20 and remaining (22.08%) of dug passes through all sieves shown in (Table 3).

Organoleptic evaluation

Colour, odour and taste evaluation in volunteers confirmed that taste of suspension was good (Table 4).

Flow property of Tikhur powder formulation

The results of micromeritics studies for dry suspension of tikhur were shown in table 5. The Carr's index value between the 12-16% indicates good compressibility. The angle of repose less than 40° indicates good flowability of powder. Hausner's ratio is an important parameter to determine the flow behavior of dry powder and indicative of inter-particle friction. Hausner's ratio value of less than 1.25 demonstrated excellent flow [36].

Physicochemical evaluation of reconstituted suspensions

The pH of formulations P1 to P4 ranged from 5.09-4.37 which is desirable for stability. Redispersibility is a parameter determined to evaluate the sedimentation behaviour of suspension. The redispersibility of all the formulations were found to be in good agreement with the theoretical value indicating the good sedimentation behaviour of formulations. An excellent redispersibility was observed for P4. Thus we can confirmed the good sedimentation behaviour of respective formulation as observed in sedimentation volume test. The viscosity of the four formulations ranged between 11.43 to 96.65 cps with formulation P4 showing the optimum value 99.65 cps at 50 rpm.

Statistical optimization of formulations [37]

2*2 factorial design was applied for preparing the trial batches. Factor A-HPMC was tested at 2 levels-1.25 g & 0.75. Factor B-Colloidal silicon dioxide was tested at 2 levels-0.75g & 0.5 g. The responses measured were 1- Sedimentation volume and 2-Angle of repose. The main effects of A and B are estimated at Low level (-), high level (+) .To estimate the effects we, add the responses multiplied by the signs in appropriate column and divide by 2. (Table 5,6).

The main effect of an on response1 (Sedimentation volume) and response 2 (angle of repose) was calculated as 0.08, 2.88 respectively.

The main effect of B on response1 (Sedimentation volume) and response 2 (angle of repose) was calculated as 0.06, 0.87 respectively.

The main effect of HPMC and Colloidal SiO2 was positive on Sedimentation volume and angle of repose. On the basis of above results, formulation P4 was selected as the optimized product.

Example. Main effect of B (Colloidal SiO2) on Response 1 (calculation)

Main effect of B (Colloidal SiO2) = $\frac{1}{2}$ [b+ab] - $\frac{1}{2}$ [(1) +a]

= $\frac{1}{2}$ [0.26+0.38] - [(0.24) +0.28]

= $\frac{1}{2}$ [0.64] - [0.52]

= 0.06

Stability studies

Short term accelerated stability study was performed for the optimized (P4) dry powder oral suspension. The formulation was packed in HDPE bottles of 50 mL capacity. Evaluation of the dry suspension was done initially and at the end of each month for3 months [38].The dry suspensions were analyzed for their physical appearance. The pH was measured immediately on preparing reconstituted suspension. It was confirmed that the developed suspension has good stability (Table 7).

Table 1: *Composition of dry suspension of Tikhur (weight in g).*

Ingredients	P1	P2	P3	P4	Use
Tikhur	0.5	0.5	0.5	0.5	API
HPMC	0.75	1.25	0.75	1.25	Suspending agent
Colloidal silicon dioxide	0.5	0.5	0.75	0.75	Glidant, Anticaking agent
Stearic acid	1	1	1	1	Lubricant
Sodium benzoate	0.05	0.05	0.05	0.05	Preservative
Sucrose	5	5	5	5	Sweetener
Flavouring agent	0.5	0.5	0.5	0.5	Flavour
Total weight(g)	8.3	8.8	8.55	9.05	---

Table 2: *Compatibility studies of Tikhur.*

Drug+excipient	Ratio	Initial colour	4th week	Conclusion
Drug	1	White	No change	Compatible
Drug+HPMC	1: 1	White	No change	Compatible
Drug+Stearic acid	1: 1	White	No change	Compatible
Drug+SiO_2	1: 1	White	No change	Compatible
Drug+Sodium benzoate	1: 1	White	No change	Compatible
Drug+Sucrose	1: 1	White	No change	Compatible
Drug+Flavor	1: 1	Buff	No change	Compatible

Table 3: *Particle size distribution of Tikhur powder.*

Sieve no.	Sieve size (µm)	Amount retained (g)	Percentage retained(g)	Cumulative % retained
20	840	38.96	77.92	77.92
40	420	9.99	19.98	97.9
60	250	0.54	1.08	98.98
80	177	0.30	0.6	99.58
120	125	0.19	0.38	99.96

Table 4: *Organoleptic evaluation.*

Formulation	Colour	Odour	Taste
P1	Buff	Aromatic	Sweet
P2	Buff	Aromatic	Sweet
P3	Buff	Aromatic	Sweet
P4	Buff	Aromatic	Sweet

Table 5: *Flow properties of Tikhur powder formulation.*

Formulation	Bulk density	Tapped density	Hausner's ratio	Carr's index	Angle of repose
P1	0.40	0.47	1.17	14.82	26.56
P2	0.41	0.50	1.21	16	33.69
P3	0.38	0.43	1.13	11.62	31.68
P4	0.34	0.39	1.14	12.82	30.31

Table 6: *Physicochemical evaluation of reconstituted suspensions.*

Formulation	pH	Density	Viscosity(cp)	Sedimentation volume	Redispersability
P1	5.09	0.99	11.43	0.24	13 inversion in 10 sec.
P2	5.42	0.98	66.65	0.28	10 inversion in 9 sec.
P3	5.11	0.98	14.15	0.26	9 inversion in 8 sec.
P4	4.37	0.99	96.65	0.38	5 inversion in 4 sec.

Table 7: *2*2 factorial design.*

Products	Symbol	A(HPMC)	B(Colloidal SiO_2	Response 1	Response 2
1	(1)	-	-	0.24	26.56
2	a	+	-	0.28	33.69
3	b	-	+	0.26	31.68
4	ab	+	+	0.38	30.31

Table 8: *Stability studies of optimized formulation (P4).*

Period	pH	Appearance
Initial	4.37	No change
1 month	4.34	No change
2 month	4.30	No change
3 month	4.30	No change

Table 9: *Evaluation of marketed sample.*

Evaluation Test	P4	Marketed sample
Colour	Buff	White
Taste	Sweet	Tasteless
Odour	Aromatic	Odourless
pH	4.37	5.07
Sedimentation volume	0.38	0.18

Comparison with Marketed Sample

The marketed product TIKHUR FLOUR manufactured by Trikund Food and Herbs Private Limited was evaluated for the parameters like colour, taste, odour, pH, sedimentation volume (Table 8,9). Formulation (P4) was compared with marketed product [35]. From the comparative study between marketed sample and P4 formulation it was found that the evaluation parameters were improved in optimized batch (P4) (Figure 1).

Conclusion

Dry suspension formulations P1, P2, P3 and P4 were prepared and evaluated for physiochemical characteristics. P4 formulation was more suitable among all and was considered for further studies. 3 months studies under accelerated conditions were performed for dry suspension by placing it in stability chamber and evaluated for physicochemical parameters. Stability studies of formulation after reconstitution with water were also performed for 7 days under

accelerated conditions of temperature and humidity. Physical parameters for P4 formulation were studied every months.

Figure 1: *Tikhur.*

No change 1 was observed in P4 formulation with respect to physical appearance, taste, pH and viscosity. Hence it was concluded that P4 formulation shows acceptable stability. Thus a dry suspension of Tikhur was formulated which provided acceptable palatability and stability. The optimized formulation, P4, will soon be tested for its efficacy in treatment of UTI (acute cystitis) in clinical trials in human patients.

Conflicts of Interest

The authors report no conflicts of interest.

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