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Formulation and Evaluation of Isopropyl Antipyrine oral suspensions

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Attempts were made in the present investigation to evolve a physico-chemically stable, elegant and palalable isopropyl antipyrine oral suspension using suspending agents like sodium carboxy methyl cellulose [Sod. CMC], veegum alone and combination of sodium CMC and microcrystalline cellulose [MCC] in varying proportions. The suspensions were subjected to evaluation and accelerated stability studies have been carried out on a few select formulations. The best formulation was found to have a shelf life of about 2.5 years and bioequivalence studies revealed comparible pharmacokinetic parameters as that of the marketed tablet.

ISOPROPYL antipyrine is a pyrazolone derivative also known by the name 'propyphenazone'. It exerts a pronounced antipyretic, analgesic and anti-inflammatory actions similar to that of amidopyrine and phenazone. In human beings side effects of isopropyl antipyrine are very few. Prolonged use of amidopyrine[1] or phenazone results in severe side effects such as activation of gastric or duodenal ulcers, hepatitis, hypertension, agranulocytosis and aplastic anemia due to which their use is discouraged and banned in many countries including India. Hence isopropyl antipyrine is the recommended substitute for amidopyrine. Currently isopropyl antipyrine oral suspension is not available in Indian market. Hence formulation or isopropyl antipyrine oral suspension which has distinct advantages over solid dosage form in terms of greater bioavailability[2] and acceptance among paediatric and geriatric patients has been taken into consideration.

EXPERIMENTAL

Materials

Isopropyl antipyrine was obtained as gift sample from Juggath Pharma, Bangalore. Sodium carboxy methyl cellulose, 16 cps at 1 % w/v and microcrystalline cellulose were obtained from Rolex lab, Bombay, Veegum from S.D. fine Chemicals, Bangalore. Flavours such as black current, american ice cream soda, orange and cardamom [Bush Boake and Allen, Madras] and the sweetener aspartame [Pierrel Incorporation, Italy] were employed. All the other chemicals were of analytical grade.

METHODS

Preparation of Suspension

The sieved [100/200] isopropyl antipyrine was added to a mixture of Tween 80 [1.5 gm] and purified water [10 ml], left overnight for complete wetting. The Parabens were incorporated in water [30 ml] by warming to 70-80° and sugar was added to make a syrup. The suspending agent/ agents were allowed to swell in about 25 ml water for about 1 hour after which they were dispersed with the aid of a mechanical stirrer to form a smooth paste. Then glycerine, sugar syrup were incorporated into the polymer solution followed by the addition of sodium saccharin / aspartame, isopropyl antipyrine, aerosil, flavours, colouring agent [Sunset Yellow FCF] and mixed uniformly after addition of each ingredient. Finally the suspension was made upto required volume with purified water and homogenised for half an

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Table 1 : Quantity of Each Ingredient used in the formulation

Ingredients	Quantity [In grams for solids and ml for liquids]				
	F1	F2	F3	F4	F5
Propyphenazone	1.50	1.50	1.50	1.50	1.50
Glycerine	5.00	5.00	5.00	5.00	5.00
Citric acid	1.00	1.00	1.00	1.00	1.00
Sodium Saccharin	0.30	0.30	-	-	-
Sucrose	60	60	60	60	60
Aspartame	-	-	0.30	0.30	0.40
Microcrystalline cellulose	-	-	0.75	0.75	0.75
Sod. CMC	0.50	-	0.30	0.40	0.50
Veegum	-	0.50	-	-	-
Aerosil	-	-	0.04	0.04	0.04
Tween 80	1.50	1.50	1.50	1.50	1.50
Methyl paraben	0.18	0.18	0.18	0.18	0.18
Propyl paraben	0.02	0.02	0.02	0.02	0.02
Chloroform	-	0.40	0.40	0.40	-
Orange flavour	-	0.50	0.50	0.50	-
Cardamom flavour	-	0.04	0.04	0.04	-
Black currant flavour	0.50	-	-	-	0.50
American ice cream Soda fl.	–	–	–	–	0.40
Sunset Yellow F.C.F.	0.01	0.01	0.01	0.01	0.01
Purified water [q.s.]	100	100	100	100	100

List of ingredients used for various suspension formulations.

hour. The compositions of various suspensions prepared are depicted in table 1.

Evaluation of the suspension

The formulations were evaluated for various parameters at different intervals (1, 3, 6, 12, 24 and 48 days). Changes in palatability were evaluated by a panel of unbiased taste sensitive individuals. Changes in appearance were determined by measuring absorbance of filtered formulations at 482 nm[3]. Fifty ml of each of the formulations were stored in stoppered measruing cylinders. The height of sedimentation was recorded to calculate the sedimantation volume[4].

After the sedimentation studies, the cylinders were rolled on a horizontal surface at the rate of 10 - 15 per minute. The ease of redispersibility was judged comparitively. Changes in viscosity with ageing was studied using Brookfield DV II + Digital viscometer and the results are presented in table 2. The drug content was determined spectrophotometrically at 550 nm[5] in a separate set of formulations prepared excluding the colouring agent using a Systronics make colorimeter [Model No 112]. The pH of the suspension was determined by using a digital pH meter [Systronics, model No : 324].

Dissolution studies

Dissolution studies of the isopropyl antipyrine oral

Table 2 : Change in viscosity of the formulations with ageing

Ageing [Days]	Viscosity[CPs] F1	F2	F3	F4	F5
01	66 ± 2.0	44 ±1.0	70 ±2.3	79 ± 0.8	91 ± 0.2
03	65 ± 1.6	43 ± 0.9	70 ± 2.8	79 ± 1.1	91 ± 1.2
06	61 ± 2.0	46 ± 2.8	68 ± 1.4	77 ± 1.1	90 ± 1.3
12	59 ± 1.9	49 ± 3.3	66 ± 1.6	76 ± 1.3	88 ± 1.0
24	56 ± 4.2	58 ± 2.1	65 ± 2.4	76 ± 0.9	86 ± 1.2
48	54 ± 1.8	63 ± 1.6	65 ± 2.4	75 ± 0.9	86 ± 0.8

Mean ± S.D n = 3

Suspensions were evaluated at different time intervals for changes in viscosity using Brookfield DV II + Viscometer under room temperature conditions. Each value represents mean ± standard deviation of three determinations.

Table 3: Cumulative % drug release from formulations

Time [Mins]	Cumulative % drug release from formulations F1	F2	F3	F4	F5
01	59.99±1.33	33.25 ± 1.48	49.98 ± 3.01	43.23 ± 0.91	33.25 ± 0.09
03	66.65 ± 0.97	36.57 ± 1.50	63.38 ± 2.83	49.87 ± 1.58	49.87 ± 0.12
05	73.32 ± 1.24	56.52 ± 0.98	76.48 ± 1.96	56.52 ± 1.81	63.18 ± 1.21
10	79.99 ± 1.24	69.83 ± 1.11	86.66 ± 2.31	66.50 ± 1.68	79.81 ± 0.93
15	83.33 ± 1.28	76.49 ± 1.32	89.99 ± 4.30	76.48 ± 2.01	83.14 ± 1.56
30	86.67 ± 2.61	86.47 ± 2.33	93.34 ± 2.81	93.11 ± 1.07	89.79 ± 1.21
45	93.34 ± 3.21	93.13 ± 1.50	96.67 ± 1.21	96.43 ± 1.19	96.45 ± 0.91
60	96.68 ± 1.80	96.70 ± 1.80	99.78 ± 1.91	99.75 ± 0.09	98.12 ± 0.12

Mean ± S.D. n = 3

Suspensions were evaluated for the dissolution studies in USP XXI dissolution apparatus at 50 ± 1 rpm at 37° ± 1°. Each value represents the mean ± standard deviation of three determinations.

suspensions [5 ml] were carried out in U.S.P. XXI dissolution apparatus at 50 ± 1 rpm and 37° ± 1° using pH 1.2 buffer as the dissolution medium. Samples of 2 ml were withdrawn at the time intervals of 1, 3, 5, 10, 15, 30, 45 and 60 minutes and the drug content was estimated spectrophotometrically at 550 nm. The cumulative % drug release of formulations are shown in table 3.

Stability studies

The formulations were subjected to accelerated stability studies at elevated temperatures of 37°, 45°, 60° and were subjected to all the suspension evaluation parameters over a period of 48 days as mentioned earlier. Shelf life determination[6] was done for formulation F5 [Fig 1] as it proved better over other formulations by sedimentation parameters redispersibility and stability studies.

Table 4 : Pharmacokinetic Parameters for suspension and Tablet dosage form containing isopropyl antipyrine

Dosage Form	AUC μg.hr.ml^{-1}]	T_{max} [mins]	C_{max} [μg]
Suspension [Equivalent to 150 mg]	41.46 ±3.34	90	9.31 ±0.99
Tablet [150 mg]	39.58 ±1.01	90	8.61 ±1.22

Mean ± SEM

The formulations were subjected to Bioequivalence studies by cross over pattern in six male rabbits. The results are mean ± standard error of mean.

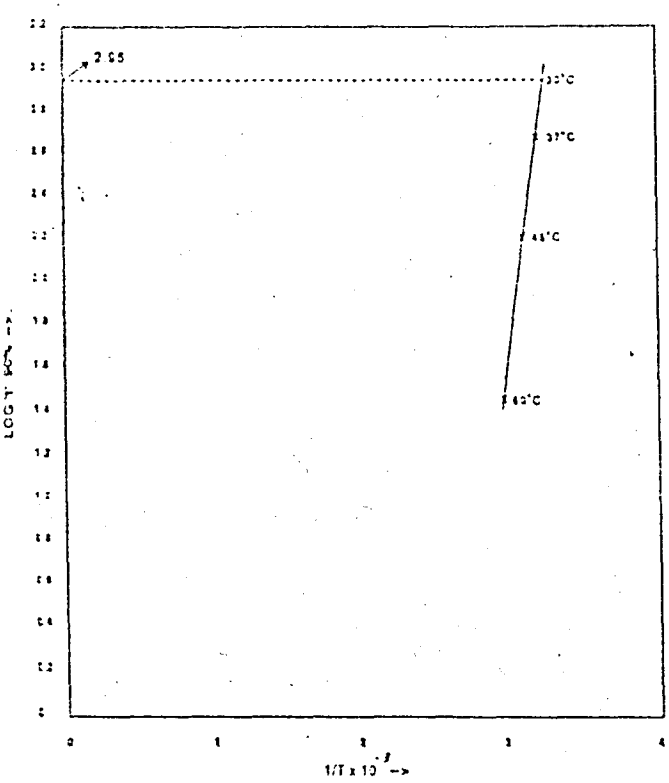

Fig. 1: A graph showing a plot of log 't' 90% V/S 1/T x 10^{-3} for formulation F5 at 37°, 45° and 60°

Bioequivalence studies

Bioequivalence studies were carried out for formulation F5 and marketed tablets of isopropyl antipyrine in 6 male rabbits weighing between 2.5 to 3.0 kg in a cross over pattern. Five ml of blood samples were withdrawn from the marginal ear vein at 30 minute intervals for 5 hours and analysed using HPLC[7]. The results of the study are given in table 4.

RESULTS AND DISCUSSION

All formulations were found acceptable in terms of palatability and appearance. The formulations F1 and F2 showed greater change in sedimentation volume on ageing and the ultimate sedimentation volume was very less comparitively and offered greater resistance to redispersion whereas F3, F4 and F5 showed appreciable sedimentation parameters and exhibited ease of redispersibility. The formulation F2 showed a greater change in viscosity of upto 43% increase over a period of 48 days which is due to the inherent property of Veegum to swell on imbibing water. The formulations F1, F3, F4 and F5 showed a maximum variation of about 20% decrease in viscosity. The drug content of all the formulations was found to be within the limits mentioned in B.P. 1993. The pH studies revealed insignificant changes on ageing. The dissolution profile of the drug in various formulations was quite comparable. The release was almost completed within one hour. The formulations subjected to stability studies were stable at 37° and 45° with very less variation in the parameters evaluated earlier whereas storage at 60° resulted in significant changes in physicochemical parameters of the suspension. Of all the formulations, F5 was found to withstand the stress conditions to a greater extent. The shelf life of this formulation was determined to be 2.5 years.

Considering F5 to be the best of all, this formulation was compared with a marketed tablet dosage form in terms

of bioavailability. The suspension formulation was found to be bioequivalent with the tablet dosage form [P > 0.05].

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