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Physical Stability and Dissolution Rate of Ibuprofen Suspensions Formulated Employing its Solid Dispersions

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Ibuprofen suspensions were formulated employing its solid dispersions in HPMC, PVP, PEG and dextrin and were evaluated for particle size, physical stability and dissolution rate. Ibuprofen suspensions formulated employing its solid dispersions exhibited good suspendability and gave higher dissolution rates of ibuprofen than those formulated with ibuprofen alone and commercial products. Suspension formulated with solid dispersion in dextrin gave highest improvement in dissolution rate and efficiency. Dissolution of ibuprofen from the suspensions obeyed Hixson-Crowell's cube root equation. Good linear relationships were observed between particle size and dissolution rate and efficiency. Smaller particles gave higher dissolution rate and efficiency values.

Ibuprofen is a widely used antiinflammatory analgesic drug. Tablets each containing 400 and 200 mg of ibuprofen and suspensions containing 100 mg of ibuprofen per 5 ml are available commercially. Ibuprofen is practically insoluble in water. I.P. (1996)[1] prescribed a dissolution rate test for ibuprofen tablets. Solid dispersion is a technique studied extensively for improving the dissolution rate of poorly soluble drugs from solid dosage forms like tablets and capsules. No work was reported on the application of solid dispersion technique in suspension formulation. In the present work solid dispersion technique was tried in the formulation of ibuprofen suspensions with an objective of improving the physical stability and dissolution rate of ibuprofen from Suspensions. Suspensions were formulated employing ibuprofen and its solid dispersion in hydroxy propyl methyl cellulose (HPMC), poly vinyl pyrrolidone (PVP), poly ethylene glycol 6000 (PEG) and dextrin. These suspensions were evaluated for particle size, physical stability and dissolution rate. The results are reported in the present communication.

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EXPERIMENTAL

Ibuprofen was a gift sample from M/s. Veco Pharma Ltd. Visakhapatnam. Methyl cellulose (viscosity:65 cps in 0.5% aqueous solution at 25°) and hydroxy propyl methyl cellulose (viscosity:50 cps in 2% aqueous solution at 20°) were gift samples from M/s. Dr. Reddy's Laboratories Ltd. Hyderabad. Poly ethylene glycol 6000, poly vinyl pyrrolidone (Mol. Wt. 40,000), dextrin (CDH), glycerin (Qualigens), sodium benzoate I.P., sucrose, acetone (Qualigens) and methanol (Qualigens) were procured from local market.

Preparation of ibuprofen solid dispersions:

Ibuprofen (4 g) and HPMC or PVP or PEG (0.4 g) were dissolved in methanol (20 ml) to get a clear solution. The solvent was removed by evaporation at 45° under vacuum while mixing the solution. The mass obtained was crushed, pulversied and sifted through mesh No. 100. In case of dextrin, it (16 g) was added to a solution of ibuprofen (4 g) in acetone (20 ml) and dispersed. The solvent was removed by evaporation at 40° while mixing. The mass obtained was crushed, pulverised and sifted through mesh No. 100.

TABLE 1 : FORMULAE OF IBUPROFEN SUSPENSIONS PREPARED

Ingredients (g)	Formulation				
	F1	F2	F3	F4	F5
Ibuprofen	2.0	-	-	-	-
Ibu-HPMC (9:1 SD)	-	2.2	-	-	-
Ibu-PEG 6000 (9:1 SD)	-	-	2.2	-	-
Ibu-PVP (9:1 SD)	-	-	-	2.2	-
Ibu-Dextrin (1:4 SD)	-	-	-	-	10.0
Methyl Cellulose	2.0	2.0	2.0	2.0	2.0
Glycerin	10.0	10.0	10.0	10.0	10.0
Sucrose	20.0	20.0	20.0	20.0	20.0
Sod. Benzoate	0.3	0.3	0.3	0.3	0.3
Purified Water (ml) to	100.0	100.0	100.0	100.0	100.0
pH	5.42	5.29	5.40	5.28	5.15

Preparation of ibuprofen suspensions:

Suspensions containing 100 mg of ibuprofen in 5 ml were prepared as per formulae given in Table 1. Accurately weighed quantity of ibuprofen or its solid dispersions was taken in a mortar and was levigated with a small portion of methyl cellulose mucilage. When a smooth paste has been formed the rest of the methyl cellulose mucilage was added in divided portions while triturating the contents. Sucrose was then added as a solution in water while mixing. Other ingredients were added one after another, mixed and the suspension was transferred to a measuring jar and adjusted to volume.

For comparison, two commercial brands of ibuprofen suspensions (Ibugesic, M/s. Cipla Ltd., Mumbai, Batch No. CH 8138, Mfg. Date : 12/98, Exp. Date: 11/2001 and Febrilix, M/s. Boistar Pharmaceuticals Ltd., Pune, Lot No. GC 009, Mfg. Date: 8/97, Exp. Date : 7/2000) were procured from local market and were evaluated along with the formulated ones.

Particle size measurement:

Size of ibuprofen particles in the suspensions was measured by microscopy. Average and standard deviation of 100 particles was estimated. The results are given in Table-2.

Sedimentation study:

The suspensions were transferred to stoppered measuring jars and were stored at room temperature (27± 1°). The volume of sediment formed was noted at regular intervals of time. The sedimentation volume[2], ratio of the ultimate height (Hu) of the sediment to the initial height (Ho) of the suspension (i.e. Hu/Ho) were calculated and the results are given in Table-2. Redispersibility of the sediment formed was tested by inverting the jar through 360°.

Estimation of ibuporfen:

Ibuprofen contents were estimated by measuring absorbance at 221 nm. The method obeyed Beer's law in the concentration range of 0-10 µg/ml. Excipients used in the suspensions did not interfere in the method. When a standard drug solution was assayed repeatedly (n=6), the coefficient of variation (precision) and relative error (accuracy) of the method were found to be 0.8% and 0.5% respectively.

Dissolution rate study:

The dissolution rate of ibuprofen from various suspensions was studied using USP XXI Dissolution Rate Test Apparatus employing a paddle strirrer. In 900 ml of purified water, a sample of suspension equivalent to 100 mg of ibuprofen a speed of 50 rpm and a temperature of 37± 1° were employed in each test. A 5 ml aliquot of dissolution medium was withdrawn at different intervals of time through a filter of size 0.45 µ suitably diluted and

TABLE 2 : CERTAIN PARAMETERS OF IBUPROFEN SUSPENSIONS FORMULATED

Formulation	Particle size (μ) (x ± s.d)	Sedimentation Volume (Hu/Ho)	$D.E_{15}$(%) (x ± s.d)	Hixson-Crowell's cube root dissolution rate constant k. ($mg^{1/3}$ min^{-1})	T_{50} (min.)
F1	16.30±10.32	1.00	51.97±5.27	0.353	2.8
F2	7.85±6.36	1.00	60.50±0.39	0.416	2.4
F3	8.50±5.61	1.00	60.05±1.23	0.446	2.3
F4	7.10±5.81	1.00	67.89±0.37	0.506	2.2
F5	4.95±2.10	1.00	69.57±0.33	0.530	2.1
Commercial-I	29.70±21.70	0.98	37.11±2.54	0.200	25.0
Commercial-II	33.50±21.01	0.96	40.09±1.77	0.243	13.6

Suspensions formulated employing ibuprofen alone (F1) and its solid dispersion in HPMC (F2), PEG (F3), PVP (F4) and dextrin (F5)

assayed spectrophotometrically at 221 nm for ibuprofen content.

RESULTS AND DISCUSSION

Suspension F1 was formulated employing ibuprofen as such. Whereas suspensions F2, F3, F4 and F5 were formulated employing solid dispersions of ibuprofen in HPMC, PEG, PVP and dextrin respectively. The average particle size in F1 was found to be 16.3 μ, whereas the average size in suspensions, F2, F3, F4 and F5 was found to be 7.85, 8.5, 7.1 and 4.95 μ respectively. Thus the size of the dispersed drug particles was much less in the suspensions formulated employing solid dispersions. The particle size in commercial suspensions was 29.7 and 33.5 μ in the two products tested.

All the suspensions, formulated as well as commercial, exhibited good suspendability of ibuprofen. No sedimentation was observed in the suspensions formulated during the 3 m period of storage. The suspensions formulated were very smooth without any flocculation.

The dissolution parameters of ibuprofen from various suspensions are summarized in Table 2. Dissolution efficiency (DE_{15}) values were calculated as suggested by Khan[3]. The dissolution of ibuprofen from all the suspensions obeyed Hixson-Crowell's cube root dissolution rate equation[4]. Plots of ($W_0^{1/3}$-$W^{1/3}$) Vs time were found to be linear. The correlation coefficient between ($W_0^{1/3}$-$W^{1/3}$) and time values was in the range 0.93-0.99 with various products.

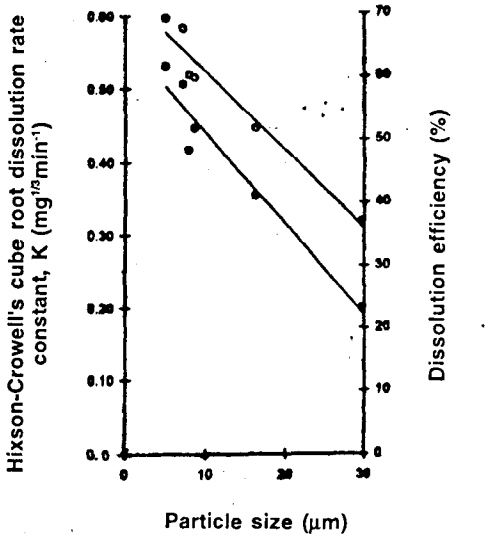

Fig. 1 : Relationship between particle size and dissolution rate (●) and dissolution efficiency (○) of ibuprofen suspensions.

Suspensions formulated employing solid dispersions (F2, F3, F4 and F5) gave significantly ($P<0.05$) higher dissolution than formulation F1 and commercial products. Suspension F5, formulated employing solid dispersion in dextrin, gave highest dissolution rate and efficiency (DE) among all the products formulated and commercial. The enhanced dissolution rate of ibuprofen form suspensions formulated employing solid dispersions is due to

the smaller particle size observed in these suspensions. Good linear relationships were observed (Fig. 1) between the particle size and dissolution rate (r=0.9526) and particle size and dissolution efficiency (r=0.964) of ibuprofen from the suspensions. Smaller particles gave higher dissolution rates.

Thus ibuprofen suspensions formulated employing its solid dispersions exhibited good suspendability and gave higher dissolution rates of ibuprofen than those formulated with ibuprofen alone and commercial products. Suspensions formulated employing solid dispersion in dextrin gave highest improvement in dissolution rate and efficiency. Good linear relationships were observed between particle size and dissolution rate and dissolution efficiency. Smaller particles gave higher dissolution rate and dissolution efficiency values.

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