Studies on Formulation and *In Vitro* Dissolution of Embelin Tablets

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The objective of the present study was to develop a tablet formulation of embelin employing the wet granulation and direct compression techniques. This study was also carried out to design a suitable dissolution medium for embelin. Effect of different diluents like lactose, microcrystalline cellulose, and co-crystallized lactose-microcrystalline cellulose were studied for improving the flow and compressibility. Binders such as starch paste and alcoholic polyvinyl pyrrolidone were used to optimize the crushing strength of the formulation. Dried starch powder was used as a disintegrating agent in both techniques. Pre and post formulation parameters were studied for all the batches. Co-crystallized lactose-microcrystalline cellulose and alcoholic polyvinyl pyrrolidone proved to be the best diluent and binder respectively. Solubility study of embelin in different media revealed that embelin has optimum solubility in phosphate buffer of pH 8 and in 2% aqueous sodium lauryl sulfate solution. Incorporation of 10% v/v ethanol in phosphate buffer of pH 7.4, significantly increased the solubility of embelin. These solutions were also found to be the most suitable media for dissolution of embelin in dissolution studies.

Embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone), is the active constituent of the fruits of *Embelia ribes* (2.5 to 3.1%), known as *Vidang* (Family, Myrsinaceae)[1]. Embelin is reported to have anthelmintic[2], antifertility[3], antitumour[4], antimicrobial[5], and analgesic activities[6]. Ayuveda prescribes 6 to 12 g oral dose per day, of the *Vidang* fruit powder[7]. Dispensing and consumption of such a large dose is very inconvenient to the patients. Hence, in the present investigation, an attempt was made to develop the tablet formulation of embelin, to improve the patient compliance and acceptability.

Since no systematic studies on design and development of embelin formulations, or *in vitro* dissolution of embelin are available in the literature, we proposed to develop a suitable tablet formulation and dissolution medium, to characterize *in vitro* release profile of embelin. The effect of pH and the effect of surfactant on the dissolution of drugs have been individually investigated by many researchers, during the past several decades[8,9]. Embelin is water-insoluble, but forms a water-soluble, violet colored complex, in alkaline medium[10]. Hence, we tried buffer systems of different physiological pH to determine the solubility profile of embelin. We also studied the effect of varying concentrations of sodium lauryl sulfate (SLS) in water, and of ethanol, in phosphate buffer of pH 7.4, on solubility of embelin. The results are reported in this communication.

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MATERIALS AND METHODS

Powder of *Vidang* (*Embelia ribes*, F: Myrsinaceae) was purchased from L. V. Gandhi and Sons, Ahmedabad. Other materials used in the study such as lactose, microcrystalline cellulose (MCC), co-crystallized lactose-MCC, directly compressible starch, magnesium stearate, talc, starch, polyvinyl pyrrolidone (PVP), dried starch powder, and sodium lauryl sulfate (SLS) of pharmaceutical grade, were obtained as gift sample from Acron Pharmaceuticals, Ahmedabad. Double distilled water was used throughout the study. All the chemicals used for the isolation and analysis of embelin, were of analytical grade.

Embelin was isolated in large amount, from *Vidang* powder, by the method described by Sarin and Ray[11]. Its identity was established by IR, NMR, and Mass spectroscopy, and by comparing these results with the spectra reported in literature[12]. Assay of isolated embelin

was carried out by UV spectrophotometric method.

Formulations of embelin:

Embelin was blended with diluents like lactose, MCC, and Co-crystallized lactose-MCC, in the ratio of 1:1. Granules were prepared using PVP (3, 5 and 7%) in isopropyl alcohol, or starch paste (5, 7 and 10%). Dried starch powder (5, 7 and 10%) was added as a disintegrating agent. To arrive at an optimal formulation, preliminary data on various derived characters and physical characters of tablets, were generated (Tables 1 and 2). The granules were lubricated with 1% magnesium stearate and 2% talc, and compressed using a Cadmach make rotary multipunch tablet press, with round punches. The tablets had an average weight of 400 mg, and each tablet contained 100 mg of embelin. The average crushing strength was 5.2 kgf, and friability was 0.4%. The composition of the formulation is shown in Table 3.

In order to minimize the processing steps, embelin tablets were prepared by direct compression technique. Embelin was blended with diluents like directly compressible starch, MCC, and co-crystallized lactose-MCC ,as shown in Table 4. Dried starch powder (5% and 10%) was added as a disintegrating agent. The final powder blend was lubricated with 1% magnesium stearate and 2% talc, and compressed as described earlier.

Evaluation of embelin tablets:

The tablets of embelin, prepared by wet granulation and direct compression techniques, were evaluated for preformulation and post-formulation parameters, such as crushing strength, friability, disintegration time, content uniformity, and *in vitro* release profile.

Solubility study of embelin:

Maximal solubility of embelin in different buffer systems of various physiological pH, varying concentration of SLS in water (0.5, 1, 2 and 3%), and varying proportions of ethanol in phosphate buffer pH 7.4 (5, 7.5 and 10%), was studied. Excess amount of embelin was taken in 10 ml of the above media, in boiling test tubes, and dissolved in triplicates by sonication. The maximal solubility of Embelin in each medium, was determined at different time intervals (0, 15 and 60 min). After filtering the content of each test tube by Whatman filter paper, the clear filtrate was acidified with a drop of concentrated HCl. The acidified media were extracted completely with diethyl ether, in separating funnels. Diethyl ether was evaporated at room temperature, and the dried residues were reconstituted in ethanol. After suitable dilution with ethanol, the embelin content was determined by taking UV reading at 291 nm, against ethanol blank. The results show that solubility varied from 0.13 to 0.268 mg/ml.

***In vitro* dissolution study of embelin tablets:**

Best formulations of EW3 and ED4, were subjected to *in vitro* dissolution study in USPXXIV dissolution apparatus Type II at 37± 0.5° and at 100 rpm, using 500 ml of different dissolution media (phosphate buffer pH 7.4 and 8.0, 10% ethanol in phosphate buffer of pH 7.4, and 2% SLS in water). Percent embelin released at 60 minutes was determined for each medium, by the method discussed in solubility experiments. Content uniformity of

TABLE 1: EFFECT OF DILUENT ON DERIVED PROPERTIES OF EMBELIN POWDER GRANULES

Batch No. Parameters\Diluents	D1 Without diluents	D2 Lactose	D3 MCC	D4 Co-crystallized lactose-MCC
Bulk density (g/ml)	0.27	0.35	0.46	0.42
Tapped density(g/ml)	0.4	0.50	0.53	0.51
Carr's index	33.5	30.0	13.20	17.64
Hausners' ratio	1.50	1.42	1.15	1.21
Angle of repose (^{0})	53.13	45.78	39.28	34.52

Ratio of embelin powder to diluent is 1:1

TABLE 2: EFFECT OF BINDERS ON DERIVED PROPERTIES OF GRANULES/TABLET PROPERTIES OF EMBELIN

Batches Parameters	W1	W2	W3	W4	W5	W6
PVP (%w/w)	3	5	7	-	-	-
Starch paste (%w/w)	-	-	-	5	7	10
Carr's index	15. 6	20.1	24.6	15.1	23.1	28.8
Hausners' ratio	1.31	1.26	1.17	1.35	1.12	0.81
Angle of repose (^{0})	30.6	31.0	34.1	28.5	30.0	30.3
Friability (%)	1.24	0.30	0.28	1.2	0.91	0.84
Crushing strength (Kgf)	3.82	5.22	5.34	2.51	3.34	5.2
Disintegration time (min)	22	20	20	21	20	20

TABLE 3: FORMULATION OF EMBELIN POWDER BY WET GRANULATION TECHNIQUE

Batches Parameters	EW1	EW2	EW3
Lactose-MCC (mg)	248	240	228
PVP (% w/w)	5	5	5
Dried starch powder (% w/w)	5	7	10
Crushing strength (Kgf)	4.8	5.3	5.5
Friability (%)	0.5	0.35	0.33
Disintegration time (min)	15	12	10

Each tablet contains 100 mg embelin powder, each tablet weigh 400 mg

the optimized batches, EW3 and EW4 was also studied, using UV spectrophotometric method. The results are mentioned in Table 5.

RESULTS AND DISCUSSION

For the isolation of embelin from *Vidang* fruit powder, the method of Sarin and Ray was found very efficient, as it involves minimum steps of extraction and purification (Yield 3.6% w/w).

Data from Table 1 revealed that embelin has very poor flow property (angle of repose: 53.13°), and a very poor compressibility (Carr's index: 33.5). MCC gave the lowest Carr's index (13.20), and lowest Hausner's ratio (1.15). Lactose-MCC also showed satisfactory Carr's index (17.64), Hausner's ratio (1.21), and angle of repose (34.52°). As MCC is required to be incorporated in large amount and not cost effective, lactose-MCC appeared to be the better alternative, as it has better compressibility and flow properties.

Results revealed that 5% PVP gives optimized results, in terms of crushing strength and friability. Starch paste at a concentration of 10%, also gave better results, but friability was comparatively higher (0.84%). It was found that a formulation containing 10% dried starch powder, gave a disintegration time of 10 minute.

In direct compression experiments, EP showed poor compressibility (Carr's index: 33.5) and flowability (angle of repose: 53.13°). Directly compressible diluents, like directly compressible starch, co-crystallized lactose-MCC, and MCC, were used to improve the flow property and compressibility of EP. Results shown in Table 4, revealed that flow property and compressibility of EP improved with 10% concentration of co-crystallized lactose-MCC. Batch. ED4 exhibited desired features in all aspects, and was selected as the optimal formulation for dissolution studies (Table 4).

Experiments with solubility study of embelin in buffer systems of different physiological pH, revealed that embelin solubilizes only in alkaline pH range, in aqueous medium. It shows optimal solubility (0.27 mg/ml) in phosphate buffer (pH 8.0), and maximal solubility of 0.32 mg/ml at pH 8.6, after 15 minutes of sonication. It shows very low solubility (0.13 mg/ml) in phosphate buffer of pH 7.4. Incorporation of ethanol up to 10% v/v in phosphate buffer (pH 7.4), further increased the solubility of embelin to 0.252 mg/ml. SLS is an anionic surfactant, which formed a water-soluble violet coloured complex with embelin. It was found that, in water with 2% w/v SLS, embelin has

TABLE 4: EFFECT OF DILUENTS ON FORMULATION PARAMETERS OF EMBELIN TABLETS BY DIRECT COMPRESSION TECHNIQUE

Batch No.	Diluents	Dried starch powder (%w/w)	Properties of powder/blend			Tablet properties		
			Carr's index	Hausner's ratio	Angle of repose (°)	Crushing strength(Kgf)	DT (min)	Friability (% w/w)
EP	-	-	33.5	1.5	53.13	-	-	-
ED1	Directly compressible starch	5	30.2	1.42	39.0	4.8	14	1.1
ED2		10	27.4	1.40	37.6	4.9	13	1.2
ED3	Co- crystallized lactose-MCC	5	20.0	1.25	35.6	5.1	11	0.8
ED4		10	21.9	1.26	32.3	5.1	10	0.6
ED5	MCC	5	24.0	1.47	36.2	5.8	4	0.4
ED6		10	34.8	1.54	34.3	5.8	4	0.4

EP: Embelin powder, DT: Disintegration Time, MCC: Microcrystalline cellulose

TABLE 5: CONTENT AND PERCENT RELEASE OF EMBELIN FROM THE OPTIMIZED BATCHES OF EMBELIN TABLET

Batch No.	Content of embelin (%w/w)	Percent embelin released from tablet in selected medium*			
		Phosphate buffer (pH 7.4)	Phosphate buffer (pH 8.0)	10% ethanolic phosphate buffer (pH 7.4)	2% SLS in water
EW3	99.20%	40.34%	93.92%	82.35%	94.72%
EP4	101.3%	42.4%	94.0%	85.34%	95.4%

an optimal solubility of 0.238 mg/ml, after 15 min of sonication.

Hence, it was concluded from the solubility experiments, that phosphate buffer of pH 8.0, 2.0% SLS in water, and 10% ethanolic phosphate buffer of pH 7.4, are the ideal dissolution media, to study in vitro release profile of embelin. The optimized batches of the embelin tablet formulations, EW3 and ED4, were studied for the content uniformity, and in vitro release profile in the above media. Dissolution study of embelin was also carried out in phosphate buffer of pH 7.4, as it is usually employed for drugs that are poorly soluble in water/acidic medium.

Dissolution of embelin at pH 7.4 is not satisfactory, as only 40-42% of embelin was released within one hour. However, incorporation of 10% v/v ethanol dramatically increased the release of embelin to 85%. This may be due to the wetting effect of ethanol, or the high solubility of embelin in ethanol. A higher dissolution of around 94%, could be achieved by using a medium with 2% SLS, or phosphate buffer (pH 8.0). This is due to the formation of water-soluble salts of embelin in basic medium, which renders the medium, violet in colour. Comparative dissolution patterns are depicted in Table 5. There were no remarkable differences in the dissolution profiles of wet granulated, and directly compressed tablets. This is the first comprehensive report on the formulation and dissolution profiles of embelin, which can be further utilized for other formulations containing *Vidang*.

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