Research Article**Enhancement of solubility and dissolution rate of poorly water soluble dipyridamole using *Emblica officinalis* fruit powder**Syed Reshma Sulthana¹, A. Anil Kumar²¹Department of Pharmaceutics, Vikas College of Pharmacy, Vissannapeta, Krishna district, Andhra Pradesh, India²Vikas College of Pharmacy, Department of Pharmaceutics Vissannapeta, Krishna district, Andhra Pradesh, India

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Abstract

Objective: The Objective of present study was to enhance the solubility of Dipyridamole and formulate Dipyridamole conventional tablets using *Emblica officinalis* fruit powder, *Ocimum basilicum* seed powder by employing Kneading technique and to carry out the Evaluation of Prepared tablets. Dipyridamole is a BCS (Biopharmaceutical classification system) class II drug which is poorly water soluble, it is freely soluble in acidic buffer pH 1.2 and shows negligible solubility in basic buffer i.e., pH 6.8 phosphate buffer. **Material and methods:** The technique employed for solubility enhancement is kneading technique of Solid dispersions. The formulations were prepared by direct compression and evaluated for various parameters such as disintegration time, hardness, and friability and Cumulative percent drug release. **Results and Conclusion:** The optimized formulation containing combination of these two natural powders has shown 98.85% of Drug release at 30 minutes which consists of 1:3 ratio of Drug and *Emblica officinalis* (Amla powder) fruit powder and the *Ocimum basilicum* (Sabja) seed powder used in the optimized formulation was 10% of the total tablet weight. The disintegration time of optimized formulation was found to be 21 seconds where as the formulation containing sodium starch glycolate as disintegrant has shown 33 sec of disintegration time. Drug interaction studies performed by using FTIR Spectroscopy shows that *Ocimum basilicum* and *Emblica officinalis* when combined with Dipyridamole there were some drug-polymer interactions seemed to be participated resulted in the improvement of solubility and dissolution characteristics. Hence, from the obtained results, it is clear that *Emblica officinalis* seed powder has shown Solubility Enhancement and *Ocimum basilicum* has shown super disintegration.

Keywords: Natural ingredient, solubility enhancement, super disintegration, *Emblica officinalis*, *Ocimum basilicum*

Introduction

There are numerous challenges in pharmaceutical formulation, but the most important is the drug solubility. Poor water solubility tops the list of critical compound properties among the five key physicochemical parameters in early compound screening, viz., dissociation constant, solubility, permeability, stability, and lipophilicity (Alsenz and Kansy, 2007). Approximately more than 40% new chemical entities (NCEs) developed in the pharmaceutical industry are practically insoluble in water. Problem of solubility is a major challenge for

formulation scientist (Bonthagarala et al., 2015). Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for showing a pharmacological response. Dipyridamole is used for controlling and treating of angina pectoris, as well as to clinically prevent recurrence of myocardial infarction and thrombosis (Gerbino and Remington, 2005). It is antiplatelet and anticoagulant drug which is a poorly water soluble, weakly basic drug which rapidly gets dissolved in stomach but in intestine it is dissolved incompletely. Dipyridamole is a drug with pH dependent solubility. Since an increase of pH in gastro-intestinal tract reduces solubility of dipyridamole hence the bioavailability of dipyridamole upon oral administration would be very low because the drug gets absorbed in the stomach but in intestine it has negligible absorption due to increase in pH of intestine (Tanya and Russell, 1994). So, there is need of solubility enhancement of Dipyridamole in intestinal pH. There are various

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Technologies for the enhancement of solubility like Micronization, Nanonization, Solid dispersions, Complexation, Crystal engineering and many other techniques (Christopher Vimalson et al., 2016).

The technique employed in the present study is Kneading technique. In some cases like pH dependent soluble drugs, using pH modifiers the solubility enhancement will be achieved effectively. There are various pH modifiers like citric acid, tartaric acid, succinic acid, Fumaric acid and some other organic acids. The present work is for focussing on the importance of natural excipients. So here naturally obtained *Emblica officinalis* fruit powder commonly called as amla powder was selected as pH modifier as it consists of various kinds of minerals, Vitamins like ascorbic acid and B-Complex and different kinds of amino acids and it also contains Phenolic compounds like Gallic acid and ellagic acid and organic acids like citric acid (Zhang et al., 2003). Indian gooseberry or amla (*Emblica officinalis*) is a euphorbiaceous plant, which is widely distributed in subtropical and tropical areas of India, China and Indonesia. Amla fruit is mainly used in many traditional medicinal systems (Khan, 2009). The pulpy portion of present around the seed of *Emblica officinalis* was used for the solubility enhancement of the drug Dipyrindamole in the present work.

The main aim of the present work is investigation of natural ingredients on solubilisation and improvement of dissolution characteristics of Dipyrindamole. So the ingredients used in the present work are mostly natural ingredients. Keeping into consideration of natural products here in the present study another natural ingredient used was *Ocimum basilicum* seed powder which is investigated for disintegration and super disintegration purpose. There are various superdisintegrants like Sodium starch glycolate, Cross carmellose sodium, Cross povidone which are already available and readily used in the Pharmaceutical industry. As the present study was focussed on to investigate natural powders, *Ocimum basilicum* seed powder was selected for investigation of disintegration and super disintegration effect. *Ocimum basilicum* is commonly called as Sabja and basil obtained from the herb basil plant which is having a wide variety of medicinal uses. The formulations were designed using the combination of *Emblica officinalis* fruit powder and *Ocimum basilicum* seed powder were carried out by direct compression method. The super disintegration property *Ocimum basilicum* seed powder was compared with Sodium starch glycolate.

Materials and methods

Materials

Dipyrindamole was obtained from Pharmaceutics laboratory (Department of Pharmaceutics at Vikas college of Pharmacy (Vissannapeta) which was received as gift sample from Ra

Chem Pharma (Hyderabad, India). The very fine Amla powder of food grade and Sabja seeds were purchased from Sree anjaneya ayurvedic pharmacy (Vijayawada, India) Magnesium stearate and Talc and all the other chemicals were used from the chemicals present in the pharmaceutics laboratory at Vikas college of Pharmacy which were of high analytical grade.

Solubility studies and Dissolution studies of Pure drug Dipyrindamole

Solubility of Dipyrindamole was determined in methanol, water, chloroform, pH 1.2 and pH 6.8 Phosphate buffer. Solubility studies were performed by taking excess amount of Dipyrindamole in different beakers containing solvent. The mixtures were shaken for 24 hrs at regular intervals. The solutions were then filtered by using whatmann's filter paper. The filtered solutions are analyzed by double beam UV Visible Spectrophotometer. Pure drug Dipyrindamole was compressed into tablets using all other excipients and dissolution was carried out by USP Type II dissolution apparatus using acidic buffer and basic buffers. Samples were collected upto 3 hours and analyzed by double beam UV visible spectrophotometer.

Preparation of *Ocimum basilicum* (Sabja seed) powder

Ocimum basilicum seeds were powdered and passed through sieve No.80. The powdered material was collected and packed and stored under good conditions.

Preparation of kneading mixture of Drug and *Emblica officinalis* (Amla powder) fruit powder

Drug and natural powder i.e., amla powder were taken in different ratios i.e., upto 1:4 ratios into a clean mortar and pestle and triturated with small quantity (few drops) of Propanol. Constant triturating was done up to 30 minutes, and then air dried at room temperature. The obtained powder was made finer using mortar and pestle, passed through sieve no.100 and stored in desiccators over fused calcium chloride. Common names of *Emblica officinalis* i.e., Amla powder (A) and *Ocimum basilicum* i.e., Sabja powder (S) are also used in the further sections of present study.

Drug content studies of Kneaded mixtures of Drug and *Emblica officinalis* fruit powder (Amla powder)

Required quantity of kneaded mixture was weighed accurately which is equivalent to 25mg of drug Dipyrindamole and transferred to 25 ml volumetric flask. The volume was made up to the mark by using 0.1 N HCl and 6.8 pH phosphate buffer in separate flasks and kept aside for 1-2 hours with occasional shaking and then filtered. The drug content was analyzed

Table 1. Formulation composition of designed formulations

Ingredients (mg)/Tablet	Formulation code										
	AS1	AS2	AS3	AS4	AS5	AS6	AS7	AS8	AS9	ASSG	R
DEOM	75	100	125	75	100	125	75	100	125	125	-
Dipyridamole	-	-	-	-	-	-	-	-	-	-	25
OBS Powder	10	10	10	20	20	20	30	30	30	-	20
SSG	-	-	-	-	-	-	-	-	-	20	-
Avicel pH 101	107	82	57	97	72	47	87	62	37	47	147
Mg Stearate	4	4	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4	4	4
Total weight (mg)	200	200	200	200	200	200	200	200	200	200	200

*DEOM= Drug and Emblica officinalis powder kneaded mixture; OBS Powder=Ocimum basilicum seed powder; SSG=Sodium Starch Glycolate; *Common names of natural powders A=Amla powder, S=Sabja powder are used as formulation codes

spectrophotometrically at wavelength of 283 nm for 0.1 N HCl and 293 nm for 6.8 pH Phosphate buffer using UV -Vis spectrophotometer.

Determination of Flow Properties of Powders of Designed Formulations

Angle of Repose

Angle of repose (θ) was determined by using a funnel whose tip was fixed at a constant height (h) of 2.0 cm from the horizontal surface. The powder was passed separately through the funnel until the tip of the conical pile touches the tip of the funnel (Lachman and Lieberman, 2009; Marshall et al., 1987). The radius of the base of the conical pile is measured as r (cm). It was calculated by formula as follows:

$$\theta = \tan^{-1} (h/r)$$

Bulk density (Db)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted (Lachman and Lieberman, 2009; Marshall et al., 1987).

It can be calculated as follows:

This initial volume was called the bulk volume. It is expressed as

$$\text{Bulk density} = M/V_o$$

M = Powder mass; V_o = apparent unstirred vol

Tapped density

The power sample under test was screened through sieve no.18 and the weight of sample equivalent to 25 gm filled in 100 ml graduated measuring cylinder. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend were measured. The tapped (p_t) was calculated using formula:

$$\text{Tapped density (p}_t\text{)} = M/V_t$$

M = weight of sample power taken, V_t = tapped volume

Compressibility index

The bulk density, tapped density was measured and compressibility index was calculated using form

$$\text{C.I.} = (P_t - P_o) / (P_t) \times 100$$

P_t = tapped density; P_o = bulk density

Hausner's ratio

Hausner's ratio is the indirect index of ease of powder flow. Hausner's ratio of the blend was calculated using the following formula (Lachman and Lieberman, 2009; Marshall et al., 1987):

Hausner's ratio = P_t/P_o P_t = tapped density, P_o = bulk density

Evaluation of tablets

Weight Variation

Ten tablets were selected randomly from each formulation batch and weighed individually for checking the weight variation as per Pharmacopoeia standards (Lachman and Lieberman, 2009).

Thickness

The thickness of the tablets was measured using a micrometer screw gauge (Lachman and Lieberman, 2009).

Friability

Friability test was carried out using Veego friability testing apparatus by taking Five tablets, weighed and revolved at 25 rpm and 100 revolutions and again the tablets were weighed (Lachman and Lieberman, 2009).

Hardness

Hardness of the tablets was measured using Pfizer hardness tester.

Drug content

Estimation of drug content was carried out by taking two

tablets from a batch then crushed into fine powder in the mortar using pestle. The obtained fine powder equivalent to 25 mg of Dipyridamole was extracted in pH 6.8 phosphate buffer. This solution was filtered through a Millipore filter of 0.45 μ m pore size. After suitable dilutions, drug content was spectrophotometrically determined at a wavelength of 293 nm (Lachman and Lieberman, 2009; United States Pharmacopoeia, 1980).

Disintegration

For carrying out determination of disintegration time the apparatus used was Disintegration testing apparatus (Electro Lab (ED-2L) Mumbai) The USP device to test the disintegration time has 6 glass tubes that 3 inches long open at the top and 10 mesh screen at bottom end. To test disintegration time one tablet is placed in each tube and the basket rack is positioned in the 1 litre capacity of buffer which is filled with the buffer we need and temperature maintained is $37 \pm 2^\circ\text{C}$. The basket is moved up and down through a distance of 5-6 cms from 28-32 cycles. According to USP standard the tablets must disintegrate and all particles must pass through 10 mesh screen. If any residue remains it must have soft mass with no hard core. There are certain limits of disintegration time mentioned in IP and USP and other standard books (Lachman and Lieberman, 2009; United States Pharmacopoeia, 1980; Wagner, 1971).

In-vitro dissolution studies

The In-vitro drug release study was conducted using USP Type-II, rotating paddle apparatus (Veego Instruments Corporation, Mumbai, India). The operating speed was at 50 rpm and carried out for 30 minutes according to USP. The dissolution medium used was 6.8 pH Phosphate buffer. The temperature was maintained at $37 \pm 0.5^\circ\text{C}$. Samples were withdrawn at pre-determined time intervals, filtered, and analyzed using UV-Visible spectrophotometer (Elico SL-210) at 293 nm (Lachman and Lieberman, 2009; United States Pharmacopoeia, 1980).

FT-IR Spectroscopy Studies

The Fourier transform infrared spectroscopy is carried out in order to identify the drug and polymer interactions. FT-IR studies were carried out for drug, natural powders and mixture of drug and natural powders. Spectrum was integrated in transmittance mode at the wave number range $400-4000\text{ cm}^{-1}$.

Statistical Analysis

Considering the evaluation data obtained from dissolution profile, Zero order and first order plots were plotted and the regression values were found to be 0.9852 and 0.9172 respectively. To know the drug release mechanism of the formulated tablets, the release data was fitted into mathematical models Higuchi and Korse-meyer peppas plots. The R^2 values are 0.9729 & 0.99 respectively.

Results and discussion

Preformulation Studies

The Dipyridamole pure drug was observed as yellow in colour and found to be pure crystalline powder and bitter in taste which is odourless and having solubility in chloroform, methanol, acidic buffers, ethanol and Di methyl Sulfoxide, and it was found to be practically insoluble in Water and basic buffers. Its melting point was found to be $168 \pm 0.5^\circ\text{C}$.

Table 2. Flow Properties of Dipyridamole

S. No.	Parameter	Observed Value
1	Angle of repose	$33^\circ.52'$
2	Bulk density	0.48 gm/cc
3	Tapped density	0.6 gm/cc
4	Cars index %	25%
5	Hausner's ratio	1.25

Dissolution studies of Pure drug Dipyridamole

When dissolution was carried out for pure drug using other excipients and without addition of any solubility enhancer the values tabulated clearly shows that it is having a good solubility in the acidic buffer and a insoluble nature in case of basic buffer, dissolution values of pure drug dipyridamole are tabulated in (Table 3). In order to make it soluble in basic buffer *Embllica officinalis* fruit powder is added in different concentrations.

Table 3. Dissolution studies of Pure drug Dipyridamole

S. No	Time	0.1 N HCl	6.8 pH buffer
1	10 min	101.1	1.11
2	20 min	100.8	2.34
3	30 min	99.8	5.14
4	45 min	96.5	7.18
5	60 min		10.88
6	2 hr		14.94
7	3 hr		17.97

Drug content studies of kneaded mixtures of Drug and *Embllica officinalis* fruit powder

After estimation of drug content of the kneaded mixtures of Drug and *Embllica officinalis* fruit powder (Amla powder) in different ratios the drug content values are increased from 1:2 ratio of Drug: *Embllica officinalis* fruit powder. So, the formulations were designed using 1:2, 1:3, 1:4 ratios of Kneaded mixture (Table 4).

Table 4. Drug content values of Kneaded mixtures

Ratio of Drug : Amla powder	Drug Content (%)
1:1	41.27
1:2	76.83
1:3	95.47
1:4	96.58

Determination of flow properties of powders of designed formulations

The flow properties of the designed formulations are found to be better when compared with the flow properties of the pure drug Dipyrindamole (Table 5).

FT-IR Spectroscopy Studies

The drug polymer interaction study results has shown that there is some difference in the peaks shown by pure drug

Dipyrindamole and the combination of drug and the natural powder. Few drug polymer interactions were participated due to which the peaks were changed, which resulted in the improvement of the solubility and dissolution characteristics.

Evaluation of formulated tablets

Disintegration time

The disintegration of AS6 formulation which contains 10% Sabja powder was quick when compared with the synthetic super disintegrant Sodium starch glycolate, all the other formulations other than optimized also shown a quick disintegration, Hence (Sabja powder) *Ocimum basilicum* seed powder can be considered as a super disintegrant according to the present study (Table 7).

In-vitro drug release of the formulations

The Dissolution was carried out using 6.8 pH Phosphate buffer. The poorly water soluble Dipyrindamole has a great

Table 5. Flow properties of the designed formulations

Formulation	AOR (θ) ^o	BD(g/cc)	TD(g/cc)	Carr's index (%)	Hausner's Ratio
AS1	26.23	0.47	0.55	17.02	1.17
AS2	27.51	0.46	0.53	15.21	1.15
AS3	27.45	0.45	0.53	17.77	1.17
AS4	28.32	0.41	0.50	21.95	0.2
AS5	27.54	0.42	0.51	21.42	1.2
AS6	29.12	0.50	0.55	10	1.1
AS7	28.32	0.37	0.41	10.8	1.10
AS8	29.40	0.36	0.42	16.66	1.16
AS9	28.34	0.37	0.45	21.62	1.21
ASSG	28.52	0.49	0.54	11.1	1.1

Figure 1. FTIR spectra of pure drug Dipyrindamole

Figure 2. FTIR spectra of drug + Amla powder

Figure 3. FTIR spectra of drug + Sabja Powder

Figure 4. FTIR spectra of optimized formulation AS6

extent of drug release by the usage of the naturally obtained *Emblica officinalis* fruit powder at different ratios, The highest drug release of 98.85% was observed for the formulation AS6 which contains 1:3 ratio of Drug and Amla powder was noted at 30 minutes of dissolution. In case of ASSG formulation the super

disintegrant used was Sodium starch glycolate 10% concentration which has shown 33 ± 2 disintegration time which is greater when compared to optimized formulation AS6 which consists of Sabja powder of 10% Concentration. The R formulation has shown Disintegration time of 22 ± 3

Table 6. Post Compression parameters of designed formulations

Formulation	Weight Variation (%)	Hardness (kg/cm ²)	Friability (%)	% Drug content (%)
AS1	1.95 ± 0.01	5.1± 0.03	0.239 ± 0.02	85.92± 0.02
AS2	1.95± 0.02	5.0± 0.04	0.118± 0.02	87.03± 0.02
AS3	1.28± 0.03	5.1± 0.03	0.301 ± 0.02	89.56± 0.01
AS4	1.2± 0.02	4.8± 0.05	0.199± 0.01	93.95± 0.01
AS5	1.16± 0.03	4.7± 0.04	0.865± 0.02	94.29± 0.02
AS6	1.36± 0.02	4.5± 0.03	0.421± 0.01	99.83± 0.02
AS7	1.51 ± 0.01	4.7± 0.04	0.317± 0.02	90.25± 0.01
AS8	1.83± 0.02	4.8± 0.05	0.210± 0.01	91.81± 0.03
AS9	1.65 ± 0.01	4.7± 0.03	0.382± 0.02	89.75± 0.02
ASSG	1.37± 0.02	5.0± 0.04	0.210± 0.01	82.16± 0.02
R	1.22± 0.01	4.1± 0.04	0.303 ± 0.02	13.47± 0.03

Table 7. Table representing Disintegration time of designed formulations

S. No.	Formulation code	Disintegration time(sec)
1	AS1	32±3
2	AS2	35±2
3	AS3	37±3
4	AS4	23±4
5	AS5	24±3
6	AS6	21±2
7	AS7	26±3
8	AS8	29±2
9	AS9	27±3
10	ASSG	33±2
11	R	22±3

which consists of Sabja powder used as Super disintegrant but in this formulation the drug release was 16.89% at 30 minutes because here in this formulation R, no solubility enhancer was used, this formulation was designed for comparison purpose. Hence it is clear that the formulations containing Natural

powders *Emblica officinalis* fruit powder and *Ocimum basilicum* seed powder has shown good results when compared to the formulations which do not contain these natural powders in the present study (Table 8).

Drug release kinetics

The results of release kinetics were shown in table 9 and figure 6-9.

Figure 5. Plot representing Cumulative drug release data Vs Time of AS6, ASSG, R Formulations**Table 8.** *In vitro* drug release values of designed formulations

Time	Formulation code										
	AS1	AS2	AS3	AS4	AS5	AS6	AS7	AS8	AS9	ASSG	R
0	0	0	0	0	0	0	0	0	0	0	0
5	20.26±1.5	31.45 ±1.4	30.59 ±0.8	24.74 ±0.3	32.76±0.1	18.97±0.8	24.65 ±0.2	25.67±0.6	28.22±0.5	24.61±0.6	2.9 ±0.9
10	31.35±1.1	42.91±0.3	41.87±0.6	37.56±0.8	44.98±0.1	34.76±0.6	39.36 ±0.6	39.30±0.4	32.12 ±0.8	36.58 ±0.3	5.1 ±0.7
15	42.29±0.9	53.87±0.3	52.90±0.9	49.80±0.1	56.51±0.6	56.84 ±0.7	52.11±0.8	52.91±0.2	58.23 ±0.2	41.02 ±0.8	9.20 ±0.1
20	53.72±0.6	65.55±0.5	63.24 ±0.3	61.45±0.9	68.35±0.6	61.32±0.1	66.23±0.9	68.50±0.6	71.62 ±1	54.70 ±0.5	11.21±0.6
25	74.41±0.5	76.3±0.5	73.88 ±0.3	74.21±1.1	79.07±0.5	83.12±0.1	78.30±0.2	82.13±0.6	84.20±0.9	68.90 ±0.9	14.60 ±0.2
30	81.92 ±1.5	84.0±0.4	89.56±0.5	91.95±0.5	93.29±0.6	98.85±1	91.25±0.3	92.8 ±0.9	90.16±0.8	84.57±4	16.89±0.4

Table 9. Model fitting for In vitro drug release kinetics of the optimized formulation

Formulation Code	Kinetic Models			
	Zero order R ²	First order R ²	Peppas R ²	Higuchi R ²
AS6	0.9852	0.9172	0.99	0.9729

Figure 6. Zero order plot of optimized formulation **Figure 7.** First order plot of optimized formulation **Figure 8.** Higuchi plot of optimized formulation

Conclusion

The present work was carried out for the design and development of Dipyridamole conventional tablets using naturally obtained powders. From the above study it may be concluded that the natural powders such as *Emblica officinalis* fruit powder (Amla powder) investigated for solubility enhancement activity is found to be a natural solubility enhancer of poorly water soluble

Figure 9. Korsemeyer-Peppas plot of optimized formulation

drug Dipyridamole and *Ocimum basilicum* seed powder (Sabja powder) was investigated for Disintegration, super disintegration and found to be super disintegrant, the Kneading technique employed was proved best for the solubility enhancement of poorly soluble drug Dipyridamole. Solubility of Dipyridamole was increased and optimized at 1:3 ratio of (Drug : *Emblica officinalis* fruit Powder) hence it can be concluded that the concept of effect of Natural ingredients on Dipyridamole is best, it is safe and cost effective for enhancing the solubility, bioavailability of poorly water soluble drugs.

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