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FORMULATION, DEVELOPMENT, AND IN-VITRO EVALUATION OF A FILM-COATED TABLET CONTAINING A FLAVONOID DIOSMIN AND HESPERIDIN COMBINATION

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ABSTRACT

In this study combination of diosmin and hesperidin was used for the treatment of a condition called chronic venous insufficiency. diosmin and hesperidin are citrus bioflavonoids that act as a vascular-protecting agents used to treat chronic venous insufficiency, hemorrhoids, lymphedema, and varicose veins. A preformulation study was carried out for the formulation of the tablet of the selected drug. A compatibility study was carried out between diosmin and hesperidin along with excipients like Avicel pH 101, Klucel EXF, Sodium Starch Glycolate, and Magnesium stearate. Formulation of tablets was carried out in various trials. Trial 1 consists of two batches, F1 and F2 but due to disintegration issues, the formula was modified and trial 2 of batch F3 and F4 was carried out. Batch F2 and F3 were found to be of low hardness and high disintegration time. Trial 3 was conducted for batches F5, F6, and F7 where binders like polyvinyl pyrrolidone, Ac-Di-Sol, and Klucel EF were used. Batch F8 and F9 were formulated as trial 4 with Klucel EXF. Batch F8 produced a satisfactory result and hence coated with agent Wincoat WT-QCAQ-1261 Brown. Batch 8-V has shown acceptable results of disintegration time and was subjected to a stability study. Finally, a concluding manufacturing process was formulated depending on the obtained results.

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Introduction

Disorders caused by Varicose veins and venous diseases impediments are comprehend to affect more than a quarter of the adult population, and the treatment of these illnesses are the primary cause of medical cost. Chronic venous insufficiency (CVI) is a disorder categorized by vicissitudes, which take place in leg secondary tissues due to prolonged venous hypertension caused by structural or functional abnormalities of the veins and/or venous valves [1, 2].

Tablets are the most common concrete dose form in contemporary use. It might be described as a component form of solid medicaments prepared by compaction. Most comprise a mixture of powders that are compacted in a die to produce a single rigid body [3].

Various vasoactive and non-vasoactive agents have been studied for the treatment of venous disease, out of which the micronized purified flavonoid fraction (MPFF) has been proved to be more beneficial for the treatment [4].

Diosmin (a citrus bioflavonoid) is an MPFF used as a vascular-protecting agent used to treat chronic venous insufficiency, hemorrhoids, lymphedema, and varicose veins. As a flavonoid, it also exhibits anti-inflammatory, free-radical scavenging, and anti-mutagenic properties. This drug has proved to be effective in the management of pain, heaviness, and swelling by reducing them. When supplemented with routine surgical treatment, it has shown good effects on severe trophic changes [5].

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Hesperidin is a bioflavonoid alone or in combination with other citrus, bioflavonoids are most often used for blood vessel conditions such as hemorrhoids, varicose veins, and poor circulation (venous stasis).

A combination of diosmin and hesperidin has shown synergism in the vasculo-protective activity, in addition to anti-inflammatory and antioxidant activity. Diosmin is an MPFF-bioflavonoid formulated in tablet dosage form so that the exposed surface area of the flavonoids can be reduced. Additionally, the coating given to the tablet prevents flavonoid degradation from the external environment [6, 7]. This formulation is used as a supplementary therapy in the treatment of chronic venous insufficiency complications in the lower limbs.

Materials and Methods

Diosmin, Vascular- protecting Agent (Bioflavonoid) was obtained from Elder Pharma.

Hesperidin, Bioflavonoid, was obtained from Biogen Chemicals, New Delhi, India. Avicel pH 101 was obtained from FMC Biopolymers, SSG (Type A) (Sodium Starch Glycolate) is obtained from Signet Chemical Corporation Pvt. Ltd., Gelatin is obtained from Biobaxy Technologies, Klucel EF, Klucel EXF is obtained from Hercules, Magnesium Stearate was obtained from Ferro Corporation, Wincoat WT-QCAQ 1261 Brown is obtained from Wincoat, Instacoat IC-S-3100 Sol Yellow is obtained from Ideal Cures Pvt. Ltd.

Preformulation Study

Preformulation research is the initial phase in developing a dosage form of a drug substance. Following are the test conducted for the preformulation study, particle size, bulk density, tapped density, Carr's index and Hausner's ratio, flow property (angle of repose), FT-IR spectra, melting point, and drug–excipient compatibility study [8, 9].

Solubility Determination

Drugs solubility was determined in five various media ranging from pH 1.0 to 7.5. These media are Water, 0.1 N HCl, Acetate Buffer pH 4.5, Phosphate Buffer pH 6.8, and pH 7.2. The excess drug was added to a definite volume of solvent till it gets precipitated and then it was kept on a shaker (RO-123R, Remi Instruments, Mumbai, India) for 24 hr. Withdrawn samples were filtered through a Whatman filter paper, and assayed by a UV spectrophotometer (1800, SHIMADZU, Japan). This procedure was repeated six times to get accuracy in the result [10].

Particle Size Determination

The particle size of the drug was determined by the Malvern particle size analyzer which uses the principle of light scattering [11].

Bulk Density Determination

25 gm of drug previously passed through sieve #20 was weighed and transferred in a 100 ml graduated cylinder. The powder was carefully leveled without compacting and read the unsettled apparent volume. The apparent bulk density was calculated in g/ml using the following formula [11].

$$\text{Bulk density} = \frac{weight\ of\ powder}{Bulk\ volume\ of\ powder} \quad (1)$$

Tapped Density Determination

25 gm of drug previously passed through sieve # 20 was weighed and transferred in a 100 ml graduated cylinder. The cylinder was then fitted on a tap density apparatus and allowed for 500 taps. Additional 750 taps were done. This was taken as the final tap volume. The tapped density was calculated in g/ml using the following formula [11].

$$\text{Tap density} = \frac{weight\ of\ powder}{Tapped\ \ volume\ of\ powder} \quad (2)$$

Compressibility Index and Hausner's Ratio

The compressibility index, also referred to as Carr's Index and Hausner's ratio are used to measuring the propensity of powder to be compressed [11]. Carr's index and Hausner's ratio were calculated using the following;

$$\text{Compressibility index} = \frac{Tapped\ density - bulk\ density}{Tapped\ \ denstiy} \times 100 \quad (3)$$

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density} \quad (4)$$

Determination of Flow Property

The frictional force in the powder can be measured by the angle of repose. The angle of repose was calculated by the fixed funnel method [11]. The angle of repose was calculated by using the following formula;

$$\text{Tan } \theta = \frac{Height\ of\ pile}{Radius\ of\ pile} \quad (5)$$

Melting Point

Melting point is prime confirmation of drug. In this method, the temperature was noted at which point the sample start melting to finish. For this drug whose analysis to be carried out was filled into a capillary tube and tied in such a way that it remains dipped in a liquid paraffin bath and the temperature was noted [12].

Compatibility Study

The investigation principal aim of this study was to recognize a established storage state for a drugs and additivies that are compatible with their formulations. In this method, a variety of excipients were a selection of mixed distinctly with a drug in a proportions commonly utilized for tablet formulation. From which 1 set is for preliminary investigation whereas 2 groups and 3 cliques of every mixture are prepared are kept at 40ºC/75% RH and 60 ºC for 1 month. After 1 month the samples are experiential visually for variation of color or their advent in powder form. The two sets of samples were used in the DSC study to determine if drug-drug interface occurred [13].

Ratio of Ingredients for Compatibility Study of Diosmin and Hesperidin

The ratio of various ingredients with Diosmin is Diosmin and Hesperidin (1:1), Diosmin: Avicel pH 101 (1:1), Diosmin: Klucel EXF (1:0.5), Diosmin: SSG (Type A) (1:0.5), Diosmin: Magnesium stearate (1:0.2), Diosmin: Colour (1:0.05) and with Hesperidine is Hesperidin: Avicel pH 101 (1:1), Hesperidin: Klucel EXF (1:1), Hesperidin: SSG (Type A) (1:5), Hesperidin: Magnesium stearate (1:1), Hesperidin: Colour (1:0.1).

Development of Formulation

The tablets were prepared through a wet granulation process. Drug A was passed through sieve# 40. Diluent and half the quantity of disintegrant were added after passing through sieve#40. Binder was passed through sieve# 40 and added to step 2 mixtures (in case of aqueous granulation). The above mixtures were transferred to RMG and allowed to dry mix for 5 minutes at an impeller 300 rpm speed. Purified water (used as granulating agent) was slowly added to RMG and granulation was done at an impeller 300 rpm speed and a chopper at 50 rpm speed. In the case of binder solution as a granulating agent, the required concentration of aqueous binder solution is prepared and granulation was done in RMG for 5 minutes.at impeller and chopper speed of 300 rpm and 150 rpm respectively. The wet granules filtered through filter# 12 were dried in FBD till the LOD is up to 2%. The dried granules were then passed through sieve# 20. The remaining half quantity of disintegrant and Hesperidin passed through sieve# 40 is added to the dried granules in a V-blender. This pre-lubrication step is carried out for 5 minutes. at 10 pm. Magnesium stearate passed through sieve# 60 is then added to step 6. This lubrication is done for 3 minutes at 10 pm. The blend is then used for tablet compression. And IPQC tests were performed for the uncoated tablets. The core tablets were coated with a suitable coating agent till the required weight gain [14].

Experimental Trials

The tablets were formulated by wet granulation by 2 dissimilar granulating agents:

- Binder solution as a granulating agent
- Water as a granulating agent

Trial 1: The initial batches were taken with the formula as that of the innovator (Batch F1 and F2).

Diosmin was passed through sieve# 40. Avicel pH 101 and a half the quantity of SSG (Type A) was added after passing through sieve#40. The above mixtures were transferred to RMG and allowed to dry mix for 5 minutes at an impeller speed of 300 rpm. An aqueous solution of Gelatin was made up of 5% w/v concentration for trial F1 and 10 % w/v concentration for trial F2 respectively. Granulation was done using the above binder solution in RMG for 5 minutes at impeller and chopper speeds of 300 rpm and 150 rpm respectively. The wet granules sifted through sieve# 12 were dried in FBD till the LOD is up to 2%. The dried granules were then passed through sieve# 30. The remaining half quantity of SSG (Type A) and Hesperidin passed through sieve# 40 was added with dried granules in a V-blender. This pre-lubrication step was carried out for 5 minutes. at 10 pm. Magnesium stearate passed through sieve# 60 was then added to step 6. This lubrication was done for 3 minutes. at 10 pm. The blend was then used for tablet compression under a controlled temperature condition of 25°C/55% RH. IPQC tests were performed for the uncoated tablets [15].

For batches, F1 and F2 disintegration time were found to be more than target although was within the range. Hence next trials were planned with reduced tablet weight and binder concentration to be reduced in further batches.

Trial 2: These batches were planned with reduced tablet weight and decreased binder concentration. (Batch F3 and F4). Diosmin was passed through sieve# 40. Avicel pH 101 and a half the quantity of SSG (Type A) was added after passing through sieve#40. The above mixtures were transferred to RMG and allowed to dry mix for 5 minutes at an impeller speed of 300 rpm. An aqueous solution of Gelatin was made up of 2% w/v concentration for trial F1 and 3 % w/v concentration for trial F2 respectively. Granulation was done using the above binder solution in RMG for 5 minutes at impeller and chopper speeds

of 300 rpm and 150 rpm respectively. The wet granules sifted through sieve# 12 were dried in FBD till the LOD is up to 2%. The dried granules were then passed through sieve# 30. The remaining half quantity of SSG (Type A) and Hesperidin passed through sieve# 40 was added with dried granules in a V-blender. This pre-lubrication step was carried out for 5 minutes. Magnesium stearate passed through sieve# 60 was then added to step 6. This lubrication was done for 3 minutes. The blend was then used for tablet compression under a controlled temperature condition of 25°C/55% RH. IPQC tests were performed for the uncoated tablets.

Issues in batch F3 and f4 were low tablet hardness and too high disintegration time. Hence alternate synthetic binder is to be used to tackle the tablet hardness issue in the next batch.

Trial 3: These batches were planned by the use of alternative binders. (F5, F6, and F7). Diosmin was passed through sieve# 40. Avicel pH 101 and a half the quantity of SSG (Type A) was added after passing through sieve#40. The above mixtures were transferred to RMG and allowed to dry mix for 5 minutes at an impeller speed of 300 rpm. An aqueous solution of Klucel EF, PVP K30, and Ac-di-Sol was made up to 2% w/v, 3% w/v, and 2% w/v concentrations for trials F5, F6, and F7 respectively. Granulation was done using the above binder solution in RMG for 5 minutes at impeller and chopper speeds of 300 rpm and 150 rpm respectively. The wet granules sifted through sieve# 12 were dried in FBD till the LOD is up to 2%. The dried granules were then passed through sieve# 30. The remaining half quantity of SSG (Type A) and Hesperidin passed through sieve# 40 was added with dried granules in a V-blender. This pre-lubrication step was carried out for 5 minutes. Magnesium stearate passed through sieve# 60 was then added to step 6. This lubrication was done for 3 minutes. The blend was then used for tablet compression under a controlled temperature condition of 25°C/55% RH. IPQC tests were performed for the uncoated tablets.

Trial 4: These batches were planned with the use of a binder in dry form. (Batch F8 and F9). Diosmin was passed through sieve# 40. Avicel pH 101 and a half the quantity of SSG (Type A) was added after passing through sieve#40. Klucel EXF was passed through sieve# 40 and added to the above mixture. The above mixtures were transferred to RMG and allowed to dry mix for 5 minutes at an impeller speed of 300 rpm. Granulation was done using purified water in RMG for 5 minutes at impeller and chopper speeds of 300 rpm and 150 rpm respectively. The wet granules sifted through sieve# 12 were dried in FBD till the LOD is up to 2%. The dried granules were then passed through sieve# 30. The remaining half quantity of SSG (Type A) and Hesperidin passed through sieve# 40 was added with dried granules in a V-blender. This pre-lubrication step was carried out for 5 minutes. Magnesium stearate passed through sieve# 60 was then added to step 6. This lubrication was done for 3 minutes. The blend was then used for tablet compression under a controlled temperature condition of 25°C/55% RH. IPQC tests were performed for the uncoated tablets. No issues were found in this batch regarding tablet hardness. Out of batch F8 and F9, batch F8 was chosen as the final batch. Batch F8 is to be taken for coating optimization. All the formulations for diosmin and hesperidin in given in **Table 1**.

Table 1. Formulation of different batches

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diosmin	491.42	491.42	491.42	491.42	450.0	450.0	450.0	491.42	491.42
Hesperidin	51.55	51.55	51.55	51.55	50.00	50.00	50.00	50.00	50.00
Avicel pH 101	108.53	98.53	88.53	78.53	105.50	120.50	110.00	86.84	96.84
SSG (Type A)	15.00	25.00	10.00	25.00	30.00	26.50	35.00	25.00	20.26
Gelatin	25.00	25.00	35.00	25.00	---	---	--	--	--
Mag. stearate	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50
Klucel EF	---	---	---	--	36.00	---	---	---	--
PVP K30	---	---	---	--	---	24.50	---	---	--
Ac-di-Sol	---	---	---	--	---	---	26.50	---	--
Klucel EXF	---	---	---	--	---	---	---	18.24	13.00
Weight	695.00	695.00	680.00	675.00	675	675	675	675.00	675.00

Compression of Tablets

Compression paratmeters like punch dimension, hardness, thickness, friability, disintegration time and average weight of formulated tablets is depicted in **Table 2**.

Table 2. Compression parameters for different batches

Parameter	Batch F1 and F2	Batch F3 and F4	Batch F5-F7	Batch F8-F9
Punch dimension	16.5 x 8 mm, Oval, SC	16.5 x 8 mm, Oval, SC	16.5 x 8 mm, Oval, SC	16.5 x 8 mm, Oval, SC
Hardness	30- 35 Kp	30- 35 Kp	30- 35 Kp	30- 35 Kp

Thickness	6.30 mm ± 0.30 mm	6.30 mm ± 0.30 mm	6.30 mm ± 0.30 mm	6.30 mm ± 0.30 mm
Average weight	695 mg ±5%	675-680 mg ± 5%	675 mg ± 5%	675 mg ± 5%
Friability	Not more than 1%	Not more than 1%	Not more than 1%	Not more than 1%
Disintegration time	Not more than 30 minutes	Not more than 30 minutes	Not more than 30 minutes	Not more than 30 minutes

Coating Optimization

A Colour coat was applied on the finalized batch of core tablets for optimization of coating parameters. Batch 8-V was chosen as the optimized coating. Details of coating agent, weight gain after coating and average weight of tablet (mg) is given in **Table 3**.

Table 3. Trials for coating

Trial	Coating Agent	Weight gain	Avg. weight of tablet (mg)
8-I	Wincoat WT-QCAQ-1261 Brown	2% w/w	688.50
8-II	Wincoat WT-QCAQ-1261 Brown	3% w/w	695.25
8-III	Wincoat WT-QCAQ-1261 Brown	5% w/w	708.70
8-IV	Instacoat Sol IC-S-3100 Yellow	2% w/w	688.50
8-V	Instacoat Sol IC-S-3100 Yellow	3% w/w	695.25
8-VI	Instacoat Sol IC-S-3100 Yellow	5% w/w	708.70

Composition of Reproducible Batch

Reproducible batch contains diosmin (491.426 mg), Hesperidine (50 mg), Avicel pH 101 (86.84 mg), SSG Type A (25 mg), Klucel EXF (18.24 mg), Magnesium stearate (3.50 mg), Instacoat sol IC-3100 Yellow (20 mg). Total weight of is 695 mg.

Evaluation of Uncoated and Coated Tablets

Appearance

The general appearance and elegance of uncoated and coated tablets were identified visually, which include tablet size, shape, color, presence or absence of an odor, taste, and surface texture.

Weight Variation

Twenty tablets were weighed individually and the average weight was determined. The individual tablet weight was compared with the average tablet weight. The highest percentage variance certified is 5% of the regular tablets weight [16].

Thickness

Five tablets were randomly selected from the individual formulations and the depth was measured by Vernier caliper scale. this enables precise measurements. Tablet thickness was controlled within a ± 0.5% variation of the standard value.

Friability Test

The Friability of uncoated tablets was determined using Friability Tester USP. Friability for the tablets was determined for 100 revolutions. The Friability of the tablets was controlled so as not to exceed 1% [17].

Hardness

Tablet was selected at random from individual formulations and hardness was measured using Schleuniger's hardness tester.

Disintegration Test

Disintegration time for Tablets was determined using 6 tablets. Disintegration time for the Immediate Release Tablets should not be more than 15 minutes [11].

Results and Discussion

Preformulation

Solubility

The solubility of the drugs was determined in different solvents and media. Found insoluble in 0.1 N HCl, slightly soluble in 0.1 N NaOH, Insoluble in pH 4.5 acetate buffer and phosphate buffer.

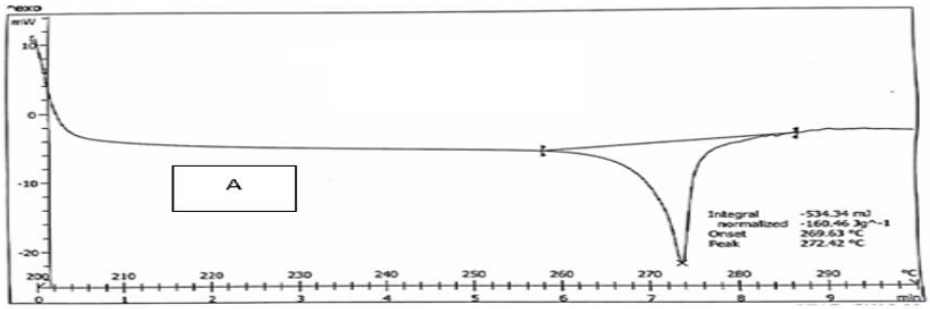
Particle Size Analysis

The particle size of APIs was determined by the Malvern particle size analyzer using the dry method.
Diosmin: D (v,0.9) means 90 % of the given API particles are less than 1.98 µm, D (v,0.5) means 50 % of the given API particles are less than 1.52 µm and D (v, 0.1) means 10 % of the given API particles are less than 1.17 µm.
Hesperidin: D (v,0.9) means 90 % of the given API particles are less than 2.01 µm, D (v,0.5) means 50 % of the given API particles are less than 1.85 µm and D (v, 0.1) means 10 % of the given API particles are less than 1.42 µm.
Density and flow properties: Bulk density, tapped density, carrs's index, hausner's ratio and angle of repose of diosmin was found to be 0.26 g/cm^3, 0.39 g/cm^3, 33.33, 1.5 and 58°. The same parameters for hesperidin was found to be 0.52 g/cm^3, 0.64 g/cm^3, 30.76, 1.23 and 44° respectively. The above observation indicates that drugs diosmin have very poor flow property whereas Hesperidin is poor in flow.

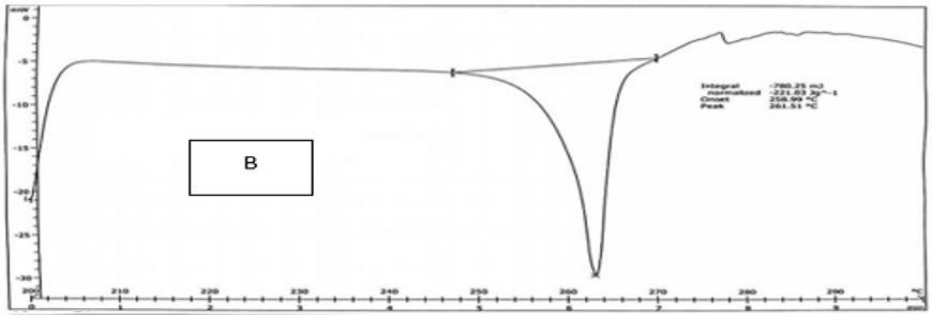
Melting Point
The observed melting point for Diosmin is 274 to 278 °C while for Hesperidin is 262 to 266 °C.

Drug -Excipient's Compatibility Study
The compatibility results of both the drugs with each other and their compatibility with individual excipients under a temperature condition of 40°C ± 2°C/75% ± 5% RH, no change has been observed after 1, 2 and 4 weeks.
After 1 month the samples were visually observed. Both the drugs were found to be compatible with all the excipients used in our formulation and with each other as well. Any type of color change or lumps was not found. DSC study result shows that there was no incompatibility between Diosmin and Hesperidin and Diosmin with its excipients and Hesperidin with its excipients.

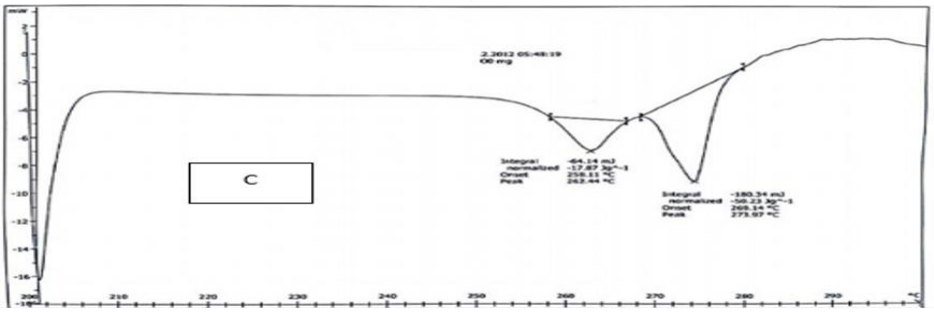
DSC Study
The DSC study was done using the following setup for each drug to study their compatibility issues. Temperature range: 200 -300 °C, Heating rate: 10 °C/ minute.



a)



b)



c)

Figure 1. DSC for Diosmin (a), Hesperidin (b), and combination of Diosmin and Hesperidin (c)

The results shown in **Figure 1** that there is an acceptable difference in the peak temperatures incombination when compared the same with their peak temperatures. Thus, we can conclude that both the drugs are compatible with each other.

Evaluation of Tablets

Evaluation of Pre-Compression Parameters of Tablet

The final blends were evaluated for their flow property and moisture content before tablet compression. Pre-compression parameters for final blend are shown in **Table 4**.

Table 4. Pre-Compression Parameters (Final blend)

Batch No.	% LOD	Angle of Repose	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio
F1	3.5%	35.1	0.52	0.52	15.38	1.11
F2	2.8%	32.8	0.54	0.54	12.84	1.09
F3	3.1%	33.4	0.59	0.59	15.31	1.10
F4	2.6%	34.5	0.50	0.50	15.45	1.12
F5	2.8%	32.9	0.57	0.57	12.56	1.08
F6	3.7%	37.4	0.51	0.51	20.51	1.15
F7	2.7%	38.6	0.54	0.54	23.07	1.16
F8	3.4%	33.2	0.53	0.53	12.82	1.09
F9	2.9%	34.7	0.51	0.51	15.10	1.11
Repro Batch	2.8%	32.9	0.54	0.54	12.89	1.09

From the values of Angle of repose, Hausner's ratio, and Carr's Index we can conclude that the blend of all the batches has shown good flow properties; but batches F2, F5, and 8 have an acceptable flow of all the batches.

Evaluation of Formulated Tablet for Post-Compression Parameters

Appearance

Brown to light brown; film-coated biconvex, oval-shaped tablets; plain on both sides.

Physical Tests

The various physical tests on tablets like thickness, hardness, and disintegration time were performed. The results of physical tests viz. average weight, thickness, hardness, friability and disintegration time are shown in **(Table 5)**.

Table 5. Physical tests for the formulated tablet batches

Batch	The average weight of the tablet	Thickness (mm)	Hardness (Kp)	% Friability	Disintegration Time (minute)
F1	696.45	6.21	38.1	0.72%	15.20
F2	695	6.18	40.2	0.61%	18.12
F3	680	6.20	37.9	0.48%	14.38
F4	675	5.9	41.0	0.45%	16.09
F5	675	6.44	34.5	0.30%	4.29
F6	675	6.83	29.9	0.51%	7.32
F7	675	6.71	28.4	0.61	7.18
F8	675	6.41	33.4	0.14%	2.34
F9	675	6.56	35.6	0.28%	2.59
Repro Batch	675	6.39	34.1	0.18%	2.48

The results show that batch F5, F8, and F9 show acceptable physical parameters.

Evaluation of Coated Tablets

The coated tablets of batch F8 were evaluated for the effect of weight gain of the coating agent on tablet disintegration time, the results are shown in **Table 6**.

Table 6. Evaluation of coated tablets

Trial	Coating Agent	Weight gain	Avg. wt. of the tablet (mg)	DT (in minutes)
8-I	Wincoat WT-QCAQ-1261 Brown	2% w/w	688.50	3.45
8-II	Wincoat WT-QCAQ-1261 Brown	3% w/w	695.25	4.09
8-III	Wincoat WT-QCAQ-1261 Brown	5% w/w	708.70	5.53
8-IV	Instacoat Sol IC-S-3100 Yellow	2% w/w	688.50	2.10
8-V	Instacoat Sol IC-S-3100 Yellow	3% w/w	695.25	4.09
8-VI	Instacoat Sol IC-S-3100 Yellow	5% w/w	708.70	4.56

Batch 8-V has shown acceptable results of disintegration time.

Stability Study
Since batch 8-V had shown acceptable results for all the evaluations, hence this batch was taken for the stability study.

Storage Condition
40°C ± 2°C / 75% RH ± 5 % RH

Packaging
Alu/PVC blister packs
No changes observed in formulated tablets when tested at intitial, 1 month, 2 months and 3 months as per stability testing guidleines.
The above stability data, reveals that the product is stable at 40°C/ 75% RH for 12 weeks (3 months).

Final Manufacturing Process

- Load the following in Rapid Mixer Granulator
  - Diosmin
  - Microcrystalline Cellulose
  - Half the qty. of Sodium Starch Glycolate (Type A)
  - Klucel EXF

- Mix for 5 minutes at slow speed impeller and chop off.
- Wet Granulation: Purified water (25 °C – 35 °C).
- Drying: Unload wet granules of step into the FBD. Pass it from sieve #12.
- Sizing: Pass dried granules of step 3 through a multi-mill equipped with a #20 mesh sieve.
- Pre-lubrication/ Blending Load the milled granules from step 4 into V-Blender. Add the following materials:
- Hesperidin
- Remaining half qty. of Sodium Starch Glycolate (Type A) Mix the above ingredients in V-Blender for 5 minutes.
- Lubrication: Add Magnesium Stearate and mix for 3 minutes.
- Compression: Compress the lubricated blend of step 6 on a rotary with 16.5 x 8 mm. SC, oval with both sides plain punch set.
  - Theoretical weight: 675.00 mg
  - Hardness: 30 Kp – 35 Kp
  - Thickness: 6.3 mm ± 0.30 mm

- Coating: Coating to be done with Instacoat IC-S-3100 Sol Yellow up to 3% w/w weight gain of core tablets.
- Packing: Alu/PVC blister packs are to be used for packing.

Conclusion

Chronic venous insufficiency (CVI) is a condition characterized by changes that take place in tissues of the leg secondary to long-standing venous hypertension caused by structural or functional abnormalities in the veins and/or venous valves. For the treatment of this disease Flavonoid Diosmin in combination with another Flavonoid Hesperidin has been formulated as an oral solid dosage form. The tablet form of this combination has been made to reduce the exposed surface area of both the flavonoid drugs. A color film coat has been given to the formulation with the reason to protect the natural substance to degrade by the external environment and mask the awful taste of the drugs.

Preformulation studies were performed on both the drugs to study the physicochemical properties.

Compatibility study had shown that the drugs are compatible with each other and compatible individually with excipients also. DSC study revealed that there were no physical changes in the drugs when in combination with each other. The tablets were formulated by wet granulation process with Hesperidin in an extra granular portion. Avicel 101, Klucel EXF, Sodium Starch Glycolate, and Magnesium Stearate are used as the diluent, binder, disintegrant, and lubricant respectively. Instacoat IC-S-3100 Sol was used as a color film coating agent. The aqueous solution of this coating agent was used. Various experimental trials, F1-F9, were performed for formula optimization of core tablets. Batch F8 was taken as an optimized batch for the coating process. The final formula for the finished product was prepared. The uncoated and coated tablets were evaluated for their physical properties according to the pharmacopeia specification. The product was evaluated for the % assay. Batch 8-V was taken as the final batch with an acceptable % assay and other results for the physical evaluations. Alu/PVdC blister was chosen for primary packaging of tablets. The packed tablets were taken for 3 months stability study at 40°C ± 2°C/75%±5% RH which has shown good results. By all the physical and chemical evaluations, we can say that the product formulated is stable. An elegant formulation is developed which can be used for marketing the treatment of CVI.

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