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Development of Film-Coated Tablet Comprising a Combination of Flavonoid Drugs "X" and "Y" and Its *In-Vitro* Evaluation

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ABSTRACT

In this study combination of drug X and drug, Y was used for the treatment of a condition called Chronic venous insufficiency. Drug X and Drug Y are a citrus bioflavonoids which act as a vascular-protecting agent used to treat chronic venous insufficiency, haemorrhoids, lymphedema and varicose veins. Preformulation study was carried out for the formulation of tablet of selected drug. Compatibility study was carried out in between drug X and Drug Y along with excipients like Avicel pH 101, Klucel EXF, Sodium Starch Glycolate, Magnesium stearate. Formulation of tablets was carried out on various trials. Trial 1 consists of two batches, F1 and F2 but due to disintegration issue, formula was modified and trial 2 of batch F3 and F4 was carried out. Batch F2 and F3 was found to be of low hardness and high disintegration time. Trial 3 was conducted for batch F5, F6 and F7 where binders like polyvinyl pyrrolidone, Ac-Di-Sol, Klucel EF were used. Batch F8 and F9 were formulated as trial 4 with Klucel EXF. Batch F8 produced satisfactory result and hence coated with agent WincoatWT-QCAQ-1261Brown. Batch8-Vhas shown acceptable results of disintegration time and were subjected for stability study. Finally, a concluding manufacturing process was formulated depending upon the obtained results.

INTRODUCTION:

Varicose veins and the impediments of venous disease are thought to affect over a quarter of the adult population and the management of these conditions are the main cause of health service cost. 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.[1]

Tablets are the most common solid dosage form in contemporary use. It may be defined as unit form of solid medicaments prepared by compaction. Most comprises mixture of powders that are compacted in a die to produce a single rigid body.[2]

Various venoactive and non-venoactive 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.[3]

Drug X (a citrus bioflavonoid) is a 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.

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

The combination of Drug X with Drug Y has shown synergism in the vasculo- protective activity, in addition with anti-inflammatory and antioxidant activity. Drug XThis MPFF-bioflavonoid formulated in tablet dosage form so that the exposed surface area of the flavonoids can be reduced. Additionally, coating given to the tablet prevents flavonoid degradation from external environment.

This formulation is used as a supplementary therapy in the treatment of chronic venous insufficiency complications in the lower limbs.[4]

MATERIALS AND METHODS:

Drug X, Vascular- protecting Agent (Bioflovonoid) was obtained from Elder Pharma.

Drug Y, Bioflaovonoid, was obtained from Biogin Chemicals. 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 studies are the first step in the development of the dosage form of a drug substance. Following are the test performed for the preformulation study, Particle size, Bulk density, Tapped density, Carr's index & Hausner's ratio, Flow property (Angle of Repose), FT IR Spectra, Melting Point and Drug –Excipient Compatibility Study.[5]

Solubility Determination:

Solubility of drugs were determined in 5 different Medias ranging from pH 1.0 to 7.5. These medias are Water, 0.1 N HCl, Acetate Buffer pH 4.5, Phosphate Buffer pH 6.8, pH 7.2. The excess of drug was added to a definite volume of solvent till it gets precipitated and then it was kept on shaker (RO-123R, Remi Instruments, Mumbai, India) for 24 hr. Withdrawn samples were filtered through a Whatman filter paper, and assayed by UV spectrophotometer (1800, SHIMADZU, Japan). This procedure was repeated six times to get accuracy in the result.[6]

Particle Size Determination:

Particle size of drug was determined by Malvern particle size analyzer which uses the principle of light scattering.[7]

Bulk Density Determination:

25 gm of drug previously passed through sieve #20 was weighed and transferred in 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; [7]

$$\text{Bulk density} = \frac{weight\ of\ powder}{Bulk\ volume\ of\ powder}$$

Tapped Density Determination:

25 gm of drug previously passed through sieve # 20 was weighed and transferred in 100 ml graduated cylinder. The cylinder was then fitted on a tap density apparatus and allowed for500 taps. Additional 750 taps were done. This was taken as final tap volume. The tapped density was calculated in g/ml using the following formula;[7]

$$\text{Tap density} = \frac{weight\ of\ powder}{Tapped\ \ volume\ of\ powder}$$

Compressibility Index & Hausner's Ratio:

The compressibility index, also referred to as Carr's Index and Hausner's ratio are used measure the propensity of powder to be compressed. Carr's index and Hausner's ratio was calculated using the following; [7]

$$\text{Compressibility index} = \frac{Tapped\ density - bulk\ density}{Tapped\ \ denstiy} * 100$$

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density}$$

Determination of Flow Property:

The frictional force in the powder can be measured by the angle of repose. Angle of repose was calculated by fixed funnel method. Angle of repose was calculated by using following formula; [7]

$$\text{Tan } \theta = \frac{Height\ of\ pile}{Radius\ of\ pile}$$

Melting Point:

Melting point is prime confirmation of drug. In this method, the temperature was noted at which point sample start melt to finish. For this drug whose analysis to be carried out was filled into capillary tube and tied in such a way that it remains dipped in liquid paraffin bath and temperature was noted. [7]

Compatibility Study:

The primary objective of this investigation was to identify a stable storage condition for drug in solid state and identification of compatible excipients for its formulation. In this method different excipients were selected and mixed separately with drug in proportion generally used for tablet formulation. Three sets of each mixture are prepared, from which 1 set is for initial analysis while two sets are kept at 40ºC/75% RH and 60 ºC for 1 month. After 1 month the samples are observed visually for change of colour or its appearance in powder form. The two sets of samples were used for DSC study which clarifies if any interaction is occurred between drug-drug. [8]

Table 1: Ratio of ingredients for compatibility study of Drug X and Y

Ingredients	Ratio	Ingredients	Ratio
Drug X: Drug Y	1:1	Drug Y: Avicel pH 101	1:1
Drug X: Avicel pH 101	1:1	Drug Y: Klucel EXF	1:1
Drug X: Klucel EXF	1:0.5	Drug Y: SSG (Type A)	1:5
Drug X: SSG (Type A)	1:0.5	Drug Y: Magnesium stearate	1:1
Drug X: Magnesium stearate	1:0.2	Drug Y: Colour	1:0.1
Drug X: Colour	1:0.05		

Development of Formulation:

The tablets were prepared by wet granulation process. Drug A was passed through sieve# 40.Diluent and half the quantity of disintegrant was added after passing throughsieve#40.Binder was passed through sieve# 40 and added to step 2 mixture (in case of aqueous granulation).The above mixtures were transferred to RMG and allowed to dry mix for 5 minutes at impeller speed of 300 rpm. Purified water (used as granulating agent) was slowly added to RMG and granulation was done at impeller speed of 300 rpm and chopper speed of 50 rpm. In case of binder solution as a granulating agent, 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 sifted through sieve# 12 were dried in FBD till the LOD is up to 2%.The dried granules were then passed through sieve# 20.Remaining half quantity of disintegrant and Drug Y passed through sieve# 40 is added to the dried granules in a V-blender. This pre-lubrication step is carried for 5 minutes. at 10 rpm. Magnesium stearate passed through sieve# 60 is then added to step 6.

This lubrication is done for 3 minutes at 10 rpm. The blend is then used for tablet compression. And IPQC tests were performed for the uncoated tablets. The core tablets were coated with the suitable coating agent till the required weight gain.

Experimental Trials:

The tablets were formulated by wet granulation by using two different granulating agents:

a) Binder solution as granulating agent

b) Water as granulating agent

Trial 1:

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

Drug X was passed through sieve# 40. Avicel pH 101 and half the quantity of SSG (Type A) was added after passing throughsieve#40. The above mixtures were transferred to RMG and allowed to dry mix for 5 minutes at impeller speed of 300 rpm. Aqueous solution of Gelatin was made upto 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 speed of 300 rpm and 150 rpm respectively. The wet granules sifted through sieve# 12 were dried in FBD till the LOD is upto 2%. The dried granules were then passed through sieve# 30. The remaining half quantity of SSG (Type A) and Drug Y passed through sieve# 40 was added with dried granules in a V-blender. This pre-lubrication step was carried for 5minutes. at 10 rpm. Magnesium stearate passed through sieve# 60 was then added to step 6. This lubrication was done for 3 minutes. at 10 rpm. The blend was then used for tablet compression under controlled temperature conditions of 25°C/55% RH.IPQC tests were performed for the uncoated tablets. [9]

For batches F1 and F2 disintegration time was 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)

Drug X was passed through sieve# 40.Avicel pH 101 and 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 impeller speed of 300 rpm. An aqueous solution of Gelatin was made upto 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 speed of 300 rpm and 150 rpm respectively. The wet granules sifted through sieve# 12 were dried in FBD till the LOD is upto 2%.The dried granules were then passed through sieve# 30.Remaining half quantity of SSG (Type A) and Drug Y passed through sieve# 40 was added with dried granules in a V-blender. This pre-lubrication step was carried for 5 minutes. at 10 rpm. Magnesium stearate passed through sieve# 60 was then added to step 6. This lubrication was done for 3 minutes. at 10 rpm. The blend was then used for tablet compression under controlled temperature condition of 25°C/55% RH.IPQC tests were performed for the uncoated tablets.

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

Trial 3:

These batches were planned by use of alternative binders. (F5, F6 and F7)

Drug X was passed through sieve# 40. Avicel pH 101 and 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 impeller speed of 300 rpm. Aqueous solution of Klucel EF, PVP K30 and Ac-di-Sol and was made upto 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 speed of 300 rpm and 150 rpm respectively. The wet granules sifted through sieve# 12 were dried in FBD till the LOD is upto 2%.The dried granules were then passed through sieve# 30.The remaining half quantity of SSG (Type A) and Drug Y passed through sieve# 40 was added with dried granules in a V-blender. This pre-lubrication step was carried for 5 minutes. at 10 rpm. Magnesium stearate passed through sieve# 60 was then added to step 6. This lubrication was done for 3 minutes. at 10 rpm. 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 use of binder in dry form. (Batch F8 and F9)

Drug X was passed through sieve# 40. Avicel pH 101 and half the quantity of SSG (Type A) was added after passing through sieve#40.Klucel EXF was passed through sieve# 40 and added to above mixture. The above mixtures were transferred to RMG and allowed to dry mix for 5 minutes at impeller speed of 300 rpm. Granulation was done using purified water in RMG for 5 minutes at impeller and chopper speed of 300 rpm and 150 rpm respectively. The wet granules sifted through sieve# 12 were dried in FBD till the LOD is upto 2%. The dried granules were then passed through sieve# 30.

The remaining half quantity of SSG (Type A) and Drug Y passed through sieve# 40 was added with dried granules in a V-blender. This pre-lubrication step was carried for 5 minutes. at 10 rpm. Magnesium stearate passed through sieve# 60 was then added to step 6. This lubrication was done for 3 minutes. at 10 rpm. The blend was then used for tablet compression under 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. OutofbatchF8and F9, batchF8was chosen as final batch. Batch F8 is to be taken for coating optimization.

Table 2: Formulation of different batches

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Drug X	491.42	491.42	491.42	491.42	450.0	450.0	450.0	491.42	491.42
Drug Y	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

Table 3: Compression parameters for different batches

Parameter	Batch F1 and F2	Batch F3 and F4	Batch F5-F7	Batch F8-F9
Punch dimension	16.5x8 mm, Oval, SC	16.5 x 8 mm, Oval, SC	16.5x8 mm, Oval, SC	16.5x8 mm, Oval, SC
Hardness	30-35 Kp	30- 35 Kp	30-35 Kp	30-35 Kp
Thickness	6.30 mm ± 0.30 mm	6.30mm ± 0.30 mm	6.30 mm ± 0.30 mm	6.30 mm ± 0.30 mm
Average weight	695mg±5%	675-680 mg ± 5%	675mg±5%	675mg±5%
Friability	Not more than1%	Not more than 1%	Not more than1%	Not more than1%
Disintegration time	Not more than 30minutes	Not more than 30 minutes	Not more than 30minutes	Not more than 30minutes

Coating Optimization:

Colour coat was applied on the finalized batch of core tablets for optimization of coating parameters.

Table 4: 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

Batch 8-V was chosen as the optimized coating.

Final Trial-Reproducible batch:

Table 5: Composition of reproducible batch

Ingredients (mg)	**Quantity (mg)**
Drug X	491.426
Drug Y	50.00
Avicel pH 101	86.84
SSG (Type A)	25.00
Klucel EXF	18.24
Magnesium stearate	3.50
Instacoat Sol IC-3100 Yellow	20.00
Total	**695.00**

Evaluation of Uncoated and Coated Tablets:

Appearance: The general appearance and elegance of uncoated and coated tablets was 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 average weight was determined. The individual tablet weight was compared with average tablet weight. The maximum percent difference allowed is 5% of the average weight of tablets. [10]

Thickness: Five tablets were selected at random from individual formulations and thickness was measured by using vernier caliper scale, which permits accurate measurement. Tablet thickness was controlled within a ± 0.5% variation of standard value.

Friability Test: 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%.[10]

Hardness: Tablet was selected at random from individual formulations and hardness was measured using Scheluniger 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 minute.[11]

RESULTS AND DISCUSSION:

Preformulation

Solubility:

Solubility of the drugs was determined in different solvents and media, which are given in table number 6.

Particle Size Analysis:

The particle size of APIs was determined by Malvern particle size analyzer using dry method and results are mentioned in table number 6.

Table 6: Details of solubility of Drug X and Drug Y

Solvent/Media	**Solubility of Drug Y**	**Solubility of Drug X**	**Particle size Distribution**	**Drug X (µm)**	**Drug Y (µm)**
0.1NHCl	Insoluble	Insoluble	D(v, 0.1)	1.17	1.42
0.1NNaOH	Slightly soluble	Slightly soluble	D(v, 0.5)	1.52	1.85
pH4.5AcetateBuffer	Insoluble	Insoluble	D(v, 0.9)	1.98	2.01
pH6.8PhosphateBuffer	Insoluble	Insoluble			
Methanol	Slightly soluble	Insoluble			
DMSO	Soluble	Soluble			

From the above table it is observed that:

*Drug X:*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 &D (v, 0.1) means 10 % of the given API particles are lessthan1.17µm.

*Drug Y:*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 &D (v, 0.1) means 10 % of the given API particles are lessthan1.42µm.

Density and flow properties:

The density of both drugs was, as shown in the following table.

Table7: Observation of density and flow property of Drug X and Drug Y

Density(g/cm^3)		**Flow properties**		
Bulk	**Tapped**	**Carr's index**	**Hausner's Ratio**	**Angle of repose**
0.26	0.39	33.33	1.5	58°
0.52	0.64	30.76	1.23	44°

TheaboveobservationindicatesthatDrugsXhaveverypoorflowpropertywhereasDrugYispoorin flow.

Melting point:

The observed melting point for drug X is 274 to 278 °C while for drug Y is 262 to 266 °C.

Drug-Excipient's compatibility study:

Compatibility results of both the drugs with each other and their compatibility with individual excipients under temperature condition of 40°C± 2°C/75%±5%RH are shown below.

Table 7: Observation of Drugs & excipients compatibility study

Ingredients	**Initial**	**40°C±2°C/75%±5%RH**		
		1week	**2weeks**	**4weeks**
Drug X	Greyish yellow colored powder	No change	No change	No change
Drug Y	Brownish yellow colored	No change	No change	No change
Drug X + Drug Y	Yellow colored powder	No change	No change	No change
Placebo	Light yellow colored powder	No change	No change	No change
Placebo + Drug X	Yellow colored powder	No change	No change	No change
Placebo + Drug Y	Light brownish yellow colored powder	No change	No change	No change
Drug X: Avicel pH101 (1:1)	Light yellow colored powder	No change	No change	No change
Drug X: Klucel EXF (1:0.5)	Light yellow colored powder	No change	No change	No change
Drug X: SSG (Type A) (1:0.5)	Light yellow colored powder	No change	No change	No change
Drug X: Magnesium stearate (1:0.2)	Light yellow colored powder	No change	No change	No change
Drug X: Color (1:0.05)	Yellow colored powder	No change	No change	No change
Drug Y: Avicel pH 101 (1:1)	Yellow colored powder	No change	No change	No change
Drug Y: Klucel EXF (1:1)	Yellow colored powder	No change	No change	No change
Drug Y: SSG (Type A) (1:5)	Yellow colored powder	No change	No change	No change
Drug Y: Magnesium stearate (1:1)	Yellow colored powder	No change	No change	No change
Drug Y: Color (1:0.1)	Yellow colored powder	No change	No change	No change

After 1 month the samples were visually observed. Both the drugs were found to be compatible with all the excipients used in our formulation & 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 Drug X and Drug Y and Drug X with its excipients and Drug Y with its excipients.

DSC Study:

The DSCstudywasdoneusingthefollowingsetupforeachdrugtostudytheircompatibilityissues.Temperaturerange:200-300 °C, Heating rate: 10°C/minute.

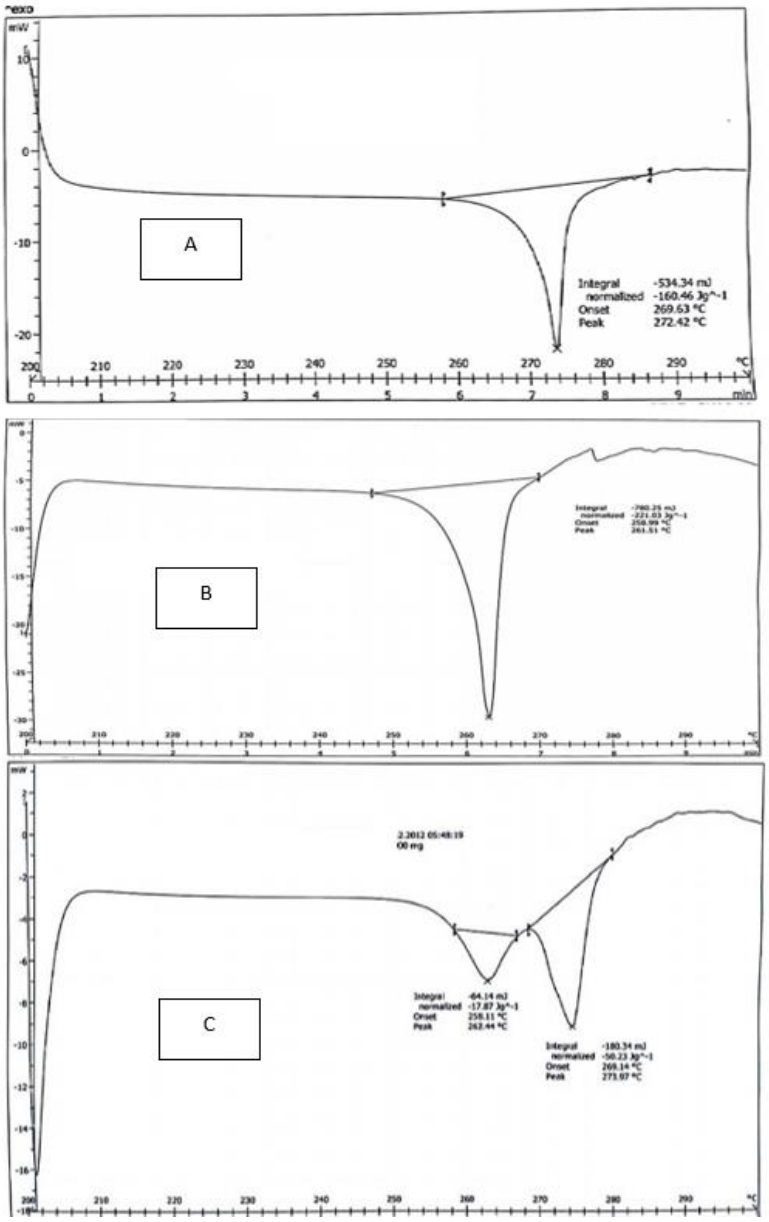

Fig 1: DSC for Drug X (A), Drug Y (B) and combination of Drug X & Drug Y (C)

The results show that, an there is an acceptable difference in the peak temperatures of the in combination when compared the same with their individual 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 its flow property and moisture content before tablet compression.

Table 8: 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 &Carr's Index we can conclude that the blend of all the batches have shown good flow properties; but batch F2, F5 andF8 has 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 was performed. The results are shown in the table 9.

Table 9: Physical tests for the formulated tablet batches

Batch	Average weight of 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 shows acceptable physical parameters.

Evaluation of coated tablets:

The coated tablets of batch F8 were evaluated for effect of weight gain of coating agent on tablet disintegration time.

Table11: Evaluation of coated tablets

Trial	Coating Agent	Weight gain	Avg. wt. of tablet(mg)	DT (in minutes)
8-I	WincoatWT-QCAQ-1261Brown	2%w/w	688.50	3.45
8-II	WincoatWT-QCAQ-1261Brown	3%w/w	695.25	4.09
8-III	WincoatWT-QCAQ-1261Brown	5%w/w	708.70	5.53
8-IV	InstacoatSolIC-S-3100 Yellow	2%w/w	688.50	2.10
8-V	InstacoatSolIC-S-3100 Yellow	3%w/w	695.25	4.09
8-VI	InstacoatSolIC-S-3100Yellow	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 thee valuations, hence this batch was taken for stability study.

*Storage condition***:**40°C ± 2°C/ 75%RH±5 %RH

Packaging: Alu/PVC blister packs

Table 10: Stability data of tabletat40°C±2°C/75%RH ±5%RH

Parameters	**Initial**	**1Month**	**2Months**	**3Months**
Description	Brown to light brown film coated tablets	Brown to light brown film coated tablets	Brown to light brown film coated tablets	Brown to light brown film coated tablets
Thickness (mm)	6.43	6.43	6.51	6.52
Hardness (Kp)	33.2	33.1	32.9	32.8
Friability	0.19%	0.20%	0.24%	0.26%

From the above stability data, it reveals that the product is stable at 40°C/75% RH for12 weeks (3 months).

Final manufacturing process:

1. Load the following in Rapid Mixer Granulator

- Drug X
- Microcrystalline Cellulose
- Half the qty. sodium Starch Glycolate (Type A)
- Klucel EXF

2. Mix for 5minutes at slow speed impeller and chopper off.
3. Wet Granulation: Purified water (25°C –35°C).
4. Drying: Unload wet granules of step in to the FBD. Pass it from sieve#12.
5. Sizing: Pass dried granules of step 3 through a multi-mill equipped with #20mesh sieve.

6. Pre-lubrication/Blending Load the milled granules from step 4 into V-Blender. Add the following materials:

- Drug Y
- Remaining half qty. of Sodium Starch Glycolate (Type A) Mix the above ingredients in V-Blender for 5 minutes.

7. Lubrication: Add Magnesium Stearate and mix for 3 minutes.

8. Compression: Compress the lubricated blend of step 6 on a rotary with 16.5x8 mm. SC, oval with both side plain punch set.

✓ Theoretical weight: 675.00mg

✓ Hardness: 30Kp–35Kp

✓ Thickness: 6.3mm±0.30mm

9. Coating: Coating to bed one with Instacoat IC-S-3100 Sol Yellow upto 3%w/w weight gain of core tablets.

10. Packing: Alu/PVC blister packs are to be used for packing.

SUMMARY AND 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 Drug X in combination with another Flavonoid, Drug Y has been formulated as an oral solid dosage form. Tablet form of this combination has been made in order to reduce the exposed surface area of both 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 Drug Y in the extra granular portion. Avicel 101, Klucel EXF, Sodium Starch Glycolate and Magnesium Stearate are used as diluent, binder, disintegrant and lubricant respectively. Instacoat IC-S- 3100 Sol was used as 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 optimized batch for coating process. The final formula for the finished product was prepared. The uncoated and coated tablets were evaluated for the physical properties according to the pharmacopeia specification. The product was evaluated for the % assay. Batch 8-V was taken as final batch with acceptable % assay and other results for the physical evaluations. Alu/PVdC blister was chosen for the 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 for the treatment of CVI.

REFERENCES:

1. Batchvarov I, Batselova M, Damyanov I. One-year DiosminTherapy (600 mg) in Patients with Chronic Venous Insufficiency – Results and Analysis. Journal of Biomedical Clinical Sciences, 2010. 3(1), Pages -51-54
2. Bolhuis G, Smallenbroek A. Interaction of Tablet Disintegrants and Magnesium Stearate During Mixing: Effect on Tablet Disintegration. Journal of Pharmaceutical Sciences, 70(12), 1981.Page Numbers.1328-1330.
3. Gohel M, Davies A. Pharmacological Agents in the Treatment of Venous Disease: An Update of the Available Evidence. CurrVascPharmacol.2009. 7(3), Page Numbers.303-308
4. Katsenis K.Micronized Purified Flavonoid Fraction (MPFF): A Review of Its Pharmacological Effects, Therapeutic Efficacy and Benefits in the Management of Chronic Venous Insufficiency. CurrVascPharmacol. 2005. 3(1), Page Numbers.1-9.
5. Galge D, Raut R. Formulation and Evaluation of Irbesartan Immediate Release Tablets. International Research Journal of Pharmacy. 2012. 3(4), Page Numbers.410-415.
6. Shah JC, Chen JR, Chow D.PreformulationStudy of Etoposide: Identification of physicochemical characteristics responsible for the low and erratic oral bioavailability of etoposide. Pharm Res. 1989. 6(5), Page Numbers.408-12.
7. Chaurasia G.A Review on Pharmaceutical Preformulation Studies in Formulation and Development of New Drug Molecules. Int J Pharm Sci Res.2016. 7(6), Page Numbers.2313-2020.
8. Migoha CO,Ratansi M, Kaale E, et. al.Preformulation Studies for Generic Omeprazole Magnesium Enteric Coated Tablets. BioMed Research International, 2015.Article Id 307032, Page Numbers.1-9.
9. Lachman L, Liberman HA. The theory and Practice of Industrial Pharmacy. 3rd ed. Bombay: Varghese Publishing House. 1987. Page Numbers.430-440.
10. Zaid AN, Al-Ramahi RJ, Ghoush AA, et. al.Weight and Content Uniformity of Lorazepam Half-Tablets: A Study of Correlation of a Low Drug Content Product. Saudi Pharm J. 21(1), 2013. Page Numbers.71-75.
11. GuptaMM, PandeyS, ChauhanBS, et. al. Design, Development and Evaluation of Rosuvastatin Calcium and Diltiazem Hydrochloride Bilayer Tablet Using Combination Concept of Sustained Layer with Conventional Layer. Turkish J. Pharm. Sc. 2014. Page Numbers.269- 284.