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FORMULATION AND EVALUATION OF GLUCOSAMINE SULPHATE POTASSUIM CHLORIDE 1500 MG & DIACEREIN 50 MG FILM COATED TABLET

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ABSTRACT

Diacerein is a symptomatic slow-acting drug in osteoarthritis with anti-inflammatory, anti-catabolic and pro-anabolic properties on cartilage and synovial membrane. Diacerein shows protective effects against subchondral bone remodelling. Based on a various pharmacological and biopharmaceutical studies and review of clinical trials and meta-analyses, that the efficacy of Diacerein is similar to that of non-steroidal anti-inflammatory drugs (NSAIDs) after the first month of treatment, and superior to that of paracetamol and other NSAID. Additionally, Diacerein has shown a prolonged effect on symptoms of several months once treatment was stopped. The use of Diacerein is associated with common gastrointestinal disorders such as soft stools and diarrhoea, common mild skin reactions, and, uncommonly, hepatobiliary disorders. However, NSAIDs and paracetamol are known to cause potentially severe hepatic, gastrointestinal, renal, cutaneous and cardiovascular reactions. Generally Diacerein 50 mg with Glucosamine are shows the synergistic effect in treatment of osteoarthritis and chronic pain. The consultant and Doctor not prefer the Diacerein in single dose but prefer in combination. In the market the Diacerein is available 50 mg film coated tablet form. Glucosamine is naturally hygroscopic is nature when exposed to air and moisture and degradable whether in the form of tablet or raw material. To overcome this problem Glucosamine needs to bond with suitable stabilizer. Glucosamine Sulphate in the form of Salt i.e. Sodium chloride and potassium chloride are stable. The normal dose of Glucosamine is 500-1500 mg TID. It is very difficult to compress the tablet at the label claim 1500 mg because some additive are also required in the formulation and the average weight are 1800 mg. As per the pre formulation studies it is concluded that tablet average weight less than 70 mg are very difficult to compress and more than 1500 mg are difficult to swallow in adult patient. Glucosamine is a special formulation that prove the pharmacological value to nourish the joint health. Glucosamine stimulates the formation or manufacture of collagen, the protein portion of the fibrous substance that holds joints together and provides a shock-absorbing cushion, as a person ages, the cartilage that cushions the joints often loses its ability to support healthy cellular growth. In addition, the synovial fluid which lubricates these joints also deteriorates. This condition, called osteoarthritis, often leads to rough bones that rub together and cause distress with every twist or bend. In this condition patient regularly required the Glucosamine tablet in 1500 mg three times a day. As per the pre formulation and formulation studies, it is observed that it is very difficult to compress the tablet at huge weight (Glucosamine 1500 mg + Diacerein 50 mg) because D tooling compression machine have maximum limit is 1500 mg. For such critical formulation weight cam is adjusted in lower direction to increase the weight and feeding of granules in feed frame through force feeder resolve the dissolution problem as force feeder required less lubricant and all the lubricant are hydrophobic in nature. This tablet is prepared by wet granulation method by using Non Aqueous binding showed good results physical evaluation parameters and chemical parameters such as Assay, and Dissolution values. The granules lubricated with lubricants / Glidant / Antiadhrants were good in their flow properties. Assay and dissolution studies were conducted by the HPLC method.

KEYWORDS: Stable glucosamine So4 KCL & Diacerein 50 mg tablets, solid formulation of tablet, Force Feeder compression Machine.

2. INTRODUCTION

Diacerein and Glucosamine Sulphate Potassium Chloride and Sodium chloride are generally used for joint health. Both the drugs are used in combination for synergistic effect to treat the osteoarthritis. Glucosamine support the collagen and protein portion of the fibrous substance that holds joints together and provides a shock-absorbing cushion. As the age of a person increases, the cartilage that cushions the joints often loses its ability to support healthy cellular growth. Also the synovial fluid which lubricates these joints also deteriorates as the age of a person increase or weight. This condition, called osteoarthritis, often leads to rough bones that rub together and cause distress with every twist or bend. In this condition to treat the patient Non-Steroidal anti-inflammatory drugs (NSAID) are used. NSAID May be COX1 or COX2 inhibitor destroyed cartilage. Other side effect in prolong used of NSAID are GIT damage, Haemorrhage. Medicinal science discovered a nutrients that help in preserving joint tissue and fluids. Glucosamine is a necessary nutrient in the production of cartilage and synovial fluid.

Pure Glucosamine is fully "hygroscopic" and degradable when it come in contact to moisture and air. To mask the hygroscopic nature of Glucosamine, it needs to be bound to a stabilizer to be sold commercially. The sulphate and the HCL forms are two of the most common "agents" that Glucosamine is bound and shows its stability. After Glucosamine is bound, it is stable and will not degrade. These are various difficulties and limitations in the formulation of Glucosamine formulation. For example, oral forms, such as tablets or capsules, require anti-oxidants, such as sodium hyposulphite to present in their formulations, which blocking the oxidation of the amino group.

Pure Diacerein is slightly hygroscopic in nature when exposed to air and light. The aqueous binding in granulation reduced the assay, stability, and potency of the drug hence non aqueous binding with Alcohol, and acetone required to overcome the problems.

3. MATERIALS

3.1 API structure and Properties

3.1.1 Glucosamine Sulphate Potassium chloride

INN: No INN has been specifically assigns for glucosamine sulphate Potassium Chloride

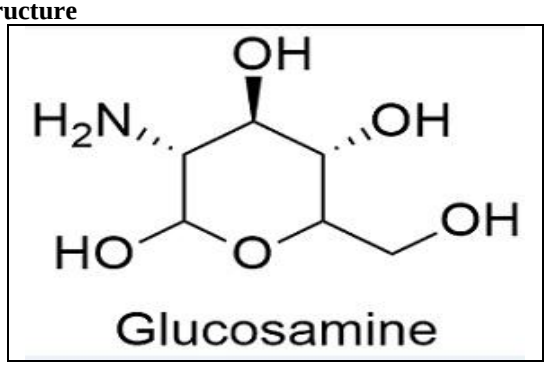
Chemical name: Bis (D Glucose, 2 amino-2 deoxy), Sulphate potassium chloride complex

Appearance: White and almost white crystalline powder.

Solubility: Freely soluble in water, sparingly soluble in methanol and practically in
soluble in acetone.

Category: Osteoarthritis, Muscle Injury Prevention, Osteochondritis; Rheumatoid
Arthritis, tendonitis

Structure



Molecular formula: $(C_6H_{14}NO_5)_2SO_4$. 2KCL
Molecular weight: 573.3 g/ mole

3.1.2 Diacerein

INN: Diacerein also known as diacetylrhein, is a slow-acting medicine of the class anthraquinone used to treat joint diseases such as osteoarthritis (swelling and pain in the joints).[1] It works by inhibiting interleukin-1 beta. An updated 2014 Cochrane review found Diacerein had a small beneficial effect on pain. Diacerein-containing medications are registered in some European Union and Asian countries and included as a treatment option on several international therapeutic guidelines.

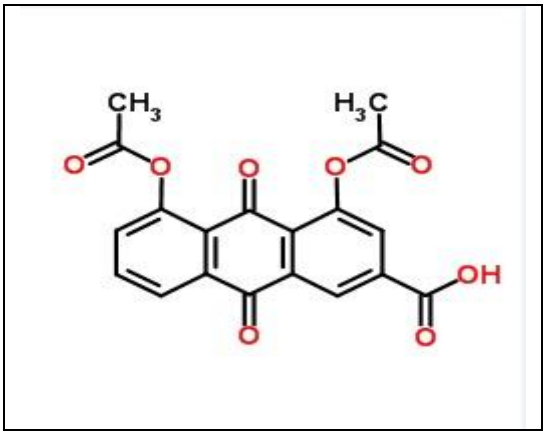
Chemical name: Diacetylrhein; Diacerhein; 2-Anthracenecarboxylic acid, 4,5-bis (acetyloxy)-9,10-dihydro-9,10-dioxo-; 2-Anthroic acid, 9,10-dihydro-4,5--9,10-dioxo-, diacetate; 9,10-Dihydro-4,5-dihydroxy-9,10-dioxo- 2-anthroic acid, diacetate

Appearance: White crystalline powder, hygroscopic in nature.

Solubility: Diacerein is practically insoluble in water 0.01 mg/mL (20 °C)

Category: Anti-inflammatory and anti-rheumatic products

Structure



Molecular formula: $C_{19}H_{12}O_8$
Molecular weight: 368.294 g/mol $g \cdot mol^{-1}$

3.1.3. Sources of obtaining the Active and Additives.

Glucosamine sulphate was obtained as gift samples from ZEON LIFESCIENCE LIMITED, PONTA SAHIB, and DIST. SIRMOUR. H.P. (India). (Manufactured by. Bio gene Extract Limited. Bangalore. Karnataka, and Costal Laboratories. India).

Diacerein is obtained a gift sample from Zeon Life Sciences limited, Ponta Sahib. Dist. Sirmour H.P. (India) Manufactured by. Glenmark India limited. Mumbai. India.

All the remaining Additives / binder/ preservatives/ solvent/ film former/ colouring agent/ plasticizer are the free sample from Tirupati Zeon Medicare Limited, Ponta Sahib. Sirmour H.P.

3.2 List of Materials used in the Glucosamine 1500 mg and Diacerein 50 mg Tablet.

S. No.	Ingredients	Role Of Ingredients	Supplier
1	Glucosamine SO4 KCL	Active Ingredient	Zeon life sciences Ponta Sahib. H.P.
2	Diacerein	Active Ingredient	
3	Lactose	Filler	Tirupati Medicare limited, Ponta sahib. Dist. Sirmour. H.P.
4	MCCP	Filler	
5	Starch	Disintegrants	
6	Methyl Paraben	Preservatives	
7	Propyl Paraben	Preservatives	
8	Iso Propyl alcohol	Solvents	
9	PVP-K 30	Binding agents	
10	Talcum Powder	Lubricants	
11	Magnesium Stearate	Antiadhrants	
12	Sodium Starch Glycolate	Disintegrants	
13	Aerosil	Glidant	
14	Cross carmillose sodium	Super disintegrants	
15	Insta coat (Sunset Yellow)	Film forming agent	
16	Iso Propyl alcohol	solvent	
17	Methylene Dichloride	Solvents	
18	Insta coat (Polish)	Polishing Agent	

3.3 Drug and Excipients Study

Sr. No.	Drug+ Excipients	Duration (months)	Result
1	Glucosamine + Starch	6 Months	Stable
2	Glucosamine + Talcum	6 Months	Stable
3	Glucosamine + Mag. Stearate	6 Months	Stable
4	Glucosamine +MCCP	6 Months	Stable
5	Glucosamine +Lactose	6 Months	Stable
6	Glucosamine +CCS	6 Months	Stable
7	Glucosamine + PVP –K 30	6 Months	Stable
8	Glucosamine +DC starch	6 Months	Stable
9	Glucosamine + SSG	6 Months	Stable
10	Glucosamine + HPMC	6 Months	Stable
11	Glucosamine + Diacerein	6 Months	Stable
12	Diacerein + Starch	6 Months	Stable
13	Diacerein + Talcum	6 Months	Stable
14	Diacerein + Mag. Stearate	6 Months	Stable
15	Diacerein +MCCP	6 Months	Stable
16	Diacerein +Lactose	6 Months	Stable
17	Diacerein +CCS	6 Months	Stable
18	Diacerein + PVP –K 30	6 Months	Stable
19	Diacerein +DC starch	6 Months	Stable
20	Diacerein + SSG	6 Months	Stable
21	Diacerein + HPMC	6 Months	Stable

In the Drugs and excipients study both two drugs are mix individually with all the additives and keep in Glass bottle and mentioned the specified label and kept for duration of six months. During this period if the colour

change and any other physical abnormal change shows drug incompatibility**.**

3.4 Formulation table

S. NO.	INGREDIENTS	C1 (mg)	C2 (mg)	C3 (mg)	C4 (mg)	C5 (mg)
1	Glucosamine SO_4KCL	1500	1500	1500	1500	1500
2	Diacerein	50	50	50	50	50
3	Lactose	60	60	60	60	60
4	MCCP	45	50	55	60	65
5	Methyl Paraben	16	16	16	16	16
6	Propyl Paraben	4	4	4	4	4
7	Iso Propyl alcohol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
8	PVP-K 30	50	45	40	40	40
9	Talcum Powder	15	15	15	15	15
10	Magnesium Stearate	15	15	15	15	15
11	SSG	14	14	14	14	14
12	Cross Carmillose Sod.	15	15	15	15	10
13	Aerosil	16	16	16	11	11
	Film coating Materials					
14	Instacoat (Sunset Yellow)	45	45	45	45	45
15	Isopropyl alcohol	**Q.S**	**Q.S**	**Q.S**	**Q.S**	**Q.S**
16	MDC	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
17	Insta coat Polish	15	15	15	15	15
	Total Weight	**1860**	**1860**	**1860**	**1860**	**1860**

4. METHOD OF PREPARATION OF GRANULES AND COMPRESSION OF TABLET

4.1 Wet Granulation Method

Generally the low weight tablet of various formulation in range of 500- 750 mg are prepared by direct compression method. But when the dose of tablets are more than 1500 mg or 2000 mg, along with other excipients then it is very difficult to compress. The compression machine exert the force 8-10 tons from both side. There is chances of damage of machine or accident with operator and workers. In such case wet granulation method are used for preparation of Granulation. As glucosamine Sulphate are hygroscopic in nature then non aqueous solvent are used. For this the formulator used Acetone, Isopropyl Alcohol, or methylene dichloride.

Weigh accurately all the ingredient, Glucosamine pass through sieve 40, Diacerein 60 # and Lactose starch and MCCP pass through sieve 60. Then active and filler mix together. After this the binding solution is prepared by dissolving the PVP-K 30 into Isopropyl alcohol. In the rapid Mixer Granulator the shifted active and filler are mixed for five minutes. Then binding solution added through opening duct of Granulator and mix till the smooth granules are obtained.

Remove the wet granules and finally dry in the tray dryer. Initially granules are dry on air drying and then start the heater and set the temperature at 40 ºC. The final dried granules contains the moisture not more than 1.5%. By IR moisture balance.

Lubricants are mixed together and pass through sieve 60 and lubricate the granules for five minutes in Octagonal blander.

4.2 Compression of tablet

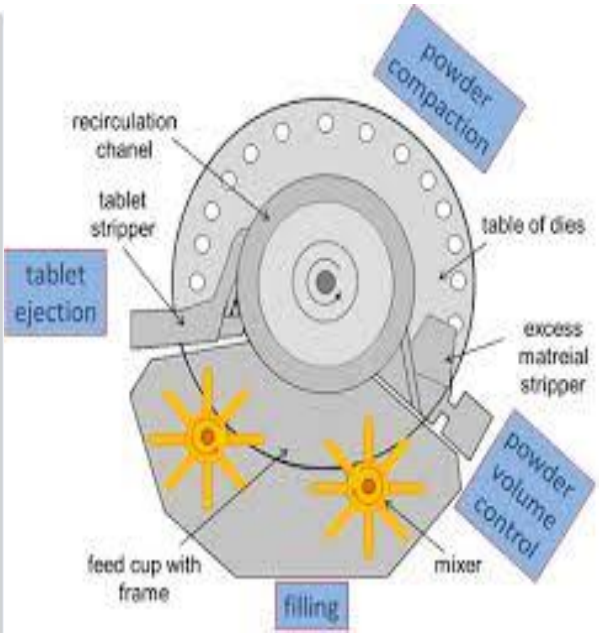
Finally dried and lubricated granules are compressed at calculated weight by using the D Tooling 27 station Fluid Pack Accura (force feeder) at 12 RPM. The punches used for compression are buffed by using buffing machine. The finally compressed tablet are sorted by using tablet sorting machine.

4.3 Tablet Coating

Compressed Tablets are coated in the conventional coating pan / auto coater. In Auto coater the appearance of the tablet are not the desired qualities. All the compressed tablets are coated in the conventional coating pan at 6-7 RPM, and spay rate is 1000 ml / 40 minutes. Insta coat readymade coating material are used containing Sunset Yellow as coloring material Titanium dioxide, HPMC, PEG, Talcum. Finally coated tablet are polished by using Insta coat polishing agent in polishing pan.

5. EQUIPMENTS AND INSTRUMENTS

Tablet Compression Machine by Fluid Pack Accura (force feeder), Tablet dissolution apparatus Type II by Electro lab. Limited., Electronic Balance Model, Sansui; pH meter by Hanna Instrument, Italy; Pfizer Hardness Tester, Roche Friability test apparatus; Hot Air Oven by Meta lab Scientific Industries, Mumbai. Try dryer, rapid mixer granulator, Conventional coating pan, Polishing pan.



6. POST COMPRESSION PARAMETERS

6.1 Thickness of compressed tablet

The thickness of the compress tablets of Glucosamine 15000 mg and Diacerein was determined using a Digital Vernier calliper. Ten tablets from each type of formulation were used and average values were calculated. It is expressed in mm.

6.2 Hardness

The resistance of tablets during passing through hopper, Blister Cartooning, breakage, under conditions of storage, transportation and Handling before usage are directly proportional to its hardness. For each formulation, the hardness of 6 tablets was determined using the Pfizer Hardener Tester and Monsanto hardness tester. The tablet was held along its oblong axis in Between the two jaws of the tester. At this point, reading should be zero kg/cm2. Then constant force was applied by rotating the knob in Monsanto tester and in case of Pfizer directly force applied until the tablet breakdown in the pieces. The reading the both cases at this point was noted.

The new electronic hardness tester by Karnavati Machine Ahmadabad is also used to determine the strength of compressed tablet. It is costly but it gives the sharp and exact result.

6.3 Friability Test

Friability Test is generally used the measure of tablet strength. Roche Friability tester was used for testing the friability using. In This test subjects a number of compressed tablets to the combined effect of shock abrasion by utilizing a circular plastic chamber which revolves at a speed of 25 revolution per minutes for 4 minutes i.e. 100 rpm, dropping the compressed tablets of Glucosamine So4 KCl and Diacerein to a distance of 6 inches in each revolution. A sample of compressed 20 tablets of was placed in Roche friability chamber which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then de-dusted, and broken tablet are removed and reweighed. A loss of less than 1% in weight in generally considered acceptable according to Pharmacopeia. Percentage friability (% F) was calculated as follows:

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

6.4 Weight variation test

As per the limitation of Pharmacopeia to find out weight variation test, 20 tablets of each type of formulation were weighed individually using single pan balance or an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.

Specifications for tablets as per Indian Pharmacopeia. 1996.

S. No.	Percentage Deviation	Average Weight of Tablet(mg)
1	10	80 mg or less
2	7.5	More than 80 mg but less that 250 mg
3	5	250 or more

6.5 Uniformity of drug content

As per the official pharmacopeia's the randomly sampled tablet from the all five compression batches should contained the Glucosamine sulphate KCL and Diacerein NLT 90% and NMT 110% of labelled amount. If from the 20 sample tablet at least 18 tablet passed and 2 tablet fail in the assay calculation then the tablet passed in uniformity of drug content. But more than 2 tablet fail in

the assay limit then take appropriate action to rectify the problems.

6.6 In vitro disintegration time

The process of breakdown or convert the tablet into pieces or into smaller particles is called as disintegration. The in vitro Disintegration time of a tablet was determined using disintegration test apparatus as per Indian Pharmacopeia specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using distilled water maintained at 37° ± 2°C which is similar to body temperature. The assembly should be raised and lowered between 30 cycles per minute in the 0.1 N HCL or Distilled water maintained at 37° ± 2°C. The time in seconds taken for complete disintegration of the tablet.

In this disintegration test if the tablets are adhere to the 10 # sieve then continue the test till all tablet are completely disintegrated.

6.7 In vitro dissolution test

Rate of dissolution are studied by using USP type-II apparatus having 50 rpm, using 900ml of 0.1 N Hydrochloric acid as dissolution solvent. Temperature of the dissolution medium was maintained at 37 ± 0.5°C. The sample of dissolution medium was withdrawn at every 5 min interval and first filtered. The absorbance of filtered solution was measured by using Ultra Violet spectrophotometric method at mentioned nm specified in official pharmacopeia and concentration of the drug was determined from standard calibration curve.

In vitro drug release studies details:
Dissolution test apparatus
0.1 N HCL as Dissolution medium
900 ml Dissolution medium volume
37 ± 0.5°C as std. Temperature
50 rpm Speed of basket paddle
5 min sampling intervals
10 ml volume Sample withdraw
Absorbance measured as specified in the official books

7. RESULT AND DISCUSSION

7.1 Pre compression Parameter and studies

S. No.	Formulation code	Angle of Repose	Bulk density (weight/ml)	Taped Density (weight/ml)
1	C1	33.32±0.70	0.52±0.02	0.45±0.04
2	C2	32.10±0.56	0.48±0.03	0.41±0.02
3	C3	30.86±0.63	0.45±0.03	0.38±0.04
4	C4	28.44±0.45	0.44±0.02	0.38±0.02
5	C5	26.40±0.69	0.41±0.03	0.35±0.02

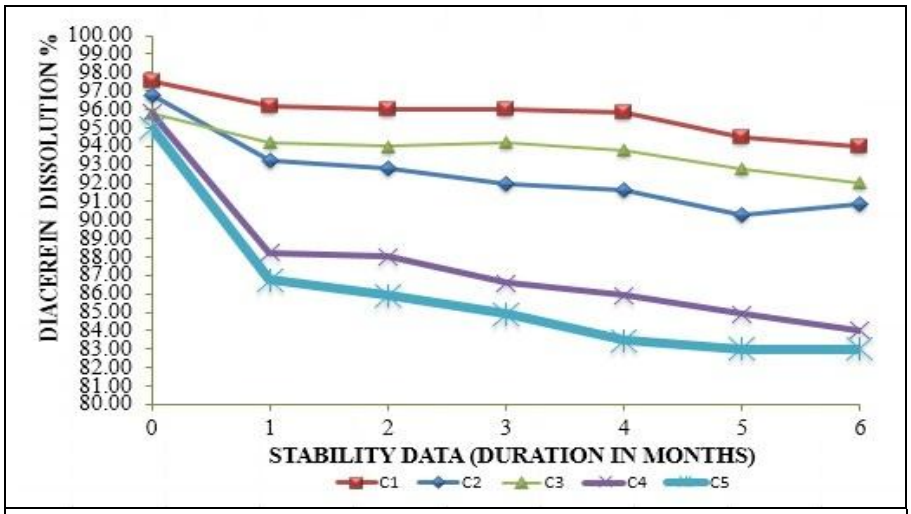
7.2 Post compression Parameter Studies.

Formula code	Hardness (KG/cm2)	Friability (%)	Thickness (mm)	Length (mm)	Wt. of Un coated tablet (mg)	Wt. of film coated Tablet (mg)
C1	9.5	0.65	7.56	21.02	1820	1862
C2	9.2	0.72	7.62	210.2	1832	1854
C3	9.0	0.82	7.64	21.03	1810	1868
C4	9.0	0.83	7.58	210.1	1824	1856
C5	8.8	0.88	7.60	210.2	1812	1860

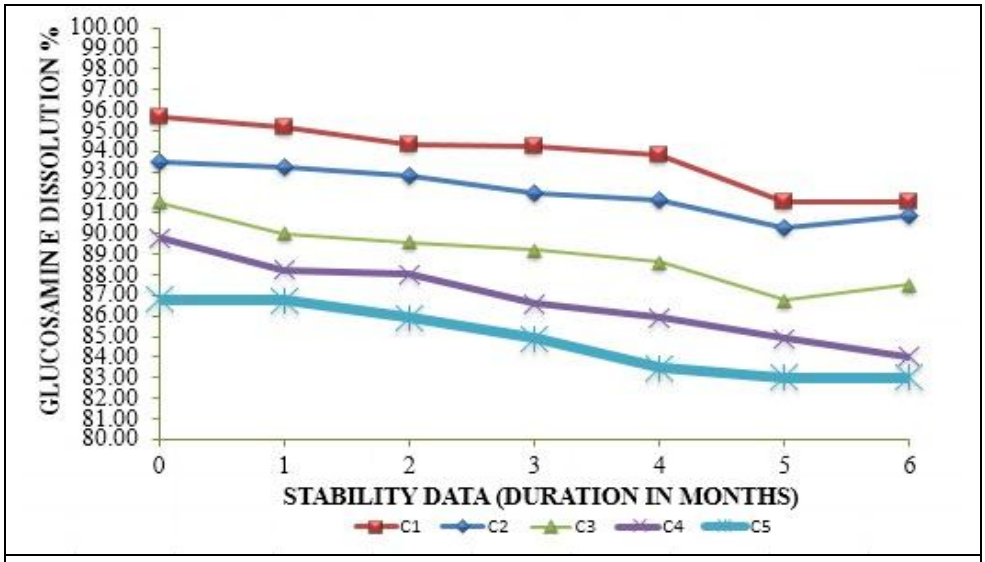
7.3 Post compression Studies

Formulation code	Assay of Drugs (%)	Disintegration time (minutes) Uncoated	Disintegration time (minutes) Film coated	Dissolution (%)
C1	99.25	5.4 to 6.2	9.0 to 11.2	95.65 %
C2	100.21	5.3 to 7.2	9.4 to 12.4	93.21 %
C3	98.56	6.2 to 8.2	10.2 to 14.4	91.56 %
C4	98.64	6.5 to 9.3	10.4 to 13.3	89.77 %
C5	99.60	7.2 to 10.5	11.2 to 16.4	86.12 %

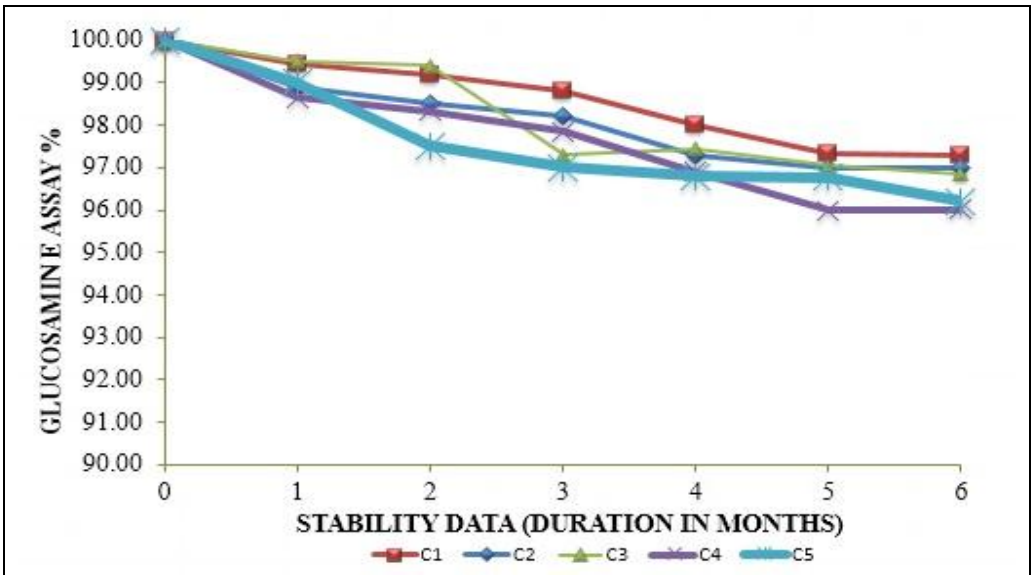
8. GRAPHS OF DISSOLUTION, STABILITY, ASSAY, HARDNESS, THICKNESS



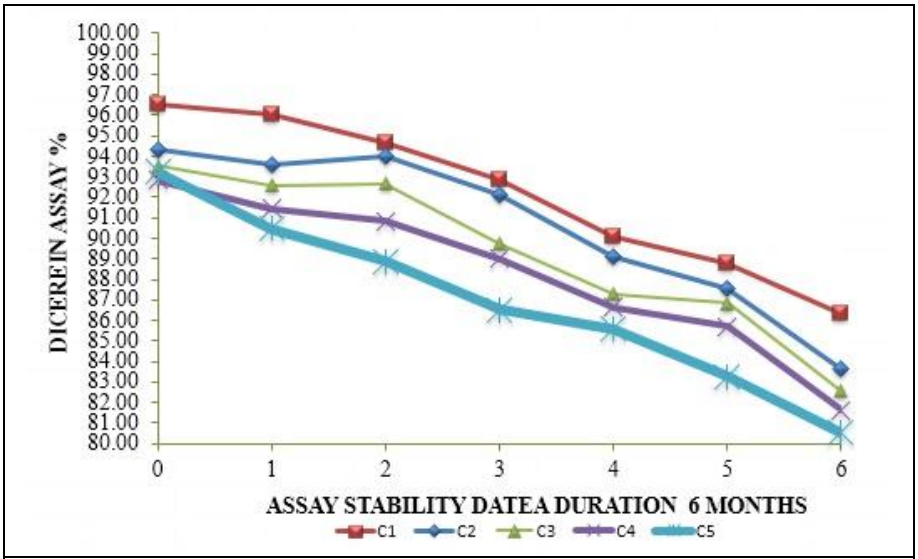
Diacerein Dissolution stability date for duration of 6 Months



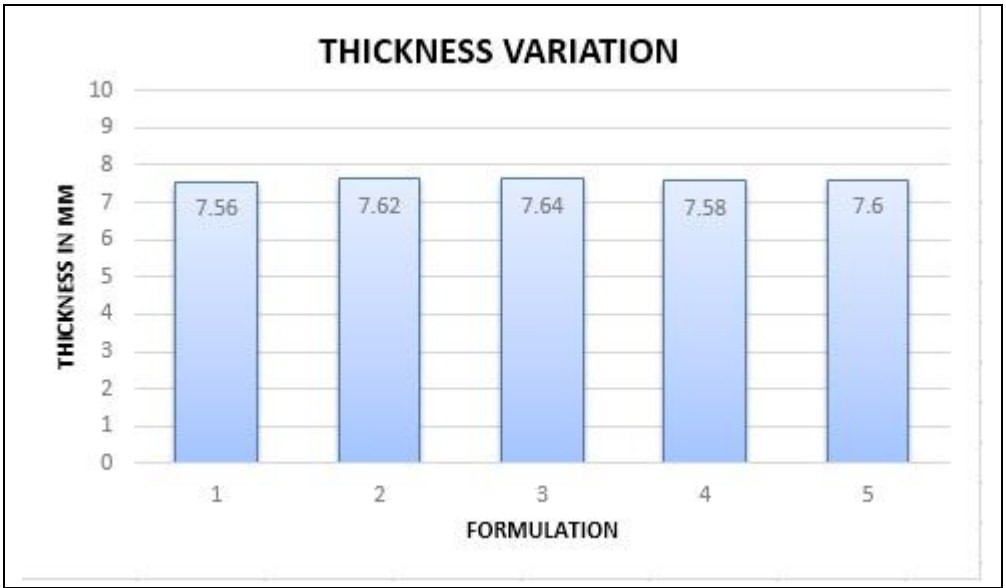
Glucosamine So4 Stability Date for duration of 6 months



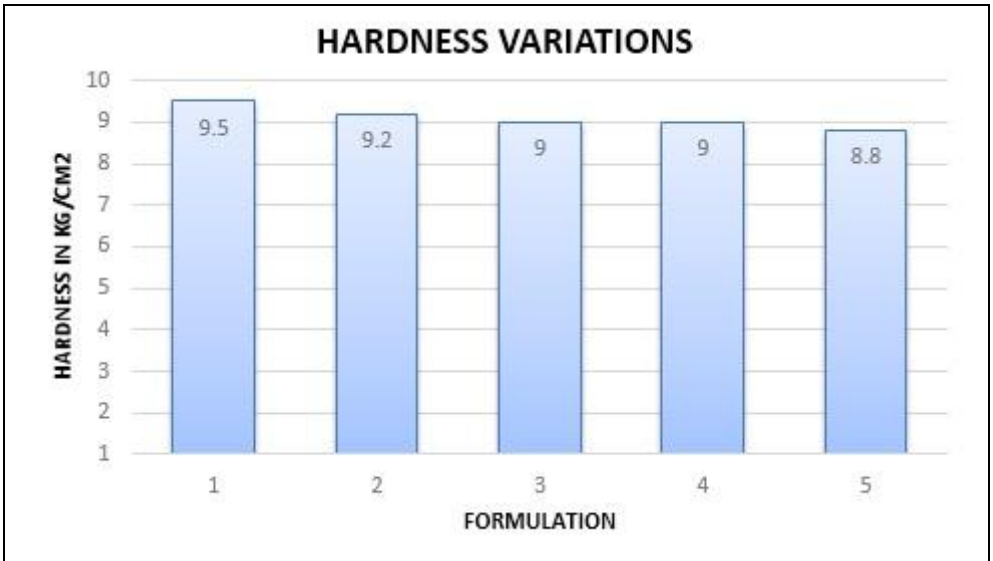
Glucosamine Assay stability Date for duration of 6 months



Diacerein Assay stability data for duration of 6 Months



Glucosamine and Diacerein Tablet Thickness Variations



Glucosamine and Diacerein Tablet Hardness Variation

9. CONCLUSION

After the completion of this experiments the result obtained and we conclude that development of Glucosamine 1500 mg and Diacerein 50 mg Tablet formulation by using PVP k 30 as Binder and cross carmillose as disintegrate are given the result of stable tablet having good hardness, required dissolution and well film coated tablet. Some result are mentioned below:

Active drug Glucosamine sulphate and Diacerein are stable with different excipient are stable viz Starch, Talcum, MCCP, Lactose, Magnesium stearate, cross carmillose sodium and PVP K 30 in duration of six month stability studies.

Film coated tablet of Glucosamine sulphate 1500 mg & Diacerein 50 mg FC tablet are Successfully prepared.

The flow property of the granules and uniformity of the compressed tablet are better in Non Aqueous binding with PVP K 30 as Compare the granules prepared by Aqueous binding with starch Paste.

The angle of repose of prepared granules is less than 30º which show the good quality of granules.

The hardness of compressed tablet by Non Aqueous PVP K 30 binding in the rage of 8.8 to 9.5 kg/cm^2.

The Thickness of the prepared tablets by all three methods was found between 7.56 mm. to 7.62 mm.

The Friability of the compressed tablet are within the range i.e. less than 1%.

The in vitro disintegration studies are found to be in 5.4 to 10.5minutes for uncoated tablet and 9.0 to 16.4 minutes.

Formulation C1 showed in vitro disintegration time is 5. 4 to 6.2 minutes for uncoated tablet and 9 to 11 minutes for film coated tablet.

On the basis of disintegration time formulation C1 which facilitate the faster Disintegration, sufficient hardness, well dissolution, good stability data, and assay, it is better formulation and stable during its shelf life. We conclude that film coated tablet are prepared by this method is stable and pass all the test mentioned in the pharmacopeia's.

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