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Formulation and Evaluation of Grape Seed Extract (Vitis Vinifera) Tablet

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ABSTRACT: Cultivation of grapes is known as viticulture.Grapes are one of the tastiest end result and extensively eaten as a clean fruit in India.Also used to make raisins, wine and different products.Grape skins are a supply of vital oils and pectin.[7]Can additionally be used as animal feed and confectionery ingredients.Raisins are rich in sugars, most of which are fructose and antioxidants.Grape production is important in the context that he is the third most cultivated fruit after citrus and bananas.Grapes are laxative and diuretic. Helps fight indigestion, hemorrhoids, urinary tract and bile duct stones. It also activates liver function, promotes digestion, reduces blood cholesterol and eliminates uric acid 6.Its juice is used in cosmetics to bleach and soften skin.Proanthocyanidins in grape seed have been shown to inhit the strong antioxidant,anti-inflammatory,anticarcinogeric and antiviral activity. Grapes are rich source of flavonoids.[8]

Keywords: Anti-oxidants,Grape seed,Proanthrocyanidins,In –vitro

INTRODUCTION

Plant (Vitisvinifera L.), a species of the vitaceae family, is one of the most important plants for food and commerce. This plant's fruits were used to make wine, grape juice, and other food goods. The plant is grown and distributed throughout all temperature ranges when average climatic conditions include sufficient precipitation, warm, dry summers, and reasonably mild winters. The metabolic start making of grape products determines their properties. A widespread and popular type of natural polyphenol generated by the phenyl propanoid pathway are flavonoids.[1] Flavonoids from grapes are mainly found in the epidermal layer of berry skin and seeds. Grape seeds are rich in protein 11%, complex phenols 7%, fat 16%, and fibre 40%. Furthermore, catechin and epicatechin -3-o-gallate, two monomeric phenolic compounds, are abundant in grape seeds. Grape seeds are rich in proteins 11%, complex phenols 7%, fat 16%, and fibre 40%. Furthermore, catechin and epicatechin -3-o-gallate, two monomeric phenolic compounds, are abundant in grape seeds.[2] The most important flavonol in both grape skin and seeds is catechin. It has been shown that dietary flavonoids from grapes can effectively regulate oxidative stress and prevent oxidative damage when consumed in the form of grape extracts and grape seed powder. Therefore, the purpose of this research was to identify the primary active substances present in the grape plant's fruits and seeds that were grown in Sulaymanyah, in the north of Iraq. One of the commercial fruit crops grown in India is grapes. Grape is the third most widely cultivated fruit after citrus and banana.[3,4]. Globally grapes production was 67909.28 thousand tonnes during 2008 as per FAO data and grapes production contributes to about16%of the total fruit production. European Union takes the lead position in grapes production with Italy occupying the top position with 11.48% followed by China with 10.73% and USA with 9.93%. India produced about 2.77percent (1878.00 thousand tonnes) of the total world production during 2008. Maharashtra (75.33%) is the country's largest producer of wine grapes. Maharashtra and Karnataka together account for about 89.65% of India's grape production.[5,6]. Grapes are commonly consumed as a fresh fruit in India. It is also used to make raisins, wine, juices, juice concentrates, pumpkins, beverages, jams and marmalades.

Grapes are easily digestible and have many therapeutic benefits Grapes are non-climacteric fruit that grow on the perennial and deciduous woody vines. Cultivation of grapes is known as viticulture. Grapes are one of the tastiest end result and extensively eaten as a clean fruit in India. Also used to make raisins, wine and different products. Grape skins are a supply of vital oils and pectin.[7] Can additionally be used as animal feed and confectionery ingredients. Raisins are rich in sugars, most of which are fructose and antioxidants. Grape production is important in the context that he is the third most cultivated fruit after citrus and bananas. Grapes are laxative and diuretic. Helps fight indigestion, hemorrhoids, urinary tract and bile duct stones. It also activates liver function, promotes digestion, reduces blood cholesterol and eliminates uric acid 6. Its juice is used in cosmetics to bleach and soften skin.Grapes are rich source of flavonoids. [8]

Nutritionalvalue

Nutritional value of grapes per 100gm

Edible part	94 %	Sodium	1 mg
Water	80.3 g	Potassium	192 mg
Protein	0.5 g	Iron	0.4 mg
Lipids	0.1 g	Calcium	27 mg
Glycosides	15.6 g	Phosphorus	4 mg
Fiber	1.5 g	Niacin	0.1 mg
Energy	61kcal	Vitamin C	6 mg

Properties of Proanthocyanidin

Proanthocyanidins as a whole cause many bioactivities that produce positive, healthful changes in the human body. It had been demonstrated that these compounds exhibit anti-oxidant properties and help the body ward off cardiovascular disease, various immune disorders, and neurodegenerative disease. [9] Perhaps the most widely known health related anecdote from products associated with grapes was the explanation of so-called “Frenchparadox”, in which red wine was shown to reduce the risk of coronary heart disease. However, all phenolic compounds with anti-oxidant properties react in the same manner with free radicals to help prevent all of the above afflictions. Total phenols (or antioxidant effect) of a plant species can be measured using the Folin-Ciocalteu reaction.[10] Results are typically expressed as gallic acid equivalents (GAE). Phenolic compounds as a whole are healthful due to both their ability to terminate free radicals and to acting as metal chelators. Both free radicals and metals are known to help catalyze lipid peroxidation reactions, which leads to many human ailments. The proanthocyanidins and other healthful phenolic compounds prevent this and other oxidation reactions *via* hydrogen donation from the phenol to the free radical containing compound.[11] The typical base structure with ring stability helps support the free radical that it is left with and therefore does not react again to initiate oxidation. However, the free radical polyphenol can also act as a terminator for a free radical reaction sequence by reacting again with another free radical. The ability of a compound to act as an antioxidant depends highly on its chemical structure.In the case of polyphenolic compounds, the group, flavonoids, contains the highest ability to act as an antioxidant due to its natural structure. [12] Containing such compounds as an *o*-diphenolic group, a 2-3 double bond conjugated with the4-oxo function, and ideally placed hydroxyl groups on the rings, the flavanoid is able to give off hydrogen and become a radical without losing much stability. As antioxidants, pro-anthocyanidins have high oxygen radical scavenging capacity in human body. [13]

Anti- inflammatory action property of flavanoids

Inflammation is a protective response of tissues against cell injury, irritation, pathogen invasions, as well as mechanism for eliminating damaged and necrotic cells. Several environmental stress factors may cause inflammation. Under normal physiological conditions, a short period of acute inflammation can overcome negative effects on injured tissue. However, if inflammation is prolonged, chronic inflammation can have developed. Chronic inflammation is the main mediator in the development of chronic diseases such as cancer, Alzheimer’s, neurodegenerative diseases, cardiovascular diseases, diabetes, arthritis, auto immune and pulmonary diseases.[14] When signal-dependent transcription factors [nuclear factor κB (NF-κB) and activating protein 1 (AP-1)] are activated, they induce the expression of genes involved in inflammatory response. Intensive production and secretion of pro-inflammatory cytokines and chemokines, once started, can form concentration gradients in affected tissues, which may lead to the amplification of the initial inflammatory response. As a result, additional immune cells are recruited, and increased levels of ROS are produced. Under normal physiological conditions, anti-inflammatory cytokines act as immune regulators to control the inflammatory reactions. [15] Deregulation of precise control mechanism of inflammation leads to chronic inflammation and promotion of chronic disease. Grape polyphenols have been shown to decrease chronic inflammation either by modulation of inflammatory pathways or by reducing ROS levels. As natural compounds, grape flavonoids and proanthocyanidins can target multiple pathways to overcome chronic inflammation,and thus are more effective compared to synthetic mono-targeted anti- inflammatory drugs. Freeze-dried extract of wine from “Jacquez” grapes, which contains mainly flavonoids, anthocyanins, proanthocyanidins and hydroxyl cinnamic acid derivatives, showed higher anti-inflammatory activity when compared to the commercial non-steroidal anti- inflammatory drug (NSAID) indomethacin.[16] It has also been demonstrated that

proanthocyanidins in grape seeds have high anti-inflammatory action, because they scavenge free radicals, prevent lipid peroxidation and inhibit formation of pro-inflammatory. Proanthocyanidins extracted from the grape seeds have also been found to have an immune-modulatory role in inflammatory conditions that exert an overproduction of nitric oxide and prostaglandin E2. The suppression effect of extracts obtained by red and white grape pomaces on chronic inflammation induced by lipo polysaccharide and galactosamine, has been investigated *invivo*. The authors found that the extract of red grape pomace suppresses the activation of inflammatory transcription factor NF-κB and thus could be used as raw material for both extraction of new anti-inflammatory candidates or as an additive in processing functional foods. [17]

Antiulcer activity procyanidin oligomers

Since the monomer component, (+)-catech in did not show the antiulcer activity, the active compounds showing mucosal protective activity were thought to be procyanidin oligo gram and polymers. Procyanidin oligo gram from (+) catechin and (±) toxifoline were prepared using the method of ariga (1990) , and the effect on gastric injury induced by HC1/Et OH solution was tested. (+)-catechin, procynidine B-3 and dimeric sand trimeric procynidins showed no protective effect against stomach damage, however, longer oligomer such as tetrameric, pentameric,and hexameric procyanidins did show potent antiulcer activity. That is the activity of a series of procyanidins increased with the increased degree of polymerization of the catechin unit. [18]

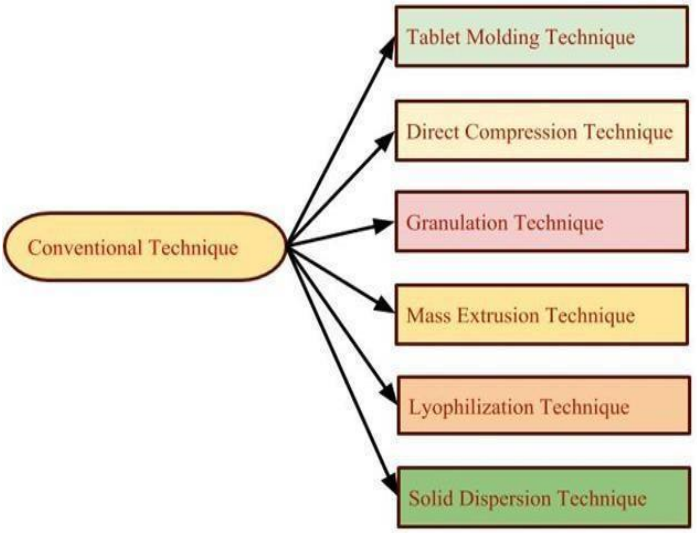
Anti-oxidantacivity

Antioxidant activity of grape seed extracts is evaluated using β-carotene –linoleate model system and linoleic acid peroxidation method. The results showed that different extracts had 65%-90% (scavenging rate) antioxidant activity at 100 ppm concentration. The present work indicated grape seed extracts may be exploitable from the preservation of food products as well as for health supplements and nutraceuticals. Shaker evaluated the anti-oxidative effect of red grape seed and peel ethanolic extracts on primary and secondary lipid oxidation in sunflower and conjugated sunflower oils.[19] After 6 days, a high anti-oxidative effect was found from the secondary oxidation products in conjugated sunflower for peel extract followed by seed extract. In one study, Kim et al evaluated the effect of heating and physical conditions of grape seed on the antioxidant activity of their extracts. The result indicated that antioxidant activity of grape seed extract was affected by heating conditions and physical conditions of grape seed.

Characteristics of grape seed extract tablet dosage form immediate release of grape seed extract tablet

Immediate release tablets are manufactured to dissolve and release their dosage form without the addition of special rate-controlling elements like coatings or other methods. Immediate release tablets are ones that dissolve quickly and disintegrate to release the medication. The oral bioavailability of a medication is influenced by physiologic processes like dissolving and disintegration. A manufacturer can diversify their market while also providing patients with a convenient dosage form or regimen with an immediate release dosage form. [20]

Conventional technique of immediate release dosage form



Plant profile

Plant name: grape
Family: vitaceae
Commonnameforalllanguage:

- Tamil –tiratchaippalam
- Malayalam- muntirippalam
- Hindi–angoor
- Telugu–draksha
- Kannada–draksigalu
- Bengali – anguru

- Punjabi – agura
- Marathi–drakes

Source: Stem and seed
Constituents: Tannins, anthocyanins, catechins, resveratrol, phenolicacids, And procyanidins
Uses: Antioxidant, anti inflammatory, anticancer, antiulcer [21].

Fig 1: Grapes

Fig 2: Grape Seed

Phytochemical invesigation of grape seed extract

Steroids: An aliquot of the seed extract (1ml) was dissolved in 10 ml of chloroform and equal volume of concentrated sulphuric acid was added by sides of the test tube.The upper layer turns red and sulphuric acid layer showed yellow with green fluorescence.This indicated the presence of steroids (Gibbs,1974).

Terpenoids: An aliquot of the seed extract (2ml) was added to 2ml of acetic anhydride and concentrated H2SO4. The formations of blue green ring indicate the presence of terpenoids (Ayoola*etal.*,2008).

Tannins: An aliquot of the seed extract (2ml) was added to few drops of 1% lead acetate, and the yellowish precipitate indicated the presence of tannins (TreareandEvans,1985). [24]

Saponins: An aliquot of the seed extract (5ml) was mixed with 20ml of distilled water and then agitated in a graduated cylinder for 15minutes.Formation of foam indicates the presence of Saponins (Kumar*etal.*,2009).

Anthocyanins: An aliquot of the seedextract (2ml) was added to 2ml of 2NH4Cl and ammonia. The appearance of pink-red which turns to blue-violet indicates the presence of anthocyanins (Farnsworth,1966).

Glycosides: 2ml glacial acetic acid, one drop of 5% FeCl3 and conc. H2SO4 were added into 5ml extract, the appearance of brown ring indicates the presence of glycosides (Khandewal, 2008). [25]

Emodins: Two ml of NH4OH and 3 ml of Benzene were added to the extract. Appearance of red colour indicates the presence of emodins (Rizk, 1982).

Alkaloids: Mayer's test: To the acidic solution, Mayer's regent (Potassium mercuric iodide solution) was added. Cream coloured precipitate indicates the presence of alkaloids (Gibbs, 1974).

Phenol: Half ml of FeCl3 solution was added into 2 ml of test solution, formation of an intense color indicates the presence of phenols (Gibbs, 1974).

Flavonoids: An aliquot of the seed extract (2-3ml) and few drops of sodium hydroxide solution were added into a test tube. Formation of intense yellow colour that became colourless on addition of few drops of dilute HCl indicates the presence of flavonoids (Khandewal, 2008). [26]

Qualitative Phytochemical Analysis of the Extracts of seeds and fruits of grape plants

Phytochemicaltes t	Grapeseed s	Grapefruit s
Saponin	+	-
Tannins	++	-
Coumarins	-	++
Alkaloids	+	-
Flavonoids	+	+
Terpenoids	+	-

MATERIALS AND METHODS

MATERIALS USED

1	Uv-Viscible spectrometer	JascoV-530.
2	Electronic balance	Ohous, Essae-Taraoka limited.
3	Friabilater	Campbell electronics, Mumbai.
4	Dissolution tester USP(XXIII)TDT-06T	Electrolab.
5	Monosanto tablet Hardness tester	Camphbell electronics, Mumbai.
6	Vernier calipers	Ultra-science Aids.
7	Tablet punching machine	Electro lab.
8	FT-IR	Scizhmadu
6	Vernier calipers	Ultra-science Aids.
7	Tablet punching machine	Electro lab.
8	FT-IR	Scizhmadu

INSTRUMENTS USED

	DRUG	**MANUFACTUREANDSUPPLIERS**
	Grape seed extract	Yarrow chem. products,Mumbai
	CHEMICALS	
1	D-Mannitol	Yarrow chem. products,Mumbai
2	Ethyl cellulose	Yarrow chem. products, Mumbai
3	Tragacanth	Global chemicals,Mumbai
4	Starch	Global chemicals,Mumbai
5	Magnesium stearate	Chemico glass scientific, Mumbai
6	Talc	Global scientific
7	Crosspovidone	Yarrow chem. products, Mumbai

Methodology

Preformulationstudies

Pre-formulation testing is an investigation of physical and chemical properties of drug substance alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form. To study the compatibility of various formulation excipients with Imatnib, sodium admixtures where prepared by mixing the drug. with each formulation excipients separately intheratioof1:1and stored in air tight containers at 30 ± 2˚C / 65 ± 5% RH. The solid air mixtures where characterized using Fourier transform infrared spectroscopy(FT-IR).[27]

Formulation of tablet

SNO	**INGREDIENTS**	**F1**	**F2**	**F3**	**F4**
1	Grape seed extract	225	225	225	225
2	Mannitol	75	75	75	75
3	Tragacanth	15	15	10	10
4	Ethyl cellulose	15	10	15	10
5	Starch	20	20	20	20
6	Talc	3	3	3	3
7	Magnesium stearate	2	2	2	2
8	Crosspovidone	-	12	12	-

Formulation and evaluation of tablet preparation of mixed blend of drug and excipient

All the ingredients were passed through mesh no.60 required quantity of ingredients was waited as given in table in co ground in mortar and pestle. The powder blend was evaluated for flow property and compressibility behavior.

Compression of tablets

Grape seed extract tablets were prepared by direct compression method using various formulation additives in varying concentrations and the detailed composition was showed in the table. All the ingredients were powdered separately in a clean and dry porcelain mortar and then they were passed through #60 mesh sieve the drug and the additives were mixed thoroughly in a inflated polyethylene pouch in a geometric ratio of their weight. Then the powder mixture was compressed into of 350 mg using 9 mm flat round punches. [34]

Fig 3: Grape Seed Extract Tablet

RESULT AND DISCUSSION

Appearance

TES T	OBSERVA	INFERENCE
Surfaceroughness	Smooth	Passes
Cracks	Absent	Passes
Depressions	Absent	Passes
Pinholes	Absent	Passes
Colour	Brown	Passes
Polish	Uniform	Passes
Odour	Present	Passes

Dimensions

TEST	F1	F2	F3	F4	AVERA GE
Thickn ess	3	3	3	3	3mm
	3	3	3	3	
	3	3	3	3	
	3	3	3	3	
	3	3	3	3	
Diame ter	9	9	9	9	9mm
	9	8	8	9	
	9	9	9	8	
	9	8	9	9	
	8	9	8	9	

Hardness

S.No	F1	F2	F3	F4
1	8.1	8.4	8.1	8.4
2	8.0	8.3	8	8.3
3	8.3	8.0	8.4	8.4
4	8.4	8.1	8.1	8.0
5	8.4	8.1	8.0	8.3

Friablity

S.No	F1	F2	F3	F4
1	0.12%	0.11%	0.12%	0.09%

Uniformityof weight

S. No	F1	F2	F3	F4
Minimum wt. of. tablets %	-1.16	-1.09	-0.9	-1.1
Maximum wt. of. tablets %	+1.21	+1.09	+0.81	+0.92

Disintegration

S.NO	F1	F2	F3	F4
TIME	20 Min	15Min	12M in	18Min

S.NO	PARAMETER	OBSERVATION
1	Bulk Density	0.59 gm/ml
2	Tapped Density	0.76 gm/ml
3	Angle of Repose	11.08^{O}
4	Compressiblity index	23.90
5	Hausner ratio	1.2
6	Hardness	9 mm
7	Thickness	0.3 mm
8	Friability	Minimum = -1.18
		Maximum = +1.21
9	Disintegration	12 mins
10	Dissolution (Spectrophotometric Analysis)	UV- visible at 420 nm

Qualitative Phytochemical Analysis of the Extracts of seeds and fruits of grape plants

The plants of grape seed extract VITIS VINIFERA is an ever green medicinal plant for the treatment of Anti-oxidant, Anti- inflammatory, Anti-cancer &Anti-ulcer activity. Now we scientifically proved the plant of fruits seeds much of therapeutic activity has been investigated in a systemic way covering preliminary phytochemical &pharmacological aspects in an attempt to be mode

Phytochemical inverstigation studies

The preliminary phytochemical inverstigation of different manufacturing products compare indicate the presents of steroids, terponoids, tannis, saponins, anthrocyaninds, glycosides, emodins, alkaloids, phenols &flavonoids. All the sample products shows good co-relation between them. Qualitative phytochemicals analysis of different extract of grape seed (vitis vinifera). [34]

PHYTOCHEMICAL TEST	GRAPE SEEDS	GRAPE FRUITS
Saponin	Present	Absent
Tannins	Present	Absent
Coumarins	Present	Absent
Alkaloids	Present	Absent
Flavonoids	Present	Absent
Terpenoids	Present	Absent

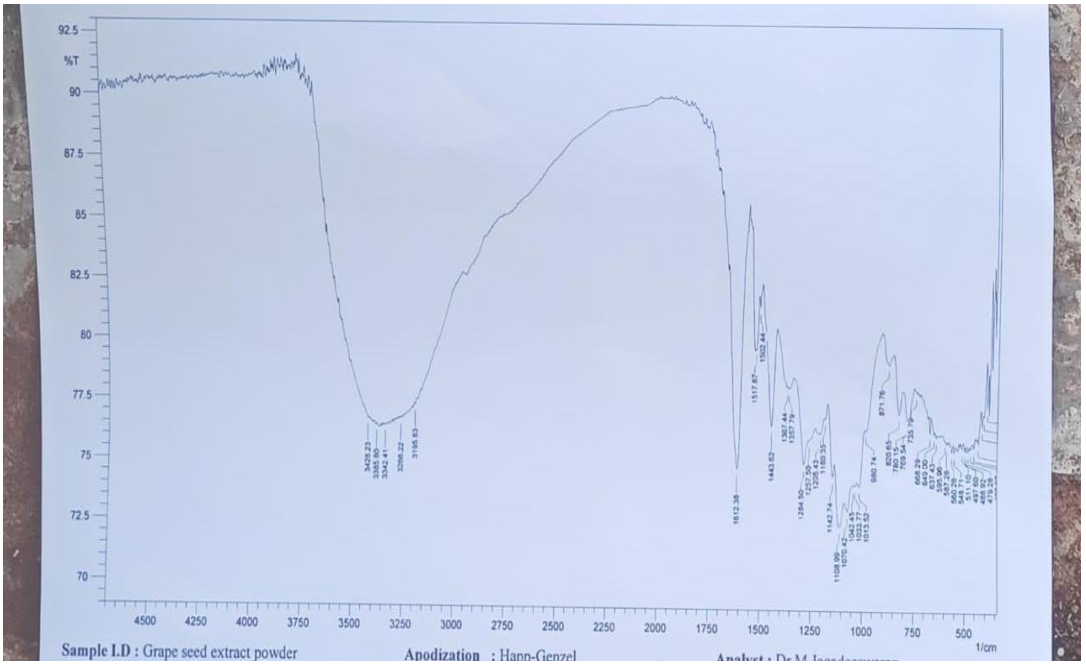


Fig 4: FT-IR Analysis of Grape Seed Extract Powder

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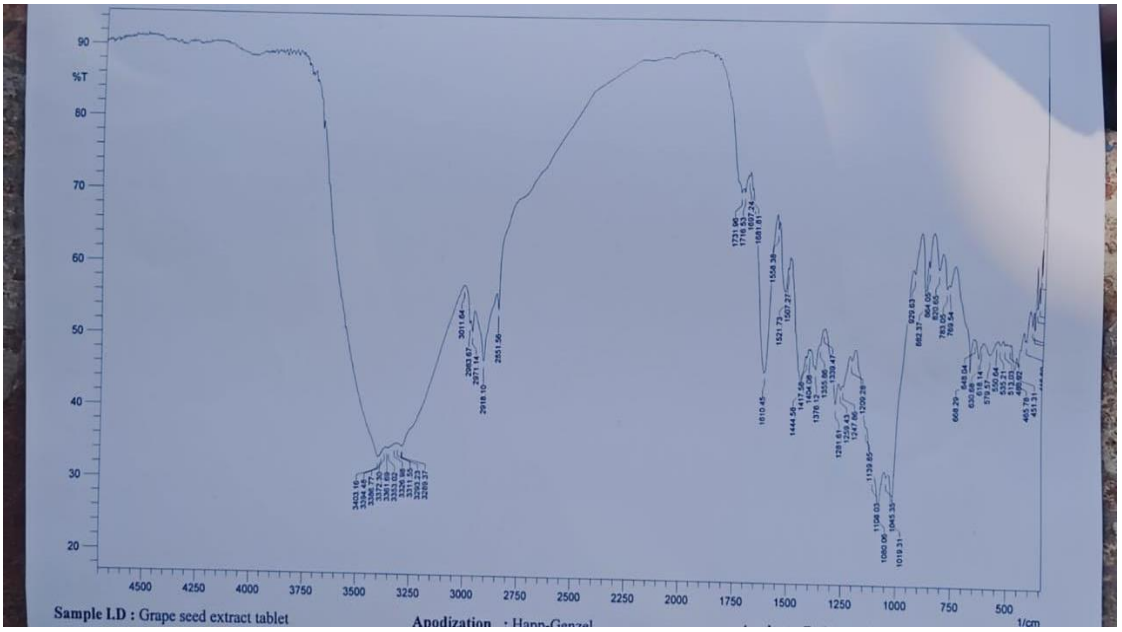

Fig 5: FT-IR Analysis of Grape Seed Extract Tablet

The FT-IR spectrum of pure grape seed extract was compared with FT-IR spectrum of physical mixture of mannitol, tragacanth, ethyl cellulose, starch, talc ,magnesium stearate , crosspovidone. There was no appearance or disappearance of any characteristics peaks. This shows that there is no chemical interaction between the drug and the polimers used in the tablet. The presents of peaks at the excepted range confirms that the materials taken for the study are genuine. [34]

Standard curve of ascorbic acid at 517 nm

S. NO	CONC (mcg/ml)	ABSORBANCE (nm)
1	0	0
2	20	0.063
3	40	0.124
4	60	0.196
5	80	0.364
6	100	0.425

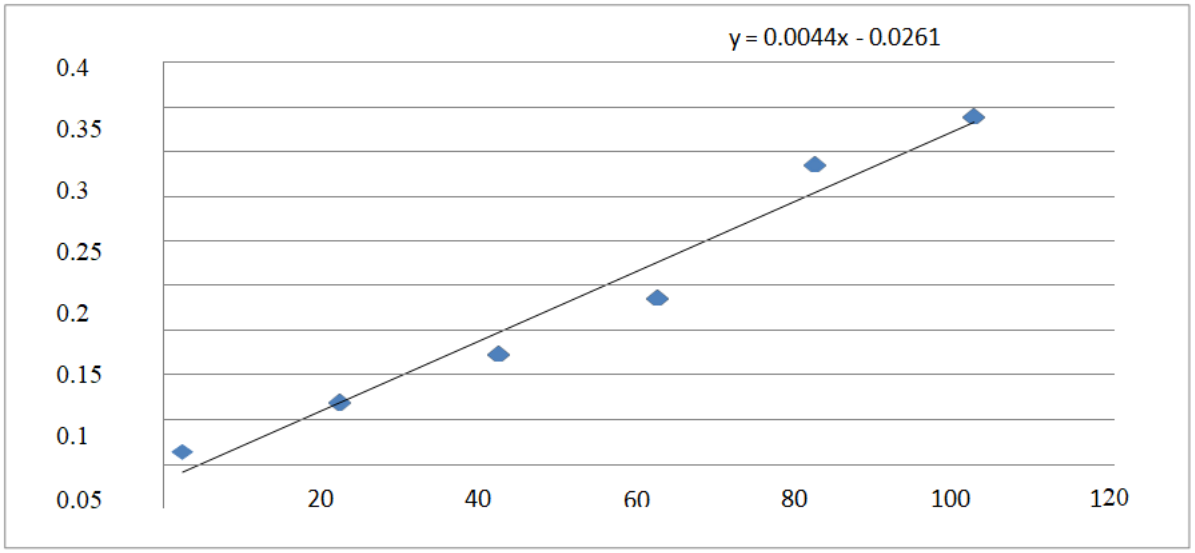

Fig 6: Calibration curve standard ascorbic acid

Precompression parameters

The mixture of all formulations was evaluated for precompression parameters before compression into tablets for angle of repose, bulk density, tapped density, hausner's ratio, compressibility index. The angle of repose value ranged from 25º 15" to 28º 75". The results were found to be below 30º and hence the blend was found to have good flow ability. Bulk and tapped densities are used for the measurement of carr's index. The bulk density and tapped density ranged from 0.235 to 0.298 and 0.275 to 0.356 respectively. The compressibility index (%)was then calculated from the bulk and tapped densities and it ranged from 14.91 to 18.47. The blend was found to have good free flowing property as the result were found to below 20%. The Hausner's ratio ranged from< 1.25 to >1.25. [35] The result indicates that the powder has cohesive properties.

F.Code	Angle of Repose (º)	Bulk density	Tapped density	Hausner's	Carr's
F1	28.81◦	0.237	0.279	1.20	16.47
F2	35.67◦	0.290	0.342	1.23	18.47
F3	32.05◦	0.258	0.317	1.21	17.13
F4	25.45◦	0.297	0.356	1.18	15.14

Post compression parameters

The thickness of the tablets was uniform in all formulations and ranged as 3mm in formulations F1to F4. The percentage friability of all batches was from 0.9 to 0.12 %.

F.CODE	AVERAGE WT	THICKNESS	DIAMETER	HARDNESS	FRIABILITY
F1	4.10	0.3	0.9	8.2	11.76%
F2	4.10	0.3	0.8	8.1	10.52%
F3	4.10	0.3	0.8	8.3	11.76%
F4	4.10	0.3	0.8	8.4	11.11%

Invitro drug release

All the formulations using 50% v/v of tragacanth binding agent showed extended time for drug release. The formulation using higher amount of polymer took extended time for complete drug release upto 12 hours. This is obviously because of increase in the tablets weight and lesser diffusivity of solvent into the formulation. Overall, the highest amount of drug release was found as 96.82% and 97.31% in 12 hours of the formulation F2 &F3. [36]

F. CODE	INVITRO DRUG RELEASE STUDY IN 12 HOURS
F1	96.34
F2	96.82
F3	97.31
F4	97.24

Dissolution value

Time (hr)	F1 (%)	F2 (%)	F3 (%)	F4 (%)
0	0	0	0	0
0.5	0.81	0.75	0.73	0.83
1	15.23	14.27	15.97	14.73
2	23.34	21.92	24.62	22.89
3	32.68	30.68	33.75	30.82
4	41.95	39.71	42.38	38.17
5	50.16	48.34	51.64	46.35

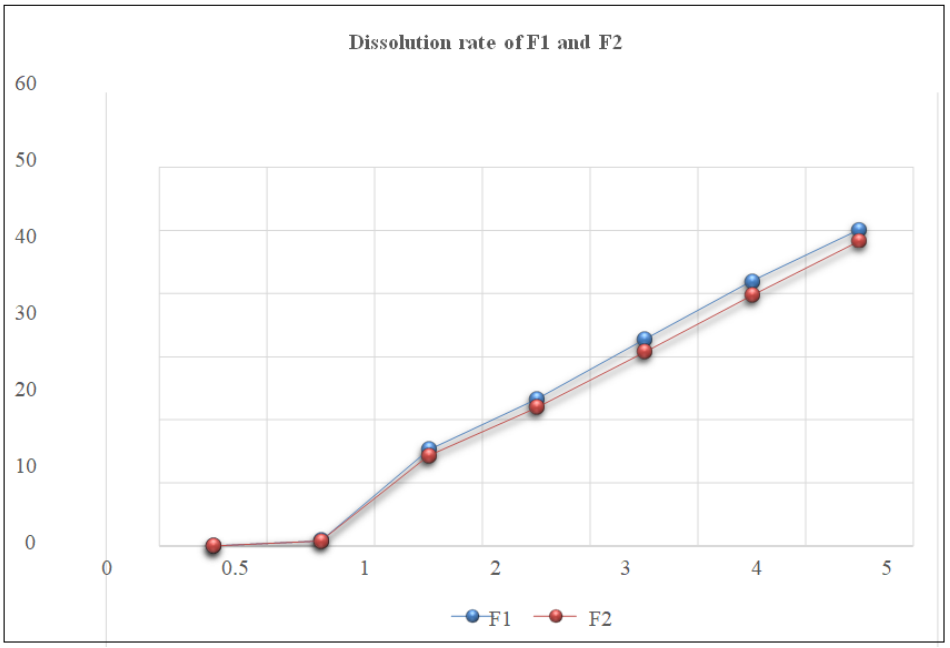

Fig 7: Dissolution Rate of F1 AND F2

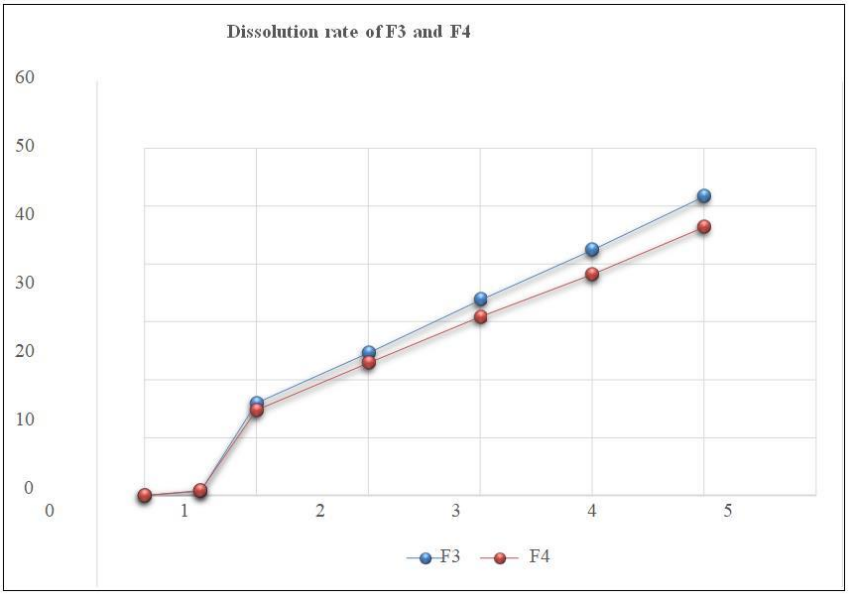

Fig 8: Dissolution Rate of F3 AND F4

SUMMARY AND CONCLUSION

The present study reports for the development of new formulation of grape seed extract tablets (vitis vinifera) following oral administration. The result demonstrate that the release of the drug is dependent on polymer of crosspovidone. It can be conclusively stated that the immediate release tablets (F3 & F4) appears to be promising system for the vitis vinifera for anti-oxidant, anti-inflammatory, anti-ulcer and anti-cancer therapy. The dependent variable hardness and invitro dissolution are influenced by concentration of polymer and slightly influenced by the binder. By observing the above results and discussion it can be concluded that the formulation with F3 gives better release profile compare with other formulation with F2 as well as combination of F2 andF3.Though the preliminary data based on in vitro dissolution profiles proved that the drug release from these tablets Ip limits. So, these systems seem to be site specific and shall be useful for the effective action of Anti- oxidant, Anti- cancer, Anti- inflammatory and Anti- ulcer. However in-vivo studies needed to carryout to establish its potential.

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