FORMULATION & EVALUATION OF MEDICATED NANO SOFT JELLY

(SUBLINGUAL ROUTE)

Submitted in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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CERTIFICATE

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This is to certify that the project entitled **Formulation & Evaluation of Medicated Nano Soft Jelly (Sublingual Route)** is a bonafied work of **Sayed Maqbool Ayesha Roll No.16PH04** submitted for the appreciation of the degree of Bachelor of Pharmacy in Department of Pharmaceutical Chemistry

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Approval for Bachelor of Pharmacy

This project entitled **Formulation & Evaluation of Medicated Nano Soft Jelly (Sublingual Route)** by **Sayed Maqbool Ayesha Roll No.16PH04** is approved for the degree of Bachelor of Pharmacy in Department of Pharmaceutical Chemistry

Examiners

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Declaration

I declare that this written submission represents my ideas in my own words and where others ideas or words have been included; I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that any violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

Student Name : **Ms. Sayed Maqbool Ayesha**

Roll Number : **16PH04**

ABSTRACT

FORMULATION & EVALUATION OF MEDICATED NANO SOFT JELLY (SUBLINGUAL ROUTE)

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Silymarin is the extract of Silybum marianum, or milk thistle, and it is a mixture of flavonolignans (of which silybin is the most prevalent substances) and one flavonoids. It is used in different liver disorders, particularly chronic liver diseases, cirrhosis, because of its antioxidant, anti-inflammatory and anti-fibrotic power. Silymarin also helps with the digestion of fats.

Silymarin is associated with poor aqueous solubility and poor bioavailability, which is due to extensive first pass metabolism. The purpose of this study is to develop and characterize medicated Nano jelly of Silymarin for increasing bioavailability and bypass extensive first pass metabolism.

The medicated Nano jellies were formulated by heating and congealing method. Batches were prepared using different concentration of gelling agents and almond gum. The prepared batches were evaluated for appearance, viscosity, size less than 240nm, pH (6.54±0.5), drug content (62% to 90%), stability, and syneresis. Analysis was done using UV-Vis Spectrophotometer, FTIR & Zeta sizer.

Keywords:- Silymarin, Nanojellies, Gelling Agents, congealing method

CONTENTS

Table of contents

List of Figures

List of Tables

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1 – INTRODUCTION

1.1 Oral medicated jellies in drug delivery:

"An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. Drugs are more frequently taken by oral administration. It is considered most natural, uncomplicated, convenient, safe means of administering drugs, greater flexibility in dosage form design, ease of production and low cost, convenience of self-administration, compactness and easy manufacturing. The most evident drawback of the commonly used oral dosage forms like tablets is difficulty in swallowing (Dysphasia), leading to patient's incompliance particularly in case of paediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water.

To fulfil these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as Oral medicated jellies (OMJs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need of water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms.

Oral medicated jellies with good taste and flavor increases the acceptability of bitter drugs by various groups of population.

Advantages of Oral medicated jellies

The performance of OMJs depends on the technology used during their manufacture. The necessary property of such tablets is the ability to disintegrate rapidly and disperse or dissolve in saliva, thereby obviating the need for water.

Various technologies have been developed that enable OMJ to perform this unique function.

- OMJ can be administer to the patients who have issues in swallowing tablets/cap., such as the geriatric patients, stroke victims, bedridden patients, patients with oesophageal problems & patients who refuse to swallow such as paediatric, elderly & psychiatric patients and thus improves patient compliance.

- "It contain the certain studies which concluded increased bioavailability and proved rapid absorption of drugs through pregastric absorption of drugs from mouth, pharynx & Oesophagus as saliva passes down.
- OMJ is most convenient for disabled, bedridden patients, travellers and busy people, who do not always have access to water.
- Good mouth feel property of OMJ helps to change the perception of medication.
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction are avoided, thus providing improved safety"[26]
- Suitable during traveling where water may not be available.
- Provides rapid drug delivery from dosage forms.
- Rapid onset of action.
- It is convenient to administer – anywhere, anytime, doesn't require water.
- The treatment can, if required, be terminated at any time.
- It may prove to be particularly suitable for the systemic delivery of drugs, which are susceptible to metabolism in the gut wall or liver.

Limitations of oral medicated jellies

- Insufficient physical resistance in standard blister packs;
- OMJ requires special packaging for properly stabilization &safety of stable product.
- It is also shows the fragile, effervescence granules property
- Incompetence to incorporate high concentrations of active drug.
- ODT is hygroscopic in nature so must be keep in dry place.

According to the Japanese Pharmacopeia 17th edition (JP XVII), jellies for oral administration are non-flowable gelatinous preparations having a certain shape and size, intended for oral administration. The United States Pharmacopoeia does not have jellies for oral administration. Instead, it prefers to use the term 'gel' which is not to be ingested. This is the definition in USP: 'Jelly (not preferred; see Gel): A semisolid dispersion of small particles or a solution of large organic molecules interpenetrated by a solution containing a gelling agent to promote stiffness.'

Jellies are usually prepared by mixing active substance(s) with suitable excipients and polymer gel base, gelatinizing and forming into a certain shape and size by a suitable method. The JP XVII states that jellies for oral administration meet the requirements of dissolution test or show an appropriate disintegration. In addition, jellies for oral administration meet the requirements of 'Uniformity of Dosage Units'.

This test is usually required for dosage forms that are packaged in single-dose container. For packaging, JP XVII states that tight containers are usually used for jellies for oral administration; for the preparations that are susceptible to degradation by evaporation of water, a low moisture-permeability container or packaging may be used."[1] [9]

1.2 Drug targeting:

Silymarin is obtained from Silybum marianum, silymarin is a polyphenolic flavonoid, extracted using 95% ethanol from the seeds of milk thistle the plant consist of approximately 70-80% of the silymarin flavonolignans and approximately 20-30% of chemically undefined fraction. The most prevalent component of the silymarin complex is silybin, which is the most active photochemical and is largely responsible for the claimed benefit of the silymarin.

It is used in different liver disorders, particularly chronic liver diseases, cirrhosis, because of its antioxidant, anti-inflammatory and anti-fibrotic power. Silymarin also helps with the digestion of fats.

Pharmacokinetics

Silymarin is not soluble in water. Silymarin is absorbed when given orally. Peak plasma concentration is achieved in 6-8 h. the oral absorption of silymarin is 23-47%. Leading to low bioavailability of the compound.

With respect to pharmacokinetics, silymarin is a low bioavailability compound if administered, with the lack of solubility in water; this is due to both its inefficient absorption in the intestine and an elevated metabolism of the first liver passage after its absorption: two mechanisms that decrease hematic concentration and consequently the arrival at the target organ.

However, this limitation can be efficaciously surpassed by using thin medicated jellies by sublingual/ buccal route. The elevated absorption of these compounds has led to assessing the safety of silymarin in its therapeutic use. The most common side effects are headache and itching which is mainly due to its prolonged and high dosage use, this can be avoided by using less dosage which is provided by sublingual route (no first pass metabolism).

The most common side effects are headache and itching which is mainly due to its prolonged and high dosage use, this can be avoided by using less dosage which is provided by sublingual route (no first pass metabolism).

Mechanism of action

Silymarin's hepatoprotective effects are purportedly accomplished via several mechanisms; these include:

- Antioxidation
- Inhibition of lipid peroxidation
- Stimulation of ribosomal RNA polymerase and subsequent protein synthesis, leading to enhanced hepatocyte regeneration.
- Enhanced liver detoxification via inhibition of phase 1 detoxification
- Enhanced glucuronidation and protection from depletion
- Anti-inflammatory effects, including inhibition of leukotriene and prostaglandin synthesis, Kupffer cell inhibition of neutrophil migration
- Slowing or even reversing of fibrosis by reduction of the conversion of hepatic stellate cells into myofibroblasts
- Anti-carcinogenesis by inhibition of cyclin-dependent kinases and arrest of cancer cell growth
- Silymarin is also found to have immunomodulatory effects on the diseased liver.

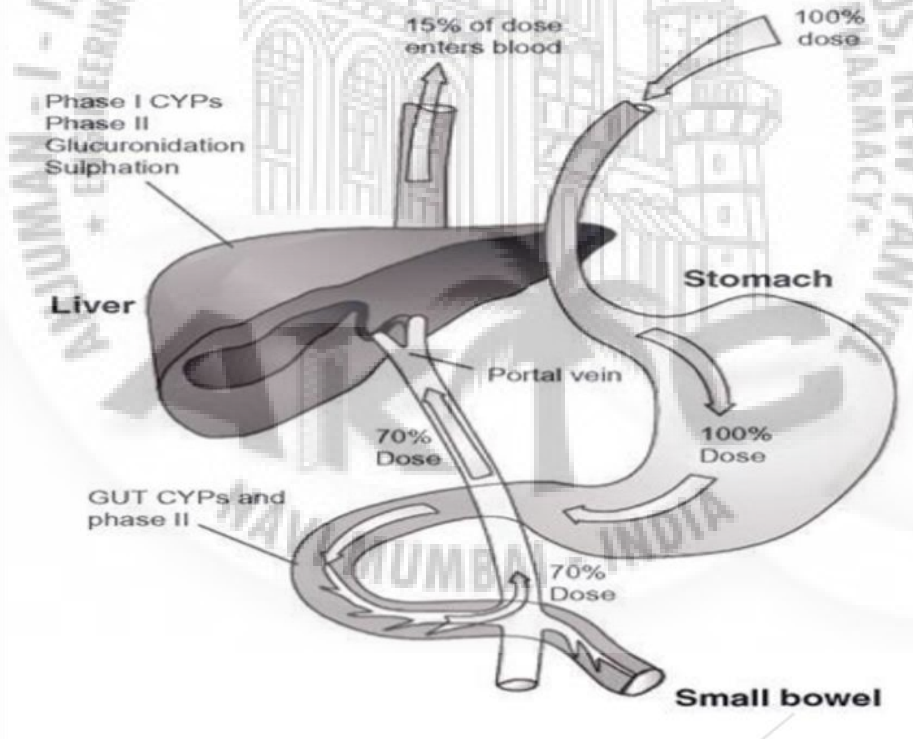


Fig no. 1 Pharmacokinetics

https://www.google.com/url?sa=i&url=https%3A%2F%2Fwhat-when-how.com%2Fhuman-drug-metabolism%2Ffirst-pass-and-plasma-drug-levels-introduction-human-drug-metabolism%2F&psig=AOvVaw1F_zKjY64UCMifAdvTdiDa&ust=1592982262761000&source=images&cd=vfe&ved=2ahUKEwje08HAr5fqAhWp_jgGHWAtDMcQjhx6BAgAEBI

Therapeutic indications

- Hepatitis
- Alcoholic liver disease
- Cirrhosis
- Hypercholesterolemia
- Amantia mushroom poisoning
- Psoriasis
- Neuroprotective and neurotropics

Silymarin is associated with poor aqueous solubility and poor bioavailability, which is due to extensive first pass metabolism. The purpose of this study is to develop and characterize medicated Nano jelly of Silymarin for increasing bioavailability and bypass extensive first pass metabolism. The medicated Nano jellies were formulated by heating and congealing method. Batches were prepared using different concentration of gelling agents and almond gum.

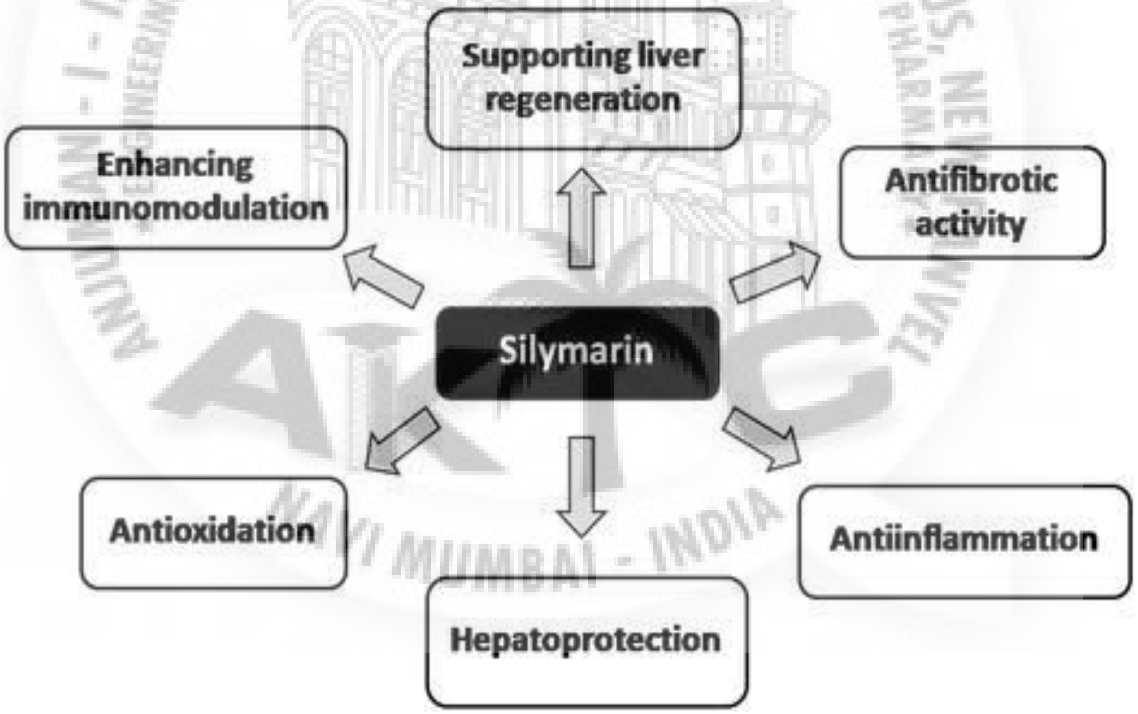


Fig no.2:- https://www.researchgate.net/figure/Mechanisms-of-action-of-silymarin-The-positive-effects-of-silymarin-on-the-liver-are_fig1_282152421

Chemistry of Silymarin

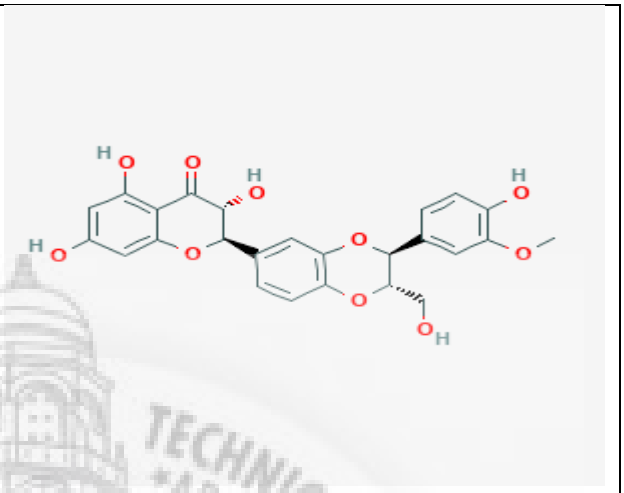
Structure	
Molecular formula	$C_{25}H_{22}O_{10}$
Molecular weight	482.4 g/mol
Iupac name	(2R,3R)-3,5,7-trihydroxy-2-[(2S,3S)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]-2,3-dihydrochromen-4-one
Synonyms	Silybin B Silibinin B SILYMARIN Milk thistle

Table no. 1 Chemistry of Silymarin [17] [18]

"The seeds of milk thistle contain approximately 70-80% silymarin flavonolignans and approximately 20-30% of chemically undefined fraction, composed of mostly polymeric and oxidized polyphenolic compounds.

Silymarin is a complex mixture of four flavonolignan isomers (silybin, isosilybin, silydianin and silychristin) with an empirical formula $C_{25}H_{22}O_{10}$.

Among the isomers silybin is the major and most active component and represents about 60-70 per cent, followed by silychristin (20%), silydianin (10%), and isosilybin (5%). The seeds also contain betaine, trimethylglycine and essential fatty acids that may contribute to silymarins hepatoprotective and anti-inflammatory activities."[25]

1.3 Nanoparticles jellies for Drug targeting:

Nano-formulations enhance the properties of conventional drugs and are specific to the targeted delivery site. Nanoparticles possess unique properties such as a large specific surface area and consequently greater reactivity than macro-sized particles.

"These nanoparticulate formulations have been shown to:

(i) improve drug permeability across the epithelium;

(ii) modify drug release kinetics (e.g., controlled release or sustained release);

(iii) provide solubilization (i.e., to deliver compounds which have physicochemical properties that strongly limit their aqueous solubility); and/or

(iv) protect compounds that are sensitive to degradation (e.g., peptides)"[12][8]

All these factors aim to promote higher sublingual or buccal bioavailability of drugs for subsequent systemic absorption. For nanoparticulate dosage forms to be effective for sublingual or buccal drug delivery, two main factors should be considered.

"Firstly, the physicochemical properties of the Nanoparticles themselves (e.g., size, charge, composition and surface properties) for optimal interaction with the sublingual or buccal mucosa. A number of different nanoparticulate systems have been evaluated for sublingual and buccal drug delivery, with polymer-based and lipid-based compositions being the most common.

The composition and structure of nanoparticles can be designed to confer a number of different properties, including mucoadhesion, bioadhesion, mucus-penetration, controlled release, and deformability (Hua et al., 2015). For example, inclusion of a hydrophilic polyethylene glycol (PEG) coating to the surface of nanoparticles has been shown to reduce its interaction with the mucus constituents, increase particle translocation through the mucus and mucosa, and enhance its delivery into lymph nodes.

In terms of optimal nanoparticle size for sublingual or buccal administration, most of the studies in this area have used nanoparticles between approximately 100 to 300 nm in size. Very few studies have comprehensively evaluated a range of particle sizes for optimal interaction with the buccal or sublingual mucosa. For example, Teubl et al. (2013) demonstrated in ex vivo studies using porcine buccal mucosa that neutral polystyrene nanoparticles (25, 50, and 200 nm) dispersed in an aqueous base were able to penetrate into the mucosal tissue intact, with the 200-nm sized nanoparticles penetrating more rapidly and into deeper regions of the mucosa.

It was suggested that the smaller nanoparticles were readily entrapped and immobilized in the mucus network. This is also supported by Holpuch et which showed that 200-nm nanoparticles were able to penetrate through the epithelium and basement membrane into the underlying connective tissue of intact normal human oral mucosal tissues that were obtained from patients undergoing surgical procedures.

It should be noted that both studies used polystyrene nanoparticles, which are unable to be metabolized and can interfere with cell metabolism.

Therefore, further studies would be useful to evaluate the effect of more clinically translatable nanoparticulate compositions over a range of particle sizes for mucosal permeability and drug absorption for sublingual and buccal drug delivery"[6].

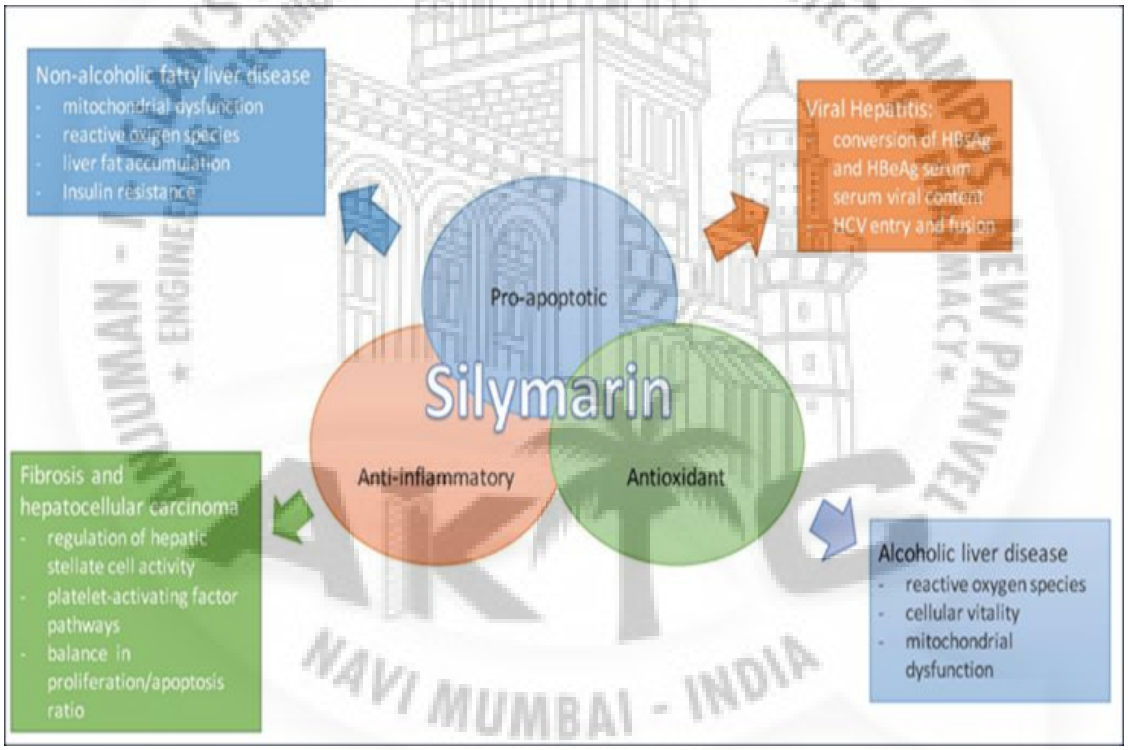


Fig no. 3 https://www.mdpi.com/1420-3049/22/2/191/html

2- REVIEW OF LITERATURE

2.1 HEPATOPROTECTIVE ACTION

A. Silymarin-loaded solid nanoparticles provide excellent hepatic protection: physicochemical characterization and in vivo evaluation

"A silymarin-loaded liquid nanoemulsion was formulated by applying the SPG membrane emulsification technique. This was further converted into solid state nanosized particles by the spray-drying technique. The physicochemical characteristics of these nanoparticles were determined by scanning electron microscopy, differential scanning calorimetry, and powder X-ray diffraction.

Their dissolution, bioavailability, and hepatoprotective activity in rats were assessed by comparison with a commercially available silymarin-loaded product. Formulation of a silymarin-loaded nanoemulsion, comprising silymarin, castor oil, polyvinylpyrrolidone, Transcutol HP, Tween 80, and water at a weight ratio of 5/3/3/1.25/1.25/100 was accomplished using an SPG membrane emulsification technique at an agitator speed of 700 rpm, a feed pressure of 15 kPa, and a continuous phase temperature of 25°C. This resulted in generation of comparatively uniform emulsion globules with a narrow size distribution.

Moreover, the silymarin-loaded solid nanoparticles, containing silymarin/castor oil/polyvinylpyrrolidone/Transcutol HP/Tween 80 at a weight ratio of 5/3/3/1.25/1.25, improved about 1,300-fold drug solubility and retained a mean size of about 210 nm. Silymarin was located in unaltered crystalline form in the nanoparticles. The drug dissolved rapidly from the nanoparticles, reaching nearly 80% within 15 minutes, indicating three-fold better dissolution than that of the commercial product. Further, the nanoparticles showed a considerably shorter time to peak concentration, a greater area under the concentration-time curve, and a higher maximum concentration of silymarin compared with the commercial product ($P<0.05$).

In particular, the area under the concentration-time curve of the drug provided by the nanoparticles was approximately 1.3-fold greater than that of the commercial product. In addition, the silymarin-loaded nanoparticles significantly reduced carbon tetrachloride-induced hepatotoxicity, indicating improved bioactivity compared with silymarin powder and the commercial product. Silymarin-loaded nanoparticles developed using SPG membrane emulsification and spray-drying techniques could be a useful system for delivery of poorly water-soluble silymarin while affording excellent hepatic protection"[5]. (**Kwan Yeol Yang et al.)**

Silymarin loaded liquid Nano emulsion was formulated with the help of SPG membrane emulsification technique. Then they were converted into solid state nano sized particle by a technique known as spray drying. These nanoparticles were evaluated by scanning electron microscope differential scanning colorimetry and powder X ray diffraction. Their dissolution,

bioavailability, and hepatoprotective is studied in rats. And is compared with silymarin-loaded product. The nano emulsion were formed with help of SPG membrane emulsification technique Formulation of a silymarin-loaded nano emulsion, at 700 rpm, a feed pressure of 15 kPa, and a continuous phase temperature of 25°C, size of 210 nm. The drug dissolved rapidly from nano particle, Almost 80% of the drug was dissolved, within 15 mins indicating 3 fold better dissolution than that of the commercial product. The silymarin loaded nano particle significantly reduced hepatotoxicity induced by carbon tetrachloride induced indicating better bioactivity in contrast to silymarin powder.

B. Silymarin/Silybin and Chronic Liver Disease: A Marriage of Many Years

"Silymarin is the extract of Silybum marianum, or milk thistle, and its major active compound is silybin, which has a remarkable biological effect. It is used in different liver disorders, particularly chronic liver diseases, cirrhosis and hepatocellular carcinoma, because of its antioxidant, anti-inflammatory and antifibrotic power. Indeed, the anti-oxidant and anti-inflammatory effect of silymarin is oriented towards the reduction of virus-related liver damages through inflammatory cascade softening and immune system modulation.

It also has a direct antiviral effect associated with its intravenous administration in hepatitis C virus infection. With respect to alcohol abuse, silymarin is able to increase cellular vitality and to reduce both lipid peroxidation and cellular necrosis. Furthermore, silymarin/silybin use has important biological effects in non-alcoholic fatty liver disease. These substances antagonize the progression of non-alcoholic fatty liver disease, by intervening in various therapeutic targets: oxidative stress, insulin resistance, liver fat accumulation and mitochondrial dysfunction.

Silymarin is also used in liver cirrhosis and hepatocellular carcinoma that represent common end stages of different hepatopathies by modulating different molecular patterns. Therefore, the aim of this review is to examine scientific studies concerning the effects derived from silymarin/silybin use in chronic liver diseases, cirrhosis and hepatocellular carcinoma.

The "marriage of many years" that links silymarin/silybin to liver diseases, derives from the progressive evidence that, with the passing of time, has led to investigation of, firstly empirically and then scientifically, the mechanisms through which they act in carrying out the therapeutic effect. The studies of pharmacokinetics and pharmacodynamics on silymarin have improved, in the last few years, its applicability in different pathologies, especially liver diseases, allowing, through the use of conjugates compounds, a more efficient application.

Through the analysis of literature, it has been demonstrated that silymarin has an effect that allows its use in all of the most frequent causes of liver damage. Indeed, silymarin has three important activities: anti-inflammatory, antioxidant and pro- apoptotic, which represent the "functional triad" that allows for antagonizing the onset and the progression of mechanisms of damage that are responsible for the progression of hepatitis to cirrhosis and HCC.

However, it is clear that, also in the end stages of liver pathologies, silymarin can act by limiting de-novo fibrogenesis and antagonizing pro-carcinogenic mechanisms that cause HCC. Nevertheless, the treatment with silymarin/silybin in routine clinical practice is strongly limited, since it is necessary to obtain scientific data deriving from well-structured trials based on large populations of patients, and to achieve a standardization of methods used for evaluating the therapeutic efficacy, especially in an NAFLD context, that is particularly promising"[12]. (**Alessandro Federico et al.,)**

Silymarin is the extract of Silybum marianum, or milk thistle, and its major active compound is silybin, which has a remarkable biological effect. It is used in different liver disorders, particularly chronic liver diseases, cirrhosis and hepatocellular carcinoma, because of its antioxidant, anti-inflammatory and antifibrotic activity. Furthermore, silymarin use has important biological effects in non-alcoholic fatty liver disease. These substances antagonize the progression of non-alcoholic fatty liver disease, by intervening in various therapeutic targets: oxidative stress, insulin resistance, liver fat accumulation and mitochondrial dysfunction. The aim of this review is to examine scientific studies concerning the effects derived from silymarin/silybin is used in chronic liver diseases, cirrhosis and hepatocellular carcinoma. The analysis of literature it is demonstrated that silymarin has few effects that allows its use in all of the most frequent causes of liver damage. Silymarin has 3 important activities anti-inflammatory, antioxidant and pro apoptotic.

2.2 Anti-Parkinson action

Anti-Parkinson Potential of Silymarin: Mechanistic Insight and Therapeutic Standing.

"Parkinson's disease (PD) involves aggregation of α-synuclein and progressive loss of dopaminergic neurons. Pathogenesis of PD may also be related to one's genetic background. PD is most common among geriatric population and approximately 12% of population suffers over age 65 years.

Currently no successful therapies are in practice for the management of PD and available therapies tend to decrease the symptoms of PD only. Furthermore, these are associated with diverse range of adverse effects profile. The neuroprotective effects of polyphenols are widely studied and documented. Among phytochemicals, silymarin is one of the most widely used flavonoids because of its extensive therapeutic properties and has been indicated in pathological conditions of prostate, CNS, lungs, skin, liver, and pancreas. Silymarin is a mixture of flavonolignans (silybin, isosilybin, and silychristin), small amount of flavonoids (taxifolin), fatty acids,and other polyphenolic compounds extracted from the dried fruit of Silybum marianum and is clinically used for hepatoprotective effects since ancient times.

Neuroprotective effects of silymarin have been studied in various models of neurological disorders such as Alzheimer's disease, PD, and cerebral ischemia. Reducing oxidative stress,

inflammatory cytokines, altering cellular apoptosis machinery and estrogen receptor machinery are mechanisms that are responsible for neuroprotection by silymarin, as discussed in this review.

Additionally, because of poor aqueous solubility, the bioavailability of Silymarin is low and only 23–47% of silymarin reaches systemic circulation after oral administration. The beneficial role of silymarin in the treatment of pathological conditions of various origins including cancer has been studied and documented. It is a mixture of flavonolignans with strong antioxidant and anti-inflammatory activities. It also has binding affinity with estrogen receptor β in CNS regions which attenuates neurotoxicity and prevents lipid peroxidation.

These effects make silymarin a valuable choice in therapeutics of neurodegenerative disorders such as PD. Additionally; it has shown significant neuroprotective effects in various in vitro and in vivo models. However, because of low aqueous solubility the bioavailability of silymarin is quite low i.e., 23–47%. Several techniques are available to improve the bioavailability of silymarin such as SMEDDS, solid dispersions, PSNs, and liposomes. Moreover, the bioavailability issue can be resolved via chemical derivatization. Thus, further research is required on these grounds in order to get molecule of clinical utility for the treatment of PD"[24]. (**Hammad Ullah et al.)**

Parkinson's disease involves aggregation of α-synuclein and progressive loss of dopaminergic neurons. PD is most common among geriatric population and approximately 1 2% of population suffers over age 65 years. No successful therapies are available and available therapies only decrease the symptoms of PD. The neuroprotective effects of polyphenols are widely studied and documented. Among phytochemicals, silymarin is one of the most widely used flavonoids because of its extensive therapeutic properties and has been indicated in pathological conditions of prostate, CNS, lungs, skin, liver, and pancreas. Reducing oxidative stress, inflammatory cytokines, altering cellular apoptosis machinery, and estrogen receptor machinery are because of poor aqueous solubility, the bioavailability of silymarin is low and only 23–47% of the drug (silymarin) reaches systemic circulation following oral administration to overcome that several techniques such as SHEDDS , Solid dispersion .

2.3 PHARMACODYNAMICS

Silymarin-A review on the pharmacodynamics and bioavailability enhancement approaches

"The main drawback of silymarin is its poor solubility therefore different approaches are been taken to enhance the solubility in turn the bioavailability of the drug. In this review we will discuss about the enhancement approaches used so far. As it is having a good safety profile, better patient tolerability and an effective drug at an affordable price, in near future new derivatives or new combinations of this drug may prove to be useful.

Oral absorption of silymarin is of about 23- 47%, leading to low bioavailability of the drug. This is due to the poor water solubility and hence different approaches by the researchers are been used to improve the solubility in turn improving the bioavailability of the drug. In order to improve the solubility and dissolution of silymarin Soo Woo j. et al. formulated silymarin in the form of self-micro emulsifying drug delivery system (SMEDDS). The optimum formulation of SMEDDS containing silymarin was obtained based on the study of pseudo-ternary phase diagram. The SMEDDS consisted of 15% silymarin, 10% glyceryl monooleate as the oil phase, a mixture of polysorbate 20 and HCO-50 (1:1) as the surfactant, Transcutol as the co-surfactant. The mean droplet size of the oil phase in the microemulsion formed from the SMEDDS was 67 nm.

The percentage release of silybin from the SMEDDS after 6 hours was 2.5 times higher than that from the reference capsule (LegalonR). After its oral administration to rats, the bioavailability of the drug from the SMEDDS was 3.6 times higher than the reference capsule. Garg R. et al. formulated floating effervescent tablets of silymarin using various materials like hydroxypropyl methylcellulose (HPMC) K 4M, K 15M, psyllium husk, swelling agent such as crospovidone, microcrystalline cellulose gas generating agent like sodium bicarbonate, citric acid.

Floating non effervescent tablets were prepared by polypropylene foam powder and different matrix forming polymers like HPMC K 4M, Carbopol 934P, xanthan gum and sodium alginate. In vitro drug release studies were performed and drug release kinetics evaluated using the linear regression method was found to follow both the Higuchi and the Korsemeyer and Peppas equation. The developed floating tablets of Silymarin may be used in clinic for prolonged drug release for at least 24 h, thereby improving the bioavailability and patient compliance"[24]. (**Ghosh A et al.,)**

The main drawback of silymarin is its poor solubility therefore different approaches are been taken to enhance the solubility in turn the bioavailability of the drug. In this review we will discuss about the enhancement approaches used so far. As it is having great safety profile, good patient tolerability and an effective drug at descent price, in future new derivatives of this drug or new combinations of this drug may prove to be useful in treating various disorders. First approaches to enhance the solubility in turn the bioavailability of the drug. Given by WOOJ et

at formulation of silymarin self-micro emulsifying drug delivery system [SMEDDS] the optimum formulation of SMEDDS containing silymarin was obtained based on study of pseudo ternary phase diagram. The percentage release of silymarin from the SHEDDS after 6 hr was 2 to 5 times higher than from reference capsule .after oral administration into rats the bioavailability of drug from SHEDDS was 3 to 6 times higher than reference capsule . in vitro drug release studies were performed and drug release studies were performed and drug release kinetics were evaluated using the linear regression method and it was found to follow both Higuchi and Korsemeyer and Peppas equation .

3- AIM & OBJECTIVE

- The major reasons for poor silymarin bioavailability are extensive metabolism, inefficient absorption, poor aqueous solubility, and fast excretion in bile and urine. All these factors demand the incorporation of silymarin into a form that can increase its bioavailability. To overcome these limitations we chose to design medicated Nano jelly of Silymarin for increasing bioavailability.
- Silymarin/silybin is used in chronic liver diseases, cirrhosis and hepatocellular carcinoma, which are more common in elderly patients as frequent administration of multiple medicines and age alter the organ functions. Geriatric patients may have difficulty in swallowing tablets or capsules, so the main purpose was to design a formulation which can eliminate this problem.
- Other group of patients suffering from such diseases is patients with history of chronic alcoholism who have issues in acceptance of medications, formulation such as jellies increase the acceptance level as they are more appealing and preferred over other dosage forms.
- The major drawback of silymarin is its poor solubility therefore different approaches are been taken to enhance the solubility in turn the bioavailability of the drug. As it is having a great safety, better patient tolerability and an efficient drug at a reasonable cost, in near future new derivatives of silymarin or new combinations of silymarin may prove to be useful.
- The main objective of this study is to develop Silymarin nano jellies for increasing bioavailability and bypassing extensive first pass metabolism, and to study the Drug release, Drug content, Spectral characteristics, pH, Viscosity and other parameters.

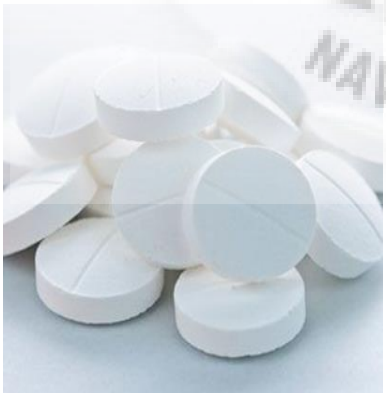


Fig no. 4 Conventional dosage form

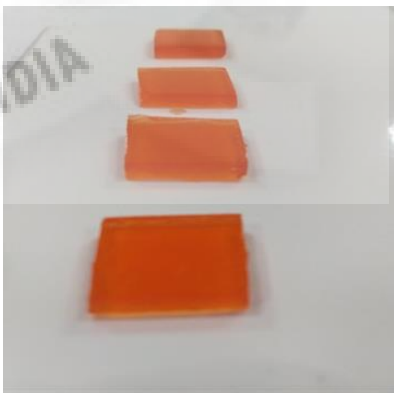


Fig no. 5 Silymarin nano jellies

4 – PLAN OF WORK

Month	Work
July – August	Selection of • Domain • Drug • Project topic
September – October	Literature review
November	Experimental work • Selection of suitable procedure (Trial and error method) • Formulating blank jellies
December	Experimental work • Selection of suitable carrier for drug • Formulating jellies containing silymarin • Physical evaluation Poster presentation(71st Indian Pharmaceutical congress, Chennai-2019)
January	Presentation • (Paper presentation – intercollege annual fest) Experimental work
February	• Evaluation and analysis of final formulation using Particle size analysis, UV/Vis spectroscopy and FTIR
March	Evaluation and analysis Poster presentation(International Conference on drug delivery, Hyderabad 2020)
April	Thesis Submission

Table no. 2 Plan of work

Fig no. 6 Temperature monitoring

Fig no. 7 Monitoring Experimental conditions

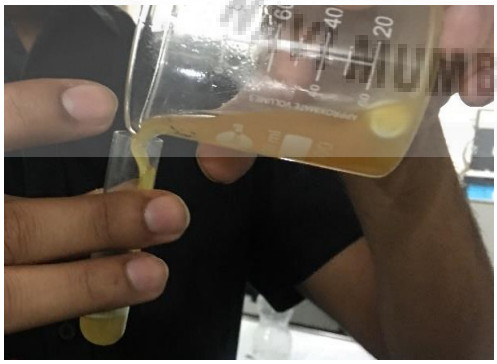


Fig no. 8 Centrifugation

5– EXPERIMENTAL WORK

5.1 MATERIALS AND METHOD

A. Method A

- Jellies were prepared by heating and congealing method. Prepared using freshly boiled and cooled distilled water used. Sucrose syrup prepared in water on heating and stirring at 80°C for about 90 minutes.

- Weighed polymer powder of almond gum and gelatin was disseminated in 10 ml of water maintained at 90°C throughout the preparation. The dissemination was stirred using a magnetic stirrer for 20 mins to facilitate hydration of gelling agent. Drug taken in to another beaker and solubilized using alcohol.

- Sucrose syrup was added to it under continuous stirring. The citric acid and preservatives were added under continuous stirring at 60°C.

- The final weight was adjusted with purified water, mixed, transfer to suitable molds, sealed and allowed to cool that room temperature (25±5°C) to form a jelly like texture. Finally, when jelly set it is wrapped in gelatin paper and stored in dry place.

- Different batches were prepared using different concentration of gelatin and almond gum.

INGREDIENTS%	A1	A2	A3
Silymarin	31.7	31.6	31.5
Almond gum	0.5	0.5	0.5
Gelatin	0.3	0.4	0.5
Citric acid	0.5	0.5	0.5
Sucrose syrup	66.7	66.7	66.7
Propylene glycol	0.002	0.002	0.002
Methyl paraben	0.1	0.1	0.1
Propyl paraben	0.1	0.1	0.1
Raspberry flavor	0.005	0.005	0.005
Amaranth color	Qs	Qs	Qs
Distilled water	Qs	Qs	Qs

Table no. 3 List of Ingredients (Method A)

B. Method B

Silymarin purchased from chemical dealer Science House. Gelling agents like gelatin and almond gum were brought from M/s. Modern Science, Nashik. All other chemicals and solvents used were of analytical grade.

- **Preparation of silymarin slurry**

  Weigh accurately glycerin, sorbitol 70% & PEG 400 & stir to get a uniform mixture. To this add silymarin and stir for 24 hours at 1000 rpm to get uniform slurry containing silymarin nanoparticles.

- **Preparation of Jelly Base**

  Jellies were prepared by heating and congealing method using different concentration of gelling agents. Weighed quantity (1.5g) of gelling agent (Agar/ gelatin) was dispersed in 50 ml of purified water maintained at 80°C throughout the preparation. The dispersion was stirred using a magnetic stirrer for 30 mins. After this add sucrose (12.5g) into this with stirring, maintaining temperature at 80°C, followed by this cool the dispersion to 50-60°C.

- **Preparation of Silymarin Jelly**

  Silymarin slurry is slowly added to jelly base with continuous stirring and maintain the stirring for 30min. Then add citric acid (0.5%), methyl paraben (0.1%), flavor, FD and C color under stirring one by one. Then dissolve sodium benzoate in purified water and add to the above solution. Adjust the weight of the jelly to 100 gm with distilled water, mixed, transfer to suitable molds, sealed and allowed to cool that room temperature (25±5°C) to form a jelly. Finally, when jelly set it is wrapped in gelatin paper and stored in dry place.

INGREDIENTS	**B1**	**B2**	**B3**
Silymarin	100mg	100mg	100mg
Almond gum	0.5	-	-
Gelatin	0.5	-	-
Agar	-	1.5	2.5
Sucrose	12.5 g	12.5 g	12.5 g
Methyl paraben	0.1	0.1	0.1
Citric acid	0.5	0.5	0.5
Raspberry flavour	0.005	0.005	0.005
Amaranth colour	Qs	Qs	Qs
Distilled water	Qs	Qs	Qs

Table no. 4 List of Ingredients (Method B)

C. Method C

- Prepare sugar syrup, to this add gelling agent with continuous stirring and is heated until completely dissolved. After that citric acid and stabilizer will be added with stirring to maintain the pH and improve the smoothness of jelly.
- Drug is dissolved in appropriate vehicle and added to this mixture with continuous stirring. Then preservative, color, flavor will be added and mixed thoroughly.
- Transfer in moulds and allow it to cool at room temperature.

INGREDIENTS	**C1**	**C2**
Silymarin	100 mg	100 mg
Gelatin	2.5 g	6 g
Citric acid	0.5 mg	0.5 mg
Sucrose	12 g	12 g
Propylene glycol	0.002 mg	0.002 mg
Methyl paraben	0.1 mg	0.1 mg
Propyl paraben	0.1 mg	0.1 mg
Raspberry flavour	0.005 mg	0.005 mg
Amaranth colour	Qs	Qs
Distilled water	Qs	Qs

Table no. 5 List of Ingredients (Method C)

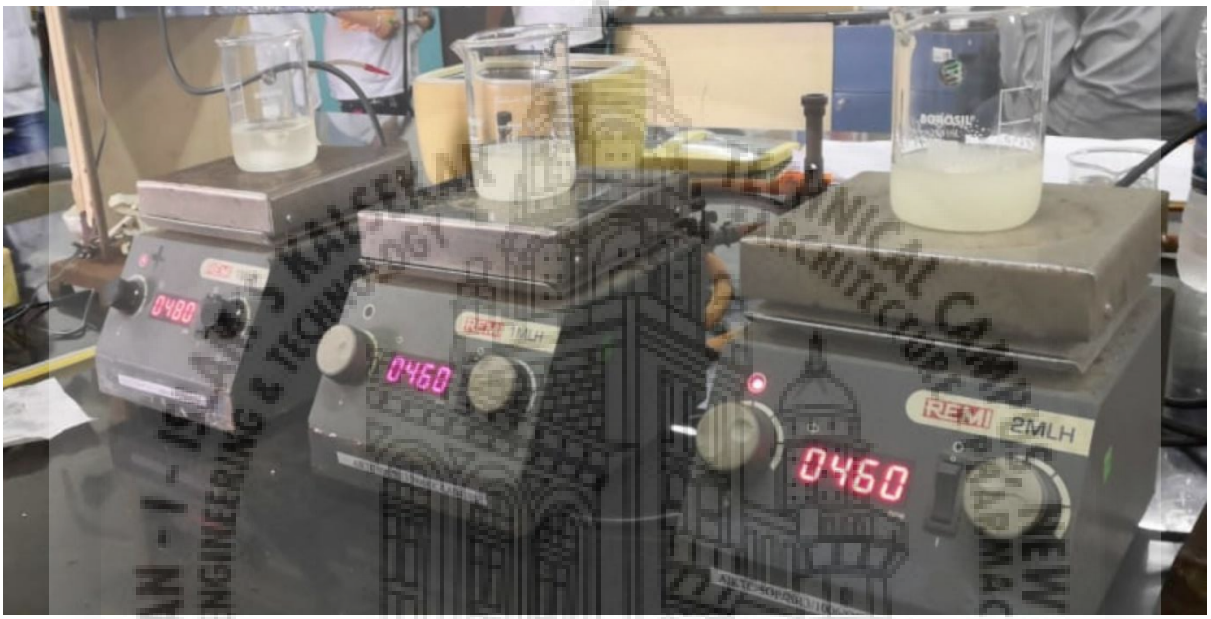


Fig No. 09 Preparation of jellies

5.2 PREFORMULATION STUDIES

Pre-formulation studies were performed for sample of drug identification and compatibility studies.

A. Organoleptic properties

The Organoleptic character of drug like odor, color, taste and appearance play an important role in the identification of the sample and hence they should be recorded in a descriptive terminology.

B. Solubility studies:

Solubility studies are an important consideration in formulation. The solubility of drug and polymer was tested with water and buffer solution.

C. Compatibility study of drug and polymer using FTIR

FT-IR Spectra were recorded with Shimadzu spectroscopic analysis FT-IR spectrophotometer with scanning range of 500-4000cm^{-1}. It was triturated in mortar and pestle and compressed under 5 ton pressures in a hydraulic pressure to form a transparent pellet. IR spectra for the pellet were determined to evaluate surface property of drug, polymer and their interaction hygroscopic in nature so it must be replaced in desiccators after using it.

D. Determination of λ max for Silymarin

λ Max of Silymarin was done by UV spectroscopy dissolving in organic solvents and diluted to 10ppm then measured at 400nm to 200nm.

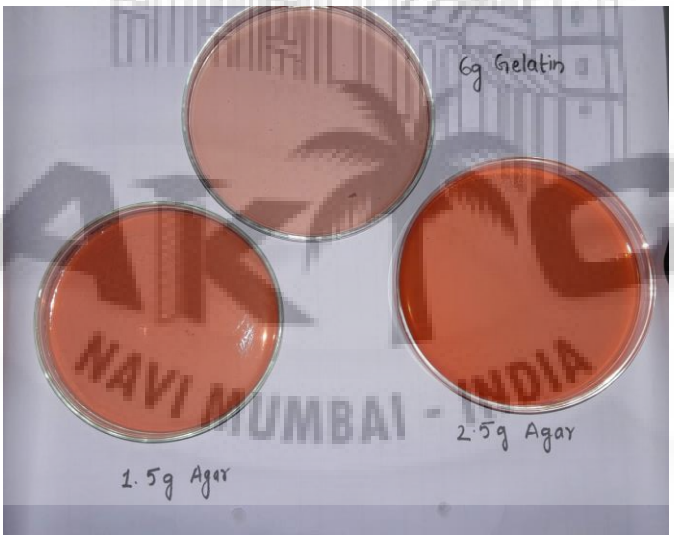


Fig no. 10 B2, B3 & C2

6 - RESULTS

6.1 EXPERIMENTAL:

The above batches were subjected to the following parameters: General Appearance, Rheological Measurement, pH, Stability, Syneresis, Drug Content, In-Vitro Drug Release

A. General appearance

Texture and clarity of the soft gel was evaluated in terms of stickiness and grittiness by mildly rubbing the jelly between two fingers. Consistency and odor were also evaluated by physical observation.

B. Rheological measurement

Viscosity of the all the batches of soft gels were measured using Fungilab viscolab. The Silymarin containing soft jelly was squeezed out from the polyethylene bag by making a cut of uniform size on the bag and viscosity was measured using spindle number L4 at fifty rpm at room temperature.

C. pH of the soft jelly

The pH of the final gel has a great influence not only on stability, but also on the taste. The pH of Silymarin containing soft jelly was measured using Electronic Digital pH meter Hanna at room temperature.

D. Syneresis

Syneresis is one of the major problems associated with almond gum gels. Syneresis means contraction of gel upon standing and separation of water from the gel. Syneresis is more pronounced in the gels where lower concentration of gelling agent is used. Gels were kept under scrutiny for signs of syneresis. The gels showing signs of syneresis were rejected and not considered for further studies.

E. Centrifugation

The slurry was centrifuged for 24 hours to check sedimentation of drug particles, no sedimentation of drug particles was observed.

Parameters	A1	A2	A3	B1	B2	B3	C1	C2
Clarity	T	T	T	T	T	T	T	T
Consistency	NG	NG	NG	NG	G	G	NG	G
Texture	SG	SG	SG	SG	NS&NG	NS&NG	SG	NS&NG
Odor	P&F	P&F	P&F	P&F	P&F	P&F	P&F	P&F
pH	6.53± 0.5	6.78± 0.54	6.63± 0.058	6.68± 0.57	6.8± 0.67	6.84± 0.24	6.64± 0.46	6.91± 0.05
Viscosity	SV	V	V	MV	HV	HV	MV	HV
Syneresis	++	+	-	-	-	-	-	-
Sedimentation	S	S	S	NS	NS	NS	S	S
Drug content	62.5	65.3	64.6	86.1	89.2	88.6	84.7	87.6

Table no. 6 Evaluation Parameters

*** T-Transparency, NG-Not Good, G-Good, SG-Sticky & Gritty, NS&NG-Non sticky & Non gritty P&F-Pleasant & Fruity, SV-Slightly Viscous, MV- Moderate Viscous, HV- Highly Viscous, S-sedimentation, NS- no sedimentation.**

Fig no. 11 Silymarin nano jelly

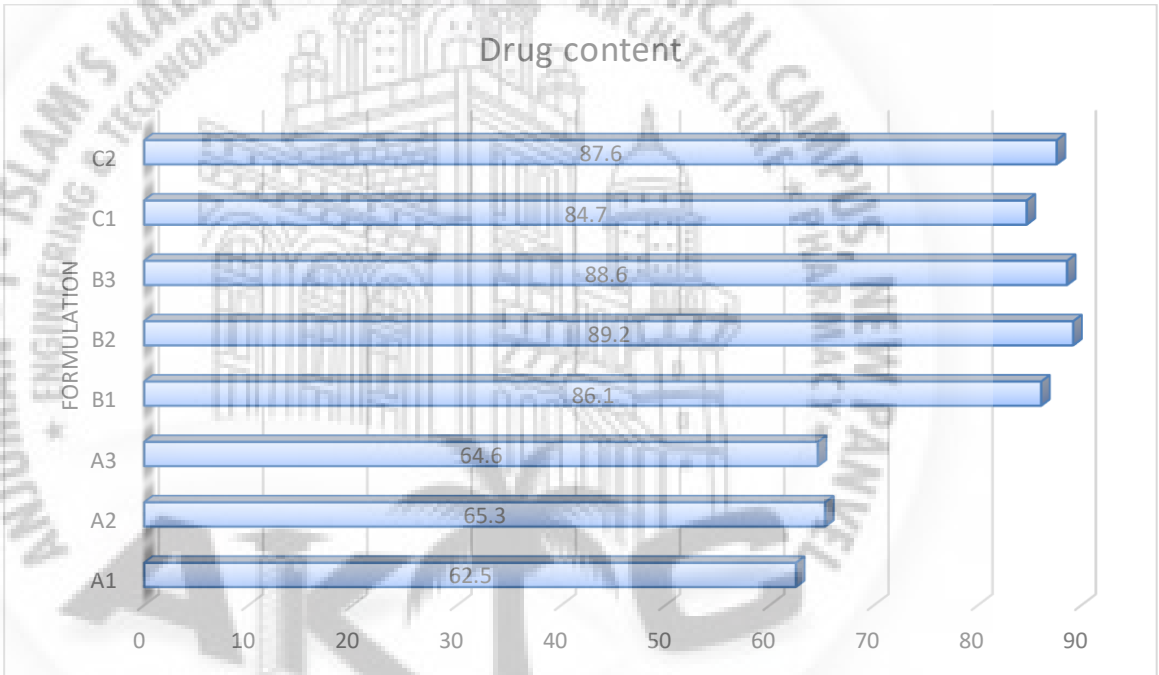
6.2. ANALYTICAL-

A. UV-VISIBLE SPECTROSCOPY

Drug content was determined by using shimadzu UV- Spectroscopy with scanning range of 200-800nm

To determine the drug content Jellies were prepared in petri dish weighed & then 10 mg equivalent were dissolved in 10ml of alcoholic solution. 1ml of the above solution is dissolved in 10ml ethanol to get 100ppm. Final sample solution was prepared by pipette 1ml of 100ppm of solution B and dissolving in 10ml ethanol. Finally it was analyzed in UV-spectrometer at 287 nm.

The drug content was calculated which is mentioned in table no. 1



Graph no. 1 Drug content

B. PARTICLE SIZE ANALYSIS

Particle size analysis was determined using Malvern Zeta sizer ZS 90 with operating range of 1-6000nm

The particle size of Silymarin Jelly formulation was determined by DLS method using Zeta analyzer. Silymarin alone and Silymarin with drug carrier size was found to be in the range of 0 - 300 nm. And 95% of the Silymarin formulation found to be less than 230 nm which is in optimum range and can penetrate into the mucosal tissue intact more rapidly.

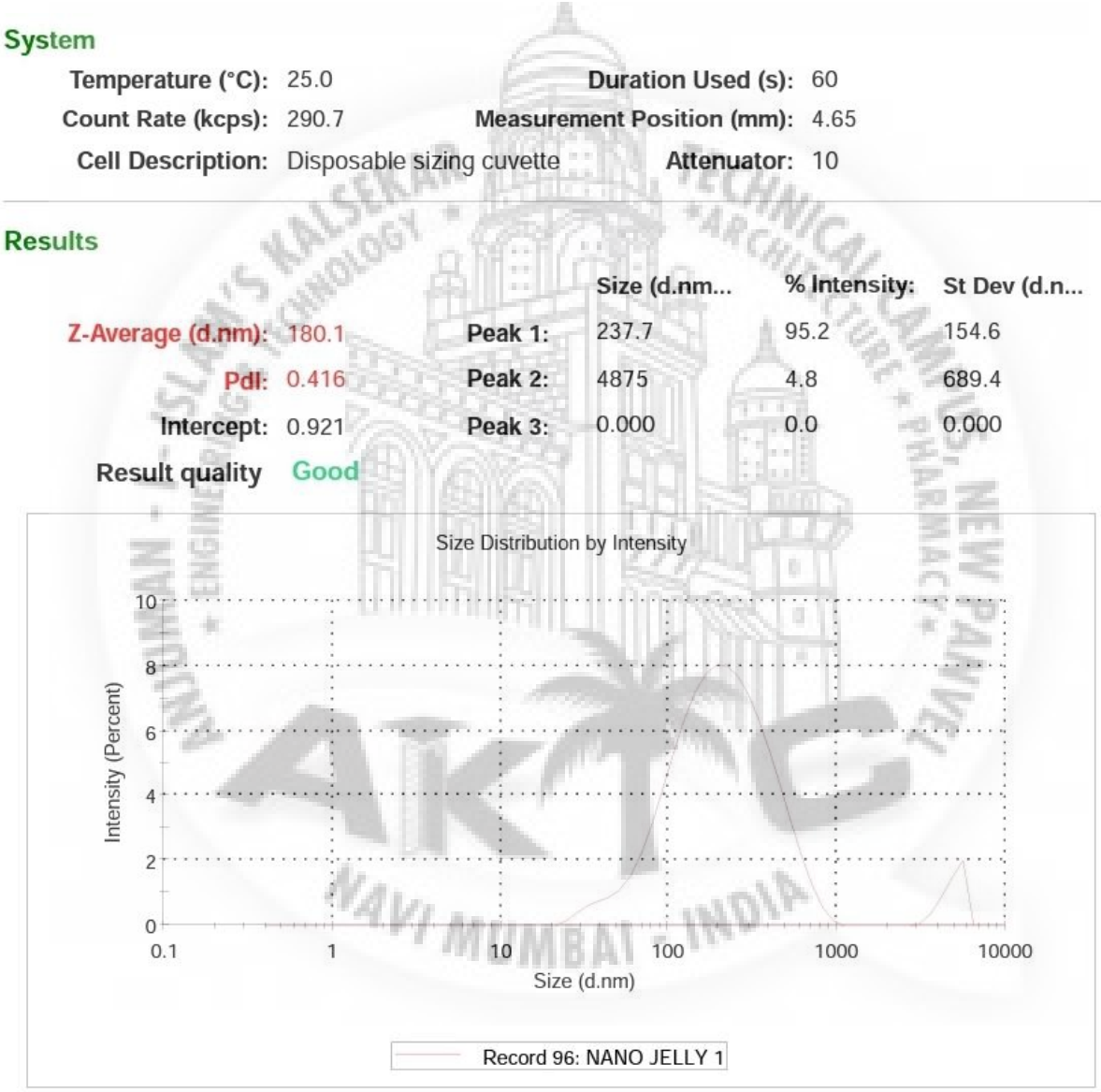
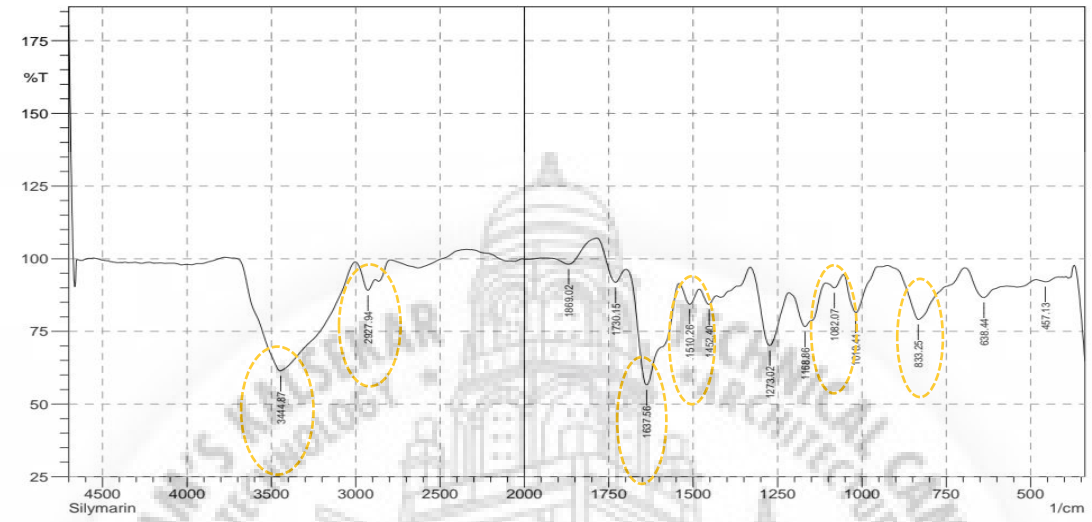


Fig no. 12 Particle size analysis

C. FOURIER TRANSFORM INFRA-RED SPECTROSCOPY (FTIR)

FT-IR Spectra were recorded with Shimadzu spectroscopic analysis FT-IR spectrophotometer with scanning range of 500-4000cm^{-1}.



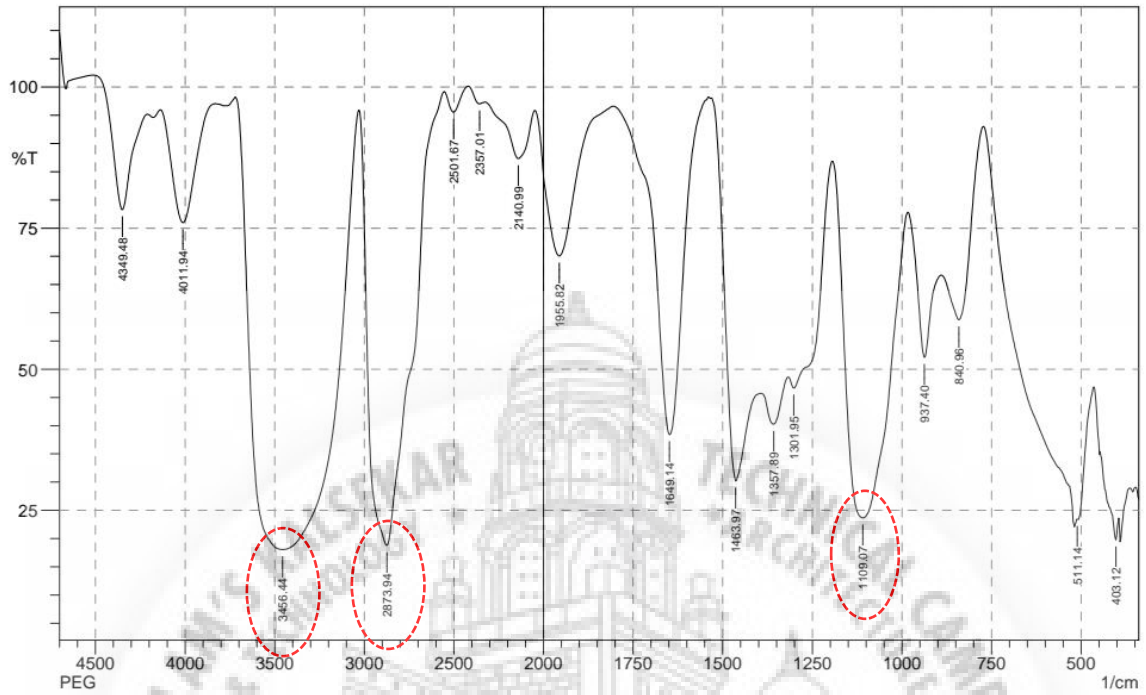
No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	457.13	92.07	1.11	484.13	416.62	2.22	0.18
2	638.44	86.67	7.36	694.37	570.93	5.56	2.06
3	833.25	79.1	18.27	925.83	694.37	11.47	8.69
4	1018.41	81.47	14.08	1055.06	952.84	5.21	3.36
5	1082.07	89.95	3.11	1107.14	1055.06	2	0.39
6	1168.86	76.63	13.14	1217.08	1107.14	8.92	3.86
7	1273.02	70.1	22.54	1330.88	1217.08	10.45	6.65
8	1452.4	84.31	3.9	1481.33	1431.18	3.2	0.51
9	1510.26	84.37	6.06	1543.05	1481.33	3.6	0.92
10	1637.56	56.53	37.89	1699.29	1543.05	20.95	16.66
11	1730.15	91.86	8.31	1786.08	1699.29	0.94	1.53
12	1869.02	98.1	5.45	1946.18	1786.08	-0.9	1.57
13	2927.94	89.13	5.98	3001.24	2883.58	3.69	1.5
14	3444.87	61.39	38.35	3720.69	3001.24	80.68	79.34

Fig no. 13 FTIR Spectra of Silymarin

FTIR Analysis; Silymarin: The IR spectrum of the drug sample was recorded and the functional groups where interpreted as per the structure and where found to be appropriate the structure of the drug. **Fig. 13** gives the IR spectra of the pure drug, gives the interpretation of the peaks obtained in the IR spectra along with their corresponding functional groups.

The given IR spectra of Silymarin, which is identified and proved, shows principle peaks such as-

- The aromatic ring stretching vibrations were evident at 1510.26 cm^{-1}.
- Peak appearing at 1637.56 cm^{-1} confirmed the presence of reactive flavonolignan ketone.
- Alcoholic -O-H Stretch was observed at 3444.87 cm^{-1}.
- Peak appearing at 1082.7 cm^{-1} confirmed the benzopyran ring with concomitant presence of out of plane -C-H deformations at 833.2 cm^{-1}
- 1273.02 cm^{-1} shows -O-C stretch.
- 2927.94 cm^{-1} shows -C-H stretching vibrations.

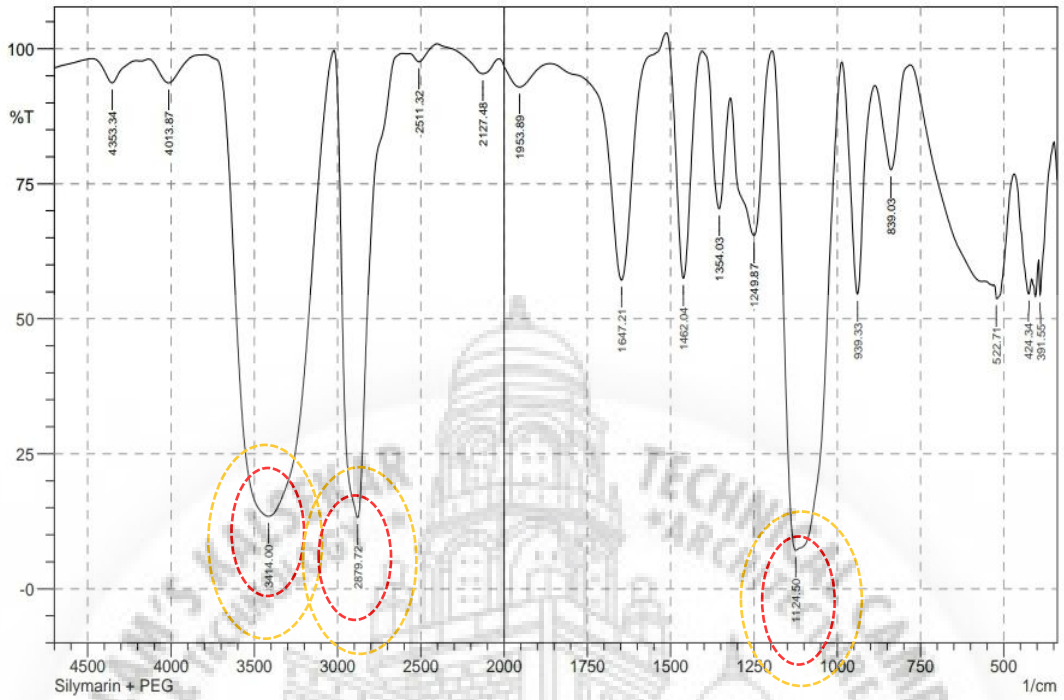


No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	403.12	19.77	5.62	447.49	395.41	30.56	2.52
2	511.14	23.38	0.03	513.07	509.21	2.43	0
3	840.96	58.79	19.11	891.11	773.46	18.75	6.54
4	937.4	52.12	20.12	983.7	891.11	18.33	5.14
5	1109.07	23.67	59.56	1193.94	983.7	78.69	60.83
6	1301.95	46.69	6.72	1317.38	1193.94	30.21	7.12
7	1357.89	40.28	6.79	1392.61	1317.38	27.09	2.53
8	1463.97	30.21	42.42	1531.48	1392.61	43.32	19.14
9	1649.14	38.42	59.16	1803.44	1539.2	33.96	30.97
10	1955.82	70.08	26.06	2048.4	1803.44	16.28	12.19
11	2140.99	87.34	9.01	2326.15	2048.4	9.55	5.38
12	2357.01	97.03	1.25	2418.74	2326.15	0.79	0.28
13	2501.67	95.57	3.99	2553.75	2418.74	1.34	1.15
14	2873.94	18.78	78.2	3030.17	2553.75	152.68	147.52
15	3456.44	18.05	1.76	3466.08	3030.17	211.74	45.94
16	4011.94	75.98	20.42	4137.31	3830.63	18.63	13.89
17	4349.48	78.3	20.1	4509.57	4210.61	12.47	10.61

Fig no. 14 FTIR Spectra of PEG 400

The FTIR spectra of PEG showed peaks at

- 3456.44 cm^{-1} corresponding to OH vibrations.
- 2873.94 cm^{-1} assign to the stretching vibrations of the C-H.
- 1649.14 cm^{-1} and 1109.07 cm^{-1} assign to the stretching vibrations of the C-H, C=O and -C-O



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	391.55	54.25	8.47	395.41	349.12	7.34	0.45
2	424.34	54.59	5.67	468.7	416.62	10.25	0.98
3	522.71	53.73	0.6	530.42	520.78	2.49	-0.01
4	839.03	77.6	17.34	887.26	781.17	6.21	3.89
5	939.33	54.55	40.96	985.62	887.26	11.49	9.46
6	1124.5	7.09	91.84	1195.87	985.62	115.76	114.46
7	1249.87	65.44	30.44	1321.24	1195.87	13.91	11.21
8	1354.03	70.37	23.87	1406.11	1321.24	6.34	4.5
9	1462.04	57.48	43.87	1512.19	1406.11	10.27	10.84
10	1647.21	57.14	43.62	1861.31	1512.19	19.98	20.09
11	1953.89	92.9	4.84	2031.04	1861.31	3.39	1.67
12	2127.48	95.4	3.46	2403.3	2031.04	3.01	2.23
13	2511.32	97.59	2.15	2569.18	2403.3	0.7	0.7
14	2879.72	13.19	86.32	3022.45	2611.62	117.11	116.09
15	3414	13.43	85.86	3793.98	3022.45	320.89	318.51
16	4013.87	93.68	4.71	4133.45	3828.7	4.85	2.82
17	4353.34	93.69	4.31	4472.92	4208.68	4.34	2.01

Fig no. 15 FTIR Spectra of Silymarin + PEG 400

PEG-loaded Silymarin showed peaks at

- 3414.00 cm^{-1} correspond to -O-H Stretch
- -C–H stretching, and the sharp peak in 2879 cm^{-1}
- 1124.50 cm^{-1} assign to the stretching vibrations of the -C-O

The peak size is increased in these regions which indicate there maybe interaction between Silymarin and PEG which can be hydrogen bonding.

The presence of characteristic peak of drug indicates the successful entrapment of drug within the Polyethylene glycol PEG in our nano jellies.

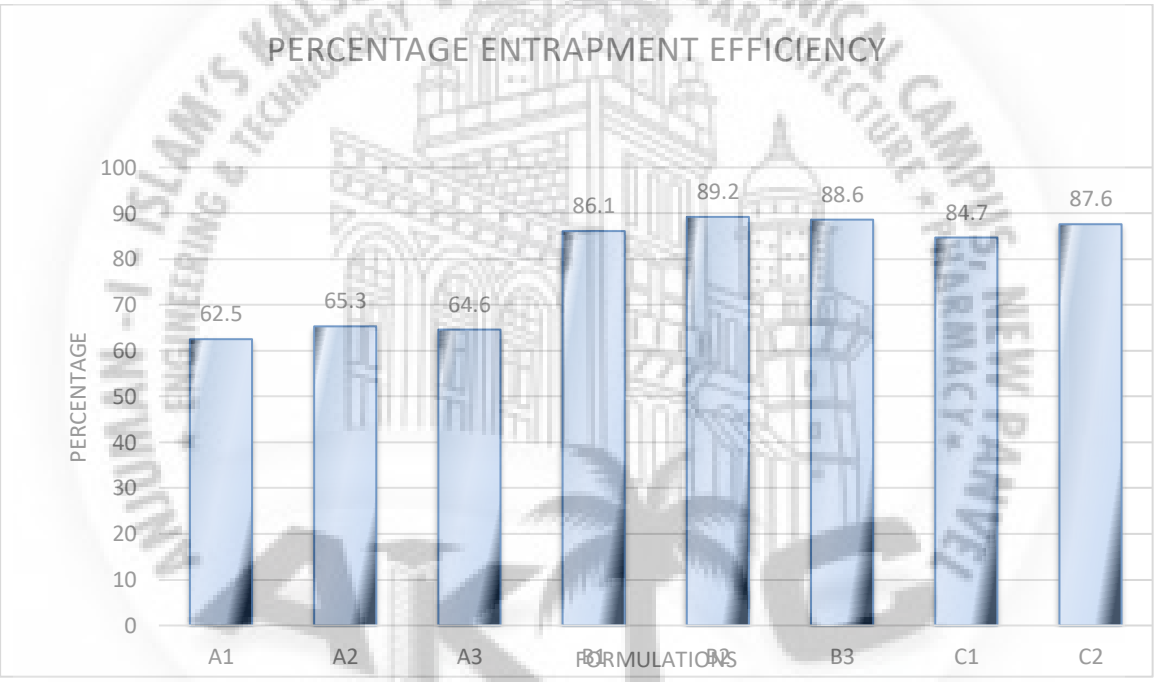
D. DRUG ENTRAPMENT EFFICIENCY

The drug entrapment efficiency of prepared beads was determined by using the equation[19,20]

EE (%) = Actual Drug Content / Theoretical Drug Content X 100

Percentage Drug Entrapment Efficiency:

The percent of drug content in the formulations were found to be in the range of 62% to 89 %.(Table no.2). The percentage entrapment efficiency was found to be 62% to 89.2%. A maximum of 89.2% drug entrapment efficiency was obtained.



Graph no. 2 Percentage entrapment efficiency

7-DISCUSSION

- The commonly used oral dosage forms like tablets have difficulty in swallowing, leading to patient's incompliance particularly in case of pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water. Pharmaceutical technologists have developed an overall dosage form known as Oral medicated jellies (OMJs).
- Oral medicated jellies (OMJs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need of water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms. Silymarin is the extract of Silybum marianum, or milk thistle, and its major active compound is silybin, which has a remarkable biological effect.
- It is used in different liver disorders, particularly chronic liver diseases, cirrhosis and hepatocellular carcinoma, because of its antioxidant, anti-inflammatory and antifibrotic power.
- Oral absorption of silymarin is of about 23- 47%, leading to low bioavailability of the drug. This is due to the poor water solubility, to improve its bioavailability and provide a prolonged silymarin release at the site of absorption, the use of nanotechnological strategies appears to be a promising method to potentiate the therapeutic action and promote sustained release of the active herbal extract.
- Nano Jellies enhances the rate of absorption due to small particle size, nano particles can entrap easily into buccal mucosal network and can rapidly penetrate through the epithelium and basement membrane and this subsequently improves the Bioavailability which is the major problem with other Silymarin oral preparations.
- The drug bypasses first pass metabolism as it is administered through sublingual route, so more drug is available into the systemic circulation this might be another factor which can increase the bioavailability of our drug.
- As the drug bypasses first pass metabolism the amount of drug required per dose is reduced & hence the side effects such as headache & itching which is due to its high dosage & frequent drug administration can be eliminated.
- Oral medicated jellies where prepared by heating and congealing method. Jellies containing almond gum as a polymer, agar and gelatin as gelling agent were prepared with an aim to dissolve the jellies in the mouth. Sugar syrup was used as

a sweetener and raspberry is used as flavoring agent. Batch B2, B3 and C2 exhibited desired gelling properties and other parameters compared to the other batches prepared.

- Particle size analysis using zeta analyzer shows that silymarin nano particles are in optimum range which is required for its easy & rapid penetration through mucosal barrier. UV-Vis spectrophotometric analysis shows uniform distribution of drug into the jellies and drug content. In FTIR studies result shows that the carrier is compatible with the drug i.e., PEG and Silymarin combined together without any change in the functional group.

- The physical appearance including clarity, precipitation, homogeneity, consistency as well as other features of the prepared Silymarin jellies were observed, that showed B2, B3 & C3 formulations were clear, cherry red in color, having semisolid consistency, homogenous and have pleasant fruity aroma.
- The jellies were evaluated for various properties such as general appearance, rheological measurements, pH, % purity, drug entrapment efficiency, syneresis, drug content and centrifugation. Drug content was found to be in the range of 62% to 90%. Batch B2 shower the highest amount of drug content 89.2%.

8-CONCLUSION

- The excellent hepatoprotective activity of silymarin, besides its antioxidant and anti-inflammatory activities, makes it a very promising drug of natural origin. Its good safety profile, easy availability, and low cos are added advantages.

- After observing all the experimental results it was conclusively demonstrated that silymarin nano jellies were formulated by heating and congealing method by using agar\gelatin as a gelling agent and almond gum as a polymer.

- Formulation containing gelatin as a gelling agent, formulated by method C, showed optimum results within all the evaluated parameters. However more promising results were observed with formulation containing agar as a gelling agent, prepared by method B.

- Jellies were formulated using method B, silymarin nano particles were incorporated into them, which will enhances the rate of absorption, nano particles can entrap easily into buccal mucosal network and can rapidly penetrate through the epithelium and basement membrane and this subsequently improves the Bioavailability which is the major problem with other Silymarin oral preparations.

- The route (sublingual route) by which the drug is administered will bypass the first pass metabolism, which will improve the bioavailability of the drug.

- It is found that sucrose based Medicated nano jellies will be ideal dosage forms for geriatric and pediatric patients. These will have an additional advantage of efficient treatment including low dose, ease of administration, immediate onset of action, reduced dosage regimen and economic.

- The Physico-chemical characterization revealed that all the formulations were found to be shown acceptable pH, viscosity, consistency, and syneresis. The drug content estimation showed uniform drug content in all the formulations.

- The stability studies proved that the prepared Medicated jellies were found to be stable for 60 days when stored at air tight container. The present work on silymarin nano Jellies will offer patient convenience and compliance and ease of administration.

9- FUTURE SCOPE

- **Measures to increase shelf-life**

  Different preservatives or combinations can be used to improve the stability of the formulation, which can result in formulation with longer stability

- **Modifications in the methods used**

  Most of the formulations may suffer few drawbacks such as a complicated procedure and low reproducibility, which are difficult to translate into industrial production. Besides, the drug loading capacity is typically very low and the preparations are unstable during storage. In future, some advanced formulation approaches such as emulsomes, mesoporous silica nanoparticles, dendrimers and carbon nanotubes can be successfully utilized for bioavailability enhancement and targeting of silymarin to hepatocytes.

- **Loading Multiple Drug**

  Oral medicated jellies as a dosage form can be adopted for drug delivery across buccal route, labial route, gingival route and sublingual route. Multiple drugs can also be incorporated in them for chronic illness treatments.

- **Pharmacological studies**

  Silymarin protects liver cell membrane against hepatotoxic agents and improves liver function in experimental animals and humans. [24] pharmacological studies can be performed to check weather silymarin nano jelly is able to perform the above mentioned activities.

- **Improve drug loading**

  As the drug content found was not more than 90% measures can be taken to load more drug or to increase the drug content.

- **Accelerated stability studies**

  Accelerated stability studies of the formulated silymarin nano jellies can be done.

- **Formulating jellies with other drugs**

  Oral delivery of poorly soluble drugs such as CBZ for pediatric, geriatric and dysphagic patients as alternatives to solid oral dosage. The jellies loaded with CBZ showed acceptable physico-chemical properties and stability [23], so drugs that are poorly soluble or have elevated first pass metabolism or low bioavailability can be formulated as medicated nano jellies which can easily eliminate the problems associated with such drugs.

10- REFERENCES

[1] https://www.researchgate.net/publication/337394779_ORAL_MEDICATED_JELLIES_-A_REVIEW_Corresponding_Author

[2] Kren V, Walterova D. Silybin and Silymarin – New effects and applications. Biomed Papers 2005; 149:29-41.

[3] Formulation Development And Evaluation Of Olmesartan Medoxamil Ororetentive Jellies.

[4] https://www.researchgate.net/publication/324803436_Anti-Parkinson_Potential_of_Silymarin_Mechanistic_Insight_and_Therapeutic_Standing

[5] https://pubmed.ncbi.nlm.nih.gov/24039417/#:~:text=Silymarin%20was%20located%20in%20unaltered%20crystalline%20form%20in%20the%20nanoparticles.&text=CONCLUSION%3A%20Silymarin-loaded%20nanoparticles%20developed,while%20affording%20excellent%20hepatic%20protection

[6] https://www.frontiersin.org/articles/10.3389/fphar.2019.01328/full#B34

[7] Kanika Nayak, Manoj Kumar Mishra, Garima Verma, Formulation and evaluation of oral soft jelly containing Glibenclamide. Indo American journal of pharmaceutical science. 2016; 3(10) : 1276-1282.

[8] Hua, S., de Matos, M. B. C., Metselaar, J. M., Storm, G. (2018). Current Trends and Challenges in the Clinical Translation of Nanoparticulate Nanomedicines: Pathways for Translational Development and Commercialization. Front. Pharmacol. 9, 790. doi: 10.3389/fphar.2018.00790

[9] Soft Chewable Drug Delivery System: Oral Medicated Jelly and Soft Chew.

[10] Formulation and Evaluation Of Domperidone Medicated Jelly Using Solvent Deposition Method For Solubility.

[11] Formulation and Evaluation of Amlodipine Besylate Oral Thin Films.

[12] https://pubmed.ncbi.nlm.nih.gov/28125040/

[13] Silymarin, A Promising Pharmacological Agent For Treatment Of Diseases, ncbi.nlm.nih.gov/pmc/articles/PMC3586829/

[14] Schadewaldt, H. The history of silymarin. Contribution to the history of liver therapy. Die Med. Welt1969, 20, 902-914.

[15] Bhattacharya, S. Milk thistle (silybum marianum L. Gaert.) seeds in health. In nuts and seeds in Health and Disease Prevention, 1st ed.; Preedy V.R., Watson R.R., Patel, V., Eds.; Academic Press: London, UK; Burington, VT, USA, San Diego, CA, USA, 2011; Chapter 90, pp. 759-766.

[16] http://onlinepharmacytech.info/docs/vol2issue10/JPST10-02-10-04.pdf

[17] https://pubchem.ncbi.nlm.nih.gov/compound/Silymarin

[18] R. Saller, R. Meier, and R. Brignoli. The use of silymarin in the treatment of liver disease, Drugs 61:2035-63

[19] Vikram Deshmukh, Atmaram Pawar, Tejeswini Deshmukh, Madhuri Deshmukh, Katedeshmukh RG, Patil RY. "Preparation and Evaluation of Slow Release Carbamazepine Alginate-Talc Beads", Current Pharma Research., 2011; 1(3): 271-279.

[20] Zhen-Hai Zhang, Yong-Shun Sun, Hui Pang, Were L.L. Munyendo, Hui-Xia Lv, Sheng-Liang Zhu. Preparation and Evaluation of Berberine Alginate Beads for Stomach-Specific Delivery. Molecules, 2011; 16: 10347-10356

[21] https://clinicaltrials.gov/ct2/show/NCT04394208

[22] https://www.thailandmedical.news/news/covid-19-supplements-silymarin-from-milk-thistle-could-perhaps-also-be-used-as-an-adjuvant-supplement-to-help-covid-19-patients

[23] Katakam Prakash, Varanasi M. Satyanarayana, Hwisa T. Nagiat, Assaleh H. Fathi, Adiki K. Shanta, Avula R. Prameela. Formulation development and evaluation of novel oral jellies of carbamazepine using pectin, guar gum, and gellan gum, Asian Journal of Pharmaceutics - October-December 2014

[24] Rui YC. Advances in pharmacological studies of silymarin. Mem Inst Oswaldo Cruz. 1991;86 Suppl 2:79-85. doi:10.1590/s0074-02761991000600020

[25] https://www.researchgate.net/publication/47619037_Silymarin-_A_review_on_the_Pharmacodynamics_and_Bioavailability_Enhancement_Approaches#:~:text=The%20non%20traditional%20use%20of,the%20bioavailability%20of%20the%20drug.Review Article CODEN: IJPRNK Impact Factor: 5.567 ISSN: 2277-8713 Amitkumar Patel, IJPRBS, 2018; Volume 7(4): 37-49 IJPRBS

11- APPENDIX

"Silymarin also have some antiviral properties which can result in its use in patient suffering from covid-19. It can also be used as an adjuvant in these patients due to its other properties.

SCOPE (Silymarin in COVID-19 Pneumonia)- phase 3 of clinical trial. A randomized placebo controlled trial to assess the clinical outcome in COVID-19 Pneumonia following administration of Silymarin owing to its role as a p38 MAPK pathway inhibitor and its antiviral, anti-inflammatory and anti-oxidant effects

As it has also been seen that many COVID-19 patients are likely to suffer liver damage either due to the novel coronavirus or due to the drugs administered, Silymarin has been known to possess anti-inflammatory properties and is also known to help in liver cells regeneration.

Hence it might be a useful supplement for COVID-19 patients.

https://www.ncbi.nlm.nih.gov/pubmed/21466434 or https://www.sciencedirect.com/science/article/pii/B978012804274800045X or https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/cld.522 or https://link.springer.com/chapter/10.1007/978-3-642-72631-6_49 or https://clinphytoscience.springeropen.com/articles/10.1186/s40816-016-0019-2

As COVID-19 patients also are prone to cardiac issues, Silymarin has been thought to be able to aid to a certain degree to prevent certain cardiac issues.

https://www.sciencedirect.com/science/article/pii/S0367326X14001464 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2359609/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4776552/

Significantly, Silymarin is also capable to help in arrhythmias that are induced as a result of cardiotoxic drugs such as choloroquine or some of the antivirals.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5080420/

Previous studies have also showed that it is able to prevent cytokine storms which is a common occurrence in COVDI-19 patients."[21] [22]

https://www.ncbi.nlm.nih.gov/pubmed/23701595 or https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2819600/ or https://journals.sagepub.com/doi/abs/10.1177/0194599811423504 or https://academic.oup.com/intimm/article/22/Suppl_1_Pt_4/iv22/2958130

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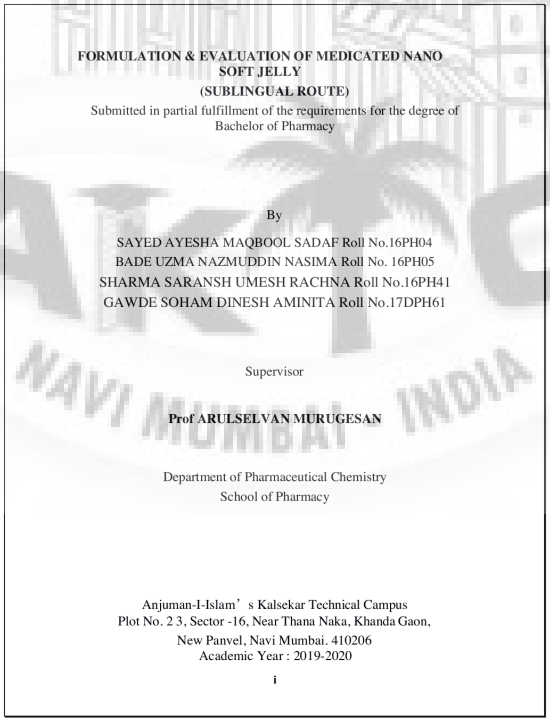

FORMULATION & EVALUATION OF MEDICATED NANO SOFT JELLY

(SUBLINGUAL ROUTE)

Submitted in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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