"EVALUATION OF ALTERNATE ORGANIC SOLVENTS AS A REPLACEMENT OF HALOGENATED SOLVENTS FOR MANUFACTURING OF DRUG PRODUCTS"

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BY

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UNDER THE GUIDANCE OF

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DECLARATION

I declare that the thesis "EVALUATION OF ALTERNATE ORGANIC SOLVENTS AS A REPLACEMENT OF HALOGENATED SOLVENTS FOR MANUFACTURING OF DRUG PRODUCTS" has been prepared by me under the guidance of Dr. Navin Vaya, A.G.M, Formulation and development department, Torrent research center, Bhat and Dr. Tejal A. Mehta, Professor, Department of Pharmaceutics & Pharmaceutical Technology, Institute of Pharmacy, Nirma University. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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ABSTRACT

Halogenated solvents, which are commonly used in manufacturing and laboratory processes have been associated with human carcinogenesis. Halogenated solvents can pose major problems when they are released into the environment. Reducing their use by using other suitable and non halogenated solvents can consequently reduce the health and environmental threats associated with use of Halogenated solvents. Therefore the aim of this project is to bring together research efforts in the quest to find "green" replacements for halogenated solvents and to direct efforts to change solvent system based on halogenated solvent to non halogenated solvents to protect the environment and health as well as industrial safety. Based upon regulatory, health and environmental aspects, solubility characteristics of the polymer used and by conducting the series of solubility trials, alternate solvents were selected. Solution properties of the alternate solvent system i.e. appearance, viscosity were compared to that of reference system. Film forming properties of the polymers in these alternate solvents were also checked by conducting film casting trials and were compared to the reference system. Films prepared were evaluated for physical and mechanical properties like appearance, thickness, tensile strength, % elongation and folding endurance and results of both the system were compared. Selected alternate solvents were further tried in coating process. By conducting various coating trials tablets were coated using reference (with using halogenated solvent) as well as alternate system and evaluated further for physical parameters. Almost in all the cases alternate solvents selected show better or comparable results; therefore we can replace these halogenated solvents with alternative solvents used as vehicle or solvent. But before implementing these solvents further suitability in actual products and stability studies are necessary.

AIM OF THE PRESENT INVESTIGATION

1. AIM OF THE PRESENT INVESTIGATION

Pharma companies are devoted to discovering and developing new medicines that will enable patient to live longer, healthier and more productive lives. The global pharmaceutical companies are investing billion of dollars in discovering and developing new medicines but pharma industry's commitment to improving health is not complete without a commitment to a healthy environment. (1)

Solvents, defined as substances able to dissolve or solvate other substances are commonly used in manufacturing and laboratory processes and are often indispensable for many applications such as cleaning, coatings, synthetic chemistry, and separations. (2) Despite abundant precaution, they inevitably contaminate our air, land, and water because they are difficult to contain and recycle. Billions of pounds of solvent waste are emitted to the environment annually, either as volatile emissions or with aqueous discharge streams. Researchers have therefore focused on reducing solvent use through the development of solvent-free processes and more efficient recycling protocols. However, these approaches have their limitations, necessitating a pollution prevention approach and the search for environmentally benign solvent alternatives. (5)

Many of the solvents used in pharmaceutical industries are known to upset our ecosystems by depleting the ozone layer and participating in the reactions that form tropospheric smog. In addition, some solvents may cause cancer or sterility in those individuals frequently exposed to them. Some of the solvents are neurotoxins. While contained use of these solvents would be acceptable from both an environmental and a health perspective, such operations are difficult to achieve, therefore alternative solvents are currently being sought to minimize the problems inherent in solvent release to the environment.

As awareness and understanding of how solvents affect the environment and human health grow, so do the regulations that govern use of these chemicals. Government agencies such as the Occupational Safety and Health Administration (OSHA) have

been installed to protect workers from solvent exposure (2) The Environmental Protection Agency (EPA) and air pollution control agencies are also becoming increasingly aware of the presence of substances in the ambient air that may be toxic at certain concentrations. This awareness has led to attempts to identify the source and to develop control programs to regulate toxic emissions. (6)

One of the important aspects in the pharma industry for a greener chemistry is the replacement of halogenated solvents with safer available other solvents in various pharmaceutical processes. Green Chemistry is the design, development, and implementation of chemical products and processes to reduce or eliminate the use and generation of substances hazardous to human health and the environment Green Chemistry challenges innovators to design and utilize matter and energy in a way that increases performance and value while protecting human health and the environment.(3)

Over the course of the past decade, green chemistry has demonstrated how fundamental scientific methodologies can protect human health and the environment in an economically beneficial manner. Significant progress is being made in several key research areas, such as catalysis, the design of safer chemicals and environmentally benign solvents. Current and future chemists are being trained to design products and processes with an increased awareness for environmental impact. Outreach activities within the green chemistry community highlight the potential for chemistry to solve many of the global environmental challenges we now face. (4) There are over 10,000 drugs sold world wide today but perhaps only 1% are made by processes that could be considered green. (1)

So the aim of this project is to bring together research efforts in the quest to find "green" replacements for halogenated solvents and to direct efforts to change solvent system based on halogenated solvent to non halogenated solvents to protect the environment and health as well as industrial safety without changing the product composition.

INTRODUCTION

2. INTRODUCTION

Halogenated organic compounds constitute one of the largest groups of chemicals. Their use and misuse in industry and agriculture represent a large entry of these chemicals into the environment, resulting in widespread dissemination and often times undesirable conditions, i.e., environmental contamination. (7)

Several of the halogenated solvents have, for some time, been associated with human carcinogenesis. While a number of specific points of disagreement remain in regard to the health and environmental impacts of halogenated hydrocarbons, a consensus has emerged that these substances can pose major problems when they are released into the environment, and that significantly reducing their use can consequently reduce the health and environmental threats associated with them. (8)

Halogenated solvents commonly used in the pharmaceutical industry are

- Trichloroethylene ($ClCH\text{-}CCl_2$),
- Perchlorethylene (tetrachloroethylene, $Cl_2C\text{-}CCl_2$),
- Methylene dichloride (CH_2Cl_2),
- Carbon tetrachloride (CCl_4),
- Chloroform ($CHCl_3$),
- 1, 1, 1-trichloroethane (methyl chloroform, $CH_3\text{-}CCl_3$)

HEALTH HAZARDS OF HALOGENATED SOLVENTS

According to the National Institute for Occupational Safety (NIOSH), National Toxicology Program (NTP), International Agency for Research on Cancer (IARC) and American Conference of Governmental Industrial Hygienists (ACGIH):
- Trichloroethylene is a suspect carcinogen;
- Methylene chloride is a potential carcinogen (ACGIH);
- Carbon tetrachloride is a suspect carcinogen (ACGIH);
- Chloroform is a suspect carcinogen;

Over-exposure of these halogenated solvents in poorly ventilated space may lead to depression, headache, sleepiness, unconsciousness and even death. Some chlorinated solvents cause cancer in rats and mice at high exposure levels. (10)

ENVIRONMENTAL HAZARDS OF HALOGENATED SOLVENTS

- Vapors of halogenated solvent degrade in the atmosphere for a period between one week (trichloroethylene) to 5-6 months (perchlorethylene and methylene chloride).

- Ozone Depletion Potential (ODP) of carbon tetrachloride and chloroform is high (more than 0.2) and their use is forbidden. ODP of trichloroethylene, perchlorethylene and methylene chloride is low and they are not regulated by the Montreal Protocol.

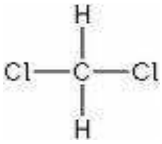
- Spillage of halogenated solvents to soil or water causes contamination. Methylene chloride is biodegradable. Other chlorinated solvents degrade only after revaporation to the atmosphere. (10)

USE OF METHYLENE DICHLORIDE IN PHARMCEUTICAL INDUSTRY

Methylene Dichloride (MDC) is a saturated aliphatic halogenated hydrocarbon. It is a clear, colorless, volatile liquid with an odour similar to ether. It was introduced as a replacement for more flammable solvents over 60 years ago because of its extensive oil and fat solubility, and low flammability potential.

In the formulation and development of pharmaceutical product MDC is being used significantly then the other halogenated solvents. MDC is mainly used as the solvent or co-solvent during various stages of the pharmaceutical processes. It is used to dissolve polymeric binders and in the film coating process using polymers. MDC is used as an effective reaction and recrystallization solvent. It is also used in the extraction of several pharmaceutical compounds and in the production of many antibiotics and vitamins. Significant use of MDC is because of its high solvency, low corrosiveness to metals, and lack of flash or fire point. (9)

PHYSICO CHEMICAL PROPERTIES OF METHYLENE DICHLORIDE (MDC) (28, 29, 30)

Synonyms	Dichloromethane (DCM), methylene dichloride, methylene bichloride, methane dichloride
CAS no.	75-09-2
Molecular formula	CH_2Cl_2
Structural formula	
Molecular weight	84.9
Ambient state	Clear, colorless, volatile liquid
Odor threshold	Between 100 and 300 ppm ethereal odor
Boiling point at (760mmHG)	39.8°C
Freezing point	-96.7°C
Density, at 20°C kg/m^3	1315.7
Specific gravity, at 20°C	1.320
Vapor density (air = 1.02)	2.93
Vapor pressure	
Kpa at 0^{o}c	19.6
Kpa at 20^{o}c	46.5
Kpa at 30^{o}c	68.1
Diffusivity in air, m^2/s	9 x 10^{-5}
Refractive index at 20°C	1.4244
Viscosity at 20°C (cp)	0.43

Surface tension: N/m (=dyne/cm) at 20°C	0.02812
Solubility	Soluble with other grades of chlorinated solvents, diethyl ether, ethanol, ethyl alcohol, phenols, aldehydes, ketones, glacial acetic acid, triethyl phosphate, acetoacetic ester, and water (13.2 g/kg at 20°C).
Flash point	None, however, as little as 10 % acetone or methyl alcohol can produce one.
Flammable (explosive) limits at 25°C, vol% in air	14-25
Auto-ignition temperature	640°C
Electrical properties at 24°	
Dielectric strength, V/cm (V/100 mils)	94.488 (24.00)
Specific resistivity at 24°, W· cm	1.81 x 10^{8}
Dielectric constant at 24°C, 100khz	10.7

NEED OF REPLACEMENT OF METHYLENE DICHLORIDE FROM HEALTH, SAFETY & REGULATORY POINT OF VIEW

- The Food and Drug Administration (FDA) and EPA consider MDC to be a suspect carcinogen based on the results of animal studies.
- The International Agency for Research on Cancer (IARC) classifies MDC as "possibly carcinogenic to humans" and the National Toxicology Program (NTP) lists it as one of the substances that "may reasonably be anticipated to be carcinogens."
- The Consumer Product Safety Commission (CPSC) now requires household products containing MDC to be labelled as hazardous substances. (8)
- MDC is one of nearly 200 substances designated as hazardous air pollutants (HAPs) under Section 112 of the Clean Air Act, as amended.
- MDC has been listed as a Toxic Chemical under Section 313 and is reportable under Title III (Toxic Chemical Release Inventory).(11)
- MDC waste solvent is considered a hazardous waste under the Resource Conservation and Recovery Act (RCRA) because it poses a human health threat as a probable human carcinogen and neurotoxin.(6)
- OSHA's permissible exposure limits (PELs) for MDC are 25 ppm as an 8-hour, time-weighted average (TWA) and 125 ppm as a short-term exposure limit (STEL).
- The federal EPA Clean Air Act Amendments address MDC emissions in the pharmaceutical industry through the Hazardous Organic National (HON) Emission Standards for Hazardous Air Pollutants
- In addition, the use of MDC in cosmetic products and as a decaffeinating agent is restricted by the Food and Drug Administration.
- Due to its high vapour pressure MDC is difficult to recover with high efficiency at low concentrations in air streams. Incineration results in

formation of hydrochloric acid, itself a hazardous emission requiring additional controls. (11)

Due to all this health & environmental hazards and restriction from the regulatory authorities it becomes necessary to replace MDC by alternative solvents to protect the environment and health as well as industrial safety.

2.1 INTRODUCTION TO FILM COATING TECHNOLOGY

All drugs have their own characteristic, like some drugs are bitter in taste or has an unpleasant odor, some are sensitive to light or oxides, some are hygroscopic in nature.(39 - 41) Because of this reason tablet coating is the choice of option to solve such problems in conventional dosage form.

In the past sugar coating was mostly borrowed from the confectionary industry. Tablet film coating is performed by two types, one is aqueous film coating (generally water is used as a solvent) and non aqueous film coating (generally organic solvent are used.) Some problems are associated with the non aqueous film coating like employee safety (it's dangerous, it smells, and it's not good to breathe.) atmosphere pollution etc. But key problem is with the approval of the regulatory authority (42). High quality aqueous film coating must be smooth, uniform and adhere satisfactorily to the tablet surface and ensure chemical stability of a drug.

ASPECTS OF TABLET COATING (39- 41)

I. Therapy

i) Avoid irritation of esophagus and stomach

ii) Avoid bad taste

iii) Avoid inactivation of drug in the stomach

iv) Improve drug effectiveness

v) Prolong dosing interval

vi) Improve dosing interval

vii) Improve patient compliance

II. Technology

i) Reduce influence of moisture

ii) Avoid dust formation

iii) Reduce influence of atmosphere

iv) Improve drug stability

v) Prolong shelve life

III. Marketing

i) Avoid bad taste

ii) Improve product identity

iii) Improve appearance and acceptability

BASIC PRINCIPLE OF TABLET COATING

The principle of tablet coating is relatively simple. Tablet coating is the application of coating composition to moving bed of tablets with concurrent use of heated air to facilitate evaporation of solvent.

TYPE OF TABLET COATING PROCESS

Sugar coating

Compressed tablets may be coated with colored or uncolored sugar layer. The coating is water soluble and quickly dissolves after swallowing. Sugarcoat protects the enclosed drug from the environment and provides a barrier to objectionable taste or order. The sugar coat also enhances the appearance of the compressed tablet and permit imprinting manufacturing's information. Sugar coating provides a combination of insulation, taste masking, smoothing the tablet core, coloring and modified release. But now a days it is replaced with film coating, because the sugar coating process was a skilled manipulative process and could last for even five days. The operator must be highly skilled for such coating. Hence film coating is preferred over sugar coating.

Film Coating

Film coating is more favored over sugar coating. A film coating is a thin polymer-based coat applied to a solid dosage form such as a tablet. The thickness of such a coating is usually between 20-100 µm. (43, 44)

Table 1: COMPARISON BETWEEN FILM COATING AND SUGAR COATING

	FEATURES	FILM COATING	SUGAR COATING
Tablet	**Appearance**	Retain contour of original core. Usually not as shiny as sugar coat type	Rounded with high degree of polish
	Weight increase because of coating material	2-3%	30-50%
	Logo or 'break lines'	Possible	Not possible
Process	**Operator training required**	Process tends itself to automation and easy training of operator	Considerable
	Adaptability to GMP	High	Difficulty may arise
	Process stages	Usually single stage	Multistage process
	Functional coatings	Easily adaptable for controlled release	Not usually possible apart from enteric coating

Film Coating Composition

Film coating formulations usually contain the following components

- Polymer,
- Plasticizer,
- Colorants / Opacquants
- Solvent / Vehicle
- Miscellaneous

Polymers

Amongst the vast majority of the polymers used in film coating are cellulose derivatives or acrylic polymers and copolymers. (43, 44)

Non-enteric polymers (45, 46)

- Hypromellose
- Hydroxyethyl cellulose
- Hydroxyethylmethyl cellulose
- Carboxymethylcellulose sodium
- Hydroxypropyl cellulose
- Ethylcellulose
- Polyvinyl alcohol

Enteric polymers

Some examples of enteric coating polymers

- Hypromellose phthalate
- Polyvinyl acetate phthalate
- Cellulose acetate phthalate
- Polymethacrylates
- Shellac

Plasticizers

Plasticizers are relatively low molecular weight materials which have the capacity to alter the physical properties of the polymer to render it more useful in performing its function as a film-coating material.(45,46) It is generally considered to be mechanism of plasticizer molecules to interpose themselves between individual polymer strands thus breaking down polymer-polymer interactions. Thus polymer is converted in to more pliable materials. Plasticizers are classified in three groups. Polyos type contains glycerol, propylene glycol, PEG (Polyethylene glycol). Organic esters contain phthalate esters, dibutyl sebacete, citrate esters, triacetin. Oils/glycerides contain castor oil, acetylated, monoglycerides, and fractionated coconut oil.

Solvents/Vehicles

The key function of a solvent system is to dissolve or disperse the polymers and other additives. All major manufactures of polymers for coating give basic physicochemical data on their polymers. These data are usually helpful to a formulator. Some important considerations for solvent are as follows: (44)

The major classes of solvents being used are

- Water
- Alcohols
- Ketones
- Esters
- Chlorinated hydrocarbons

Because of environmental and economic considerations, water is the solvent of choice; however organic coating is totally cannot be avoided.

Colorants / Opacquants

Colorants can be used in solution form or in suspension form. To achieve proper distribution of suspended colorants in the coating solution requires the use of the powdered colorants (<10 microns). Most common colorants in use are certified FD & C or D & C colorants. These are synthetic dyes or lakes. Lakes are choice for sugar or film coating as they give reproducible results (45, 46).

Opacquants are very fine inorganic powder used to provide more pastel colors and increase film coverage. These inorganic materials provide white coat or mask color of the tablet core. Colorants are very expensive and higher concentration is required. In presence of these inorganic materials, amount of colorants required decreases. Most commonly used materials are titanium dioxide, silicate (talc &aluminum silicates), carbonates (magnesium carbonates), oxides (magnesium oxide) & hydroxides (aluminum hydroxides).

Sunset yellow, tartrazine, erythrosine are examples of Organic dyes and their lakes. Iron oxide yellow, red and black is the examples of Inorganic colors. Anthrocyanins, riboflavin and carmine are the examples of natural colors.

Miscellaneous

To provide a dosage form with a single characteristic, special materials may be incorporated into a solution (44)

Flavors and sweeteners are added to mask unpleasant odours or to develop the desired taste. For example, aspartame, various fruit spirits (organic solvent), water soluble pineapple flavor (aqueous solvent) etc.

Surfactants are supplementary to solubilize immiscible or insoluble ingredients in the coating. For example Spans, Tweens etc.

Antioxidants are incorporated to stabilize a dye system to oxidation and color change. For example oximes, phenols etc.

Antimicrobials are added to put off microbial growth in the coating composition. Some aqueous cellulose coating solutions are mainly prone to microbial growth, and long-lasting storage of the coating composition should be avoided. For example alkylisothiazloinone, carbamates, benzothiazoles etc.

FILM COATING PROCESS

Film-coating of tablets is a multivariate process, with many different factors, such as coating equipment, coating liquid, and process parameters which affect the pharmaceutical quality of the final product (47 – 50)

Coating Equipment (51)

Before few years different types of coating pans are used for coating like conventional coating pans, manesty accelacota, driam (driacoater), butterfly coater etc. Now days the side-vented, perforated pan-coater is the most commonly used coating device of tablets. In equipment spray nozzle, number of spray nozzle, pan size, etc may also affect the quality of final product. Air flow system through a perforated pan ensures rapid and continuous drying conditions. The low evaporation capacity of water requires high drying efficiency of aqueous film-coating equipment.

Coating Liquid

Coating liquid may affect the final quality of the tablets. Different film former have different chemical nature and different characteristics. Viscosity may affect the spreading of coating liquid across surface of substrate. Surface tension may affect in wetting of surface. % Solid content generally affects the tablet surface and coating efficiency. (52)

Process Parameters

Spray Rate

The spray rate is a significant parameter since it impacts the moisture content of the formed coating and, subsequently, the quality and uniformity of the film. A low coating liquid spray rate causes incomplete coalescence of polymer due to insufficient wetting, which could effect in brittle films. A high coating liquid spray rate may result in over wetting of the tablet surface and subsequent problems such as picking and sticking. If the spray rate is high and the tablet surface temperature is low, films are not formed during the spraying but the post drying phase, and rapid drying often produces cracks in the films. (53)

Atomizing Air Pressure

In general, increasing the spraying air pressure decreases the surface roughness of coated tablets and produces denser and thinner films. If spraying air pressure is excessive, the spray loss is great, the formed droplets are very fine and could spray-dry before reaching the tablet bed, resulting in inadequate droplet spreading and coalescence. If spraying air pressure is inadequate, the film thickness and thickness variation are greater possibly due to change in the film density and smaller spray loss. In addition, with low spraying air pressure big droplets could locally over wet the tablet surface and cause tablets to stick to each other.

Inlet Air Temperature

The inlet air temperature affects the drying efficiency (i.e. water evaporation) of the coating pan and the uniformity of coatings. High inlet air temperature increases the drying efficiency of the aqueous film coating process and a decrease in the water

penetration into the tablet core decreases the core tablet porosity, tensile strength and residual moisture content of coated tablets. Too much air temperature increases the premature drying of the spray during application and, subsequently, decreases the coating efficiency. Measuring the pan air temperature helps to manage the optimum conditions during the coating process and, consequently, enables predicting possible drying or over wetting problems which may result in poor appearance of the film or may have unfavorable effects on the moisture and heat sensitive tablet cores.

Rotating Speed of Pan

It is well documented that increasing the rotating speed of the pan improves the mixing of tablets. The pan speed affects the time the tablets spend on the spraying zone and, subsequently, the homogeneous distribution of the coating solution on the surface of each tablet throughout the batch. Increasing the pan speed decreases the thickness variation and increase the uniformity of coatings. Too much rotating speed of the pan will cause the tablet to undergo unnecessary attrition and breakage.

APPROCHES FOR REPLACEMENT OF METHYLENE DICHLORIDE

3. APPROCHES FOR REPLACEMENT OF METHYLENE DICHLORIDE

In the formulation and development of pharmaceutical product MDC is used more significantly then the other halogenated solvents. MDC is mainly used as the solvent or co-solvent during various stages of the pharmaceutical processes. It is used as a solvent to dissolve or disperse the film forming polymer or release controlling polymer for the film coating/enteric coating or sustained/extended/delayed release products. It is also used in the granulation or to dissolve polymeric binder in the case of moisture sensitive API.

MDC is used in the products where

- In some case MDC is used to replace the water as a solvent to avoid the issue of chemical instability mainly in the case where API is hygroscopic. Hygroscopic substances attract water molecules from the surrounding environment through either absorption or adsorption. They adsorb water because of hydrate formation or specific site adsorption. With most hygroscopic materials, changes in moisture level can greatly influence many important parameters, such as chemical stability, flowability, and compactability. (12)
- To avoid the use of water incase of moisture sensitive API MDC is used. Moisture sensitive drugs absorb moisture and forms hydrate. Conversion of an anhydrous compound to a hydrate may present another challenge to formulators. Presence of water can initiate reactions such as hydrolysis to avoid such problems MDC is used in place of water. Potential problems associated with these APIs include reduced flow properties, as well as changes in dissolution rates, chemical stability and physical stability (in terms of color, for example). (12)
- Some materials have tendency to convert the polymorphic form in presence of water. To avoid the polymorphic form conversion MDC is used. Polymorphism is characterized as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal. Polymorphs have different chemical and physical properties such as

melting point, chemical reactivity, apparent solubility, dissolution rate, optical and electrical properties, vapor pressure, and density. These properties have a direct impact on the quality/performance of drug products, such as stability, dissolution, and bioavailability. This polymorphs exhibit different solubility which affects the dissolution rate of drug and consequently its bioavailability in the body is also affected. (12)

- Solubility of release controlling agent in particulate solvent is important to produce uniform distribution. Release controlling agents are used to control the release of the drug from extended or controlled or delayed release dosage forms. Examples of release controlling agents which are water insoluble are ethyl cellulose, hypromellose phthalate, hydrogenated castor oil and various grades of polymethacrylates. Therefore to dissolve or disperse these polymers other organic solvents having good solubility is required. Therefore to dissolve the water insoluble polymers MDC is used.
- If release controlling agent have more solubility in solvent system then we can prepare high concentration solution, make process parameters simpler and as well as reduce the cost. For example release controlling agents such as hydrogenated castor oil has more solubility in MDC. Therefore use of MDC is required to dissolve the hydrogenated castor oil.
- MDC is used to dissolve the polymers giving high viscosity solution in water. Release controlling agent such as carrageenan has very high viscosity in water. Use of this highly viscous solution in film coating is very difficult therefore for making process parameters such as spray rate, flow through tubings, simpler MDC is used.

3.1 PROCESS OF IDENTIFYING ALTERNATE SOLVENTS

Solvents are mainly used in the coating process to dissolve or disperse the polymers and other additives and convey them to substrate surface. Alternatives are selected on the basis of health, environment & regulatory aspects.

Regulatory Aspect

As per ICH guideline Q3C solvents are classified as below (13)

Table 2

Class	Type	Concern	Example	Conc. Limit (PPM)	PDE * (mg/ day)
Class 1	**Solvents to be avoided**	• Known human carcinogens, • Strongly suspected human carcinogens, • Environmental hazards	• Benzene • Carbon tetrachloride • 1,2-Dichloro ethane • 1,1-Dichloro ethene	2 4 5 8	
Class 2	**Solvents to be limited**	• Non-genotoxic animal carcinogens • Possible causative agents of irreversible toxicity • Solvents suspected of other significant but reversible toxicities	• Chloroform • Acetonitrile • MDC • Methanol	60 410 600 3000	0.6 4.1 6.0 30.0
Class 3	**Solvents with low toxic potential**	• Solvents with low toxic potential to man; • No health-based exposure limit is needed.	• Acetone • Ethanol • Ethyl Acetate • 1-Propanol • 2-Propanol	5000	50 mg or more
Class 4	**Solvents for which No Adequate Toxicological Data was Found**		• Trifluoroacetic acid • Trichloroacetic acid • Petroleum ether Isopropyl ether		

*PDE – Permitted Daily Exposure

All the preferred alternative solvents should be safer then MDC. Selected all the alternative comes under class 3 solvents which are least toxic except methanol. But methanol is safer then MDC. PDE of methanol is five times higher than MDC.

IDEAL PROPERTIES FOR THE ALTERNATIVE SOLVENTS (14)

- It should dissolve/disperse polymer system
- It should easily disperse other additives into solvent system
- Low concentration of polymers (2-10%) should not result in an extremely viscous solution system creating processing problems
- It should be colorless, tasteless, odorless, inexpensive, inert, nontoxic and nonflammable
- It should have rapid drying rate
- It should not produce any environmental hazard.

PREFERRED ALTERNATIVES (15)

- Water / alcohol water mixture
- Acetone
- Ethanol
- 2-Propanol
- 1-Propanol
- Ethyl Acetate
- Isopropyl acetate
- Methanol
- Methyl Ethyl Ketone
- 1-Butanol
- *t*-Butanol

Selection of alternative solvent is also influenced by the solubility or dispersibility of the film forming agent in the alternative solvent. Solubility of commonly used film forming agents is reported in the following table. (16)

SOLUBILITY OF FILM FORMING AGENTS IN ALTERNATE SOLVENTS

Table 3

FILM FORMING AGENTS	**SOLUBILITY**
Hydroxy Propyl Methyl Cellulose	Water, combination of Ethanol : water or Isopropyl alcohol : water
Carrageenan	Water
Polymethacrylates	Combination of acetone & alcohol
Hypromellose Phthalate	Acetone alone or Combination of Acetone:water,or acetone: alcohol, or ethyl acetate: alcohol
Ethyl Cellulose	ethanol (95%), ethyl acetate, methanol

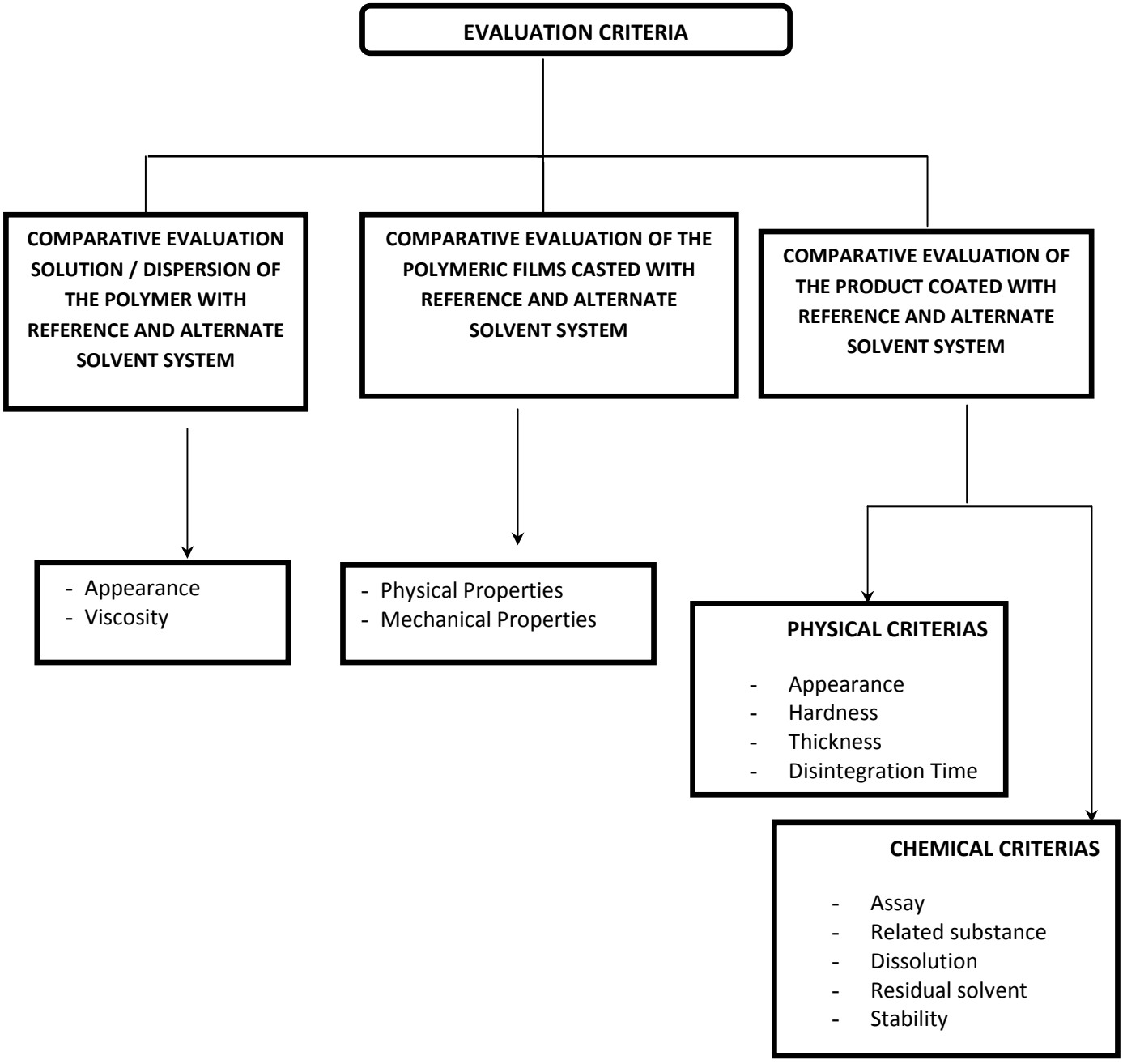
COMPARISON OF PROPERTIES OF MDC WITH ALTERNATIVE SOLVENTS (17)

Table 4

ALTERNATIVE SOLVENTS	**BOILING POINT**	**FLASH POINT**	**DENSITY** (at 20 °C) g/cm^3
MDC	39.75 °C	none	1.326
Acetone	56.2 °C	- 20 °C	0.784
Ethanol	78.15 °C	14 °C	0.789
Methanol	64.7 °C	12 °C	0.791
Isopropyl Alcohol	82.4 °C	11.7 °C	0.786
1- Propanol	97.2 °C	15 °C	0.803
1-Butanol	117 – 118 °C	36 – 38 °C	0.809
t-Butanol	82.41 °C	11.1 °C	0.780
Ethyl Acetate	77 °C	- 5.0 °C	0.897
Methyl Ethyl Ketone	79.6 °C	- 6.0 °C	0.804
Water	100 °C	none	0.998

3.2 EVALUATION CRITERIA FOR ALTERNATE SOLVENT SYSTEM FOR REPLACEMENT OF METHYLENE DICHLORIDE

Performance of the alternative solvent will be compared to reference system based upon the following evaluation criteria.



EVALUATION OF SOLUTION / DISPERSION OF THE POLYMER

- **Appearance**

  The overall appearance of solution / dispersion depends primarily on their clarity and color.

- **Viscosity**

  Measurement of viscosity involves the use of the Brookfield viscometer. The spindle is made to descend slowly into the suspension, and the dial reading on the viscometer is then a measure of the resistance the spindle meets at various levels in sediment. The resistance to the rotation of the cone produces a torque that is proportional to the shear stress in the fluid. This reading is easily converted to absolute centipoises units. (12)

EVALUATION OF CASTED FILMS

PHYSICAL PROPERTIES:

- **Appearance**: Appearance of the film includes clarity, color, surface or texture.
- **Thickness**: Thickness of the film is measured with a micrometer or vernier caliper.

MECHANICAL PROPERTIES:

- **TENSILE STRENGTH**

  Tensile strength indicates strength of the film. A tensile test is a fundamental mechanical test where a carefully prepared specimen is loaded in a very controlled manner while measuring the applied load and the elongation of the specimen over some distance. It consists of a free film strip that is placed between two grips and then stretched at a constant rate until the film fractures. Tensile properties indicate how the material will react to forces being applied in tension. (20) The tensile testing machine pulls the sample from both ends and measures the force required to pull the specimen apart and how much the sample stretches before breaking. Films of size 7 × 3 cm^2 and free of physical

imperfections should be held between two clamps held 3 cm apart. The 7 × 3 cm^2 dimension is to be selected because it is the minimum size required for sample testing on the machine. Tensile strength is measured in units of force per unit area. The unit is Newton per square meter (N/m^2), kilogram (force) per square centimeter (kg/cm^2) or pounds per square inch (PSI).

$$\textbf{Tensile Strength } (N/cm^2) = \frac{\textbf{Force at break (N)}}{\textbf{Initial cross sectional area of the film } (cm^2)}$$

- **PERCENT ELONGATION**

% elongation is the percentage increase in length that occurs before it breaks under tension. When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases. (21)

$$\textbf{\% Elongation} = \frac{\textbf{Increase in length of film x 100}}{\textbf{Initial length of the film}}$$

- **FOLDING ENDURANCE**

Folding endurance is determined by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking is the folding endurance value. (22)

EVALUATION OF THE FINAL PRODUCT

PHYSICAL CRITERIAS

- **Appearance**

The general appearance of finished product of a tablet, its visual identity & overall elegance is essential for consumer acceptance. The general appearance of tablet involves the measurement of a number of attributes such as tablet's

size, shape, color, presence or absence of an odor, taste, surface texture, concavity, physical flaws & legibility of any identifying markings. (12)

- **Thickness**

Thickness of individual tablets is measured with a micrometer or caliper in millimeter. Tablet thickness should be controlled within a ± 5% variation of a standard value. (12)

- **Hardness (Crushing strength)**

Tablets require a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacturing, packaging and shipping. Hardness of the final product is to be checked in erweka hardness tester. In this hardness tester stepper motor drives the test jaw against the sample with constant speed and the resulting force applied to break the tablet is registered by a calibrated electronic load cell.

- **Disintegration Time**

Breakdown of the tablet into smaller particles or granules is known as disintegration. The USP device to test disintegration uses 6 glass tubes, open at the top and held against a 10 mesh screen at the bottom end of the basket rack assembly. To test for disintegration time, one tablet is placed in each tube, and the basket rack is positioned in a 1 L beaker of water at 37 °C ± 2 °C. Time required to pass all the particles from 10 mesh screen is noted down. (23, 24, 25)

Disintegration time for the different type of tablet dosage forms specified in various pharmacopeias is as below in the table no 5

Table 5

Type of tablet	United State Pharmacopoeia (USP)	European Pharmacopoeia (E.P)	Indian Pharmacopoeia (I.P)
Uncoated tablet	Most uncoated tablets should dissolve within 30 min otherwise time specified in individual monograph	15 min	15 min
Film coated tablet	Time specified in the individual monograph.	30 min	30 min
Other than film coated tablet	N/A	60 min	60 min
Enteric coated tablet	Should not disintegrate within one hour in simulated gastric fluid, after one hour it should be disintegrate in simulated intestinal fluid within time specified in the individual monograph	Should remain intact in 0.1 M HCl for 2 hours and should disintegrate in phosphate buffer pH 6.8 within 1 hour	Should remain intact in 0.1 M HCl for 2 hours and should disintegrate in phosphate buffer pH 6.8 within 1 hour
Dispersible tablet	N/A	3 min.	3 min.
Effervescent tablet	N/A	5 min.	5min.
Soluble tablet	N/A	3 min.	3 min.

CHEMICAL CRITERIAS

- **Assay**

  It is a method to analyze or quantify a substance in a sample. This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia

- **Degradation products**

  Impurities in pharmaceuticals are the unwanted chemicals that remain with the active pharmaceutical ingredients (APIs), or develop during formulation, or upon aging of both API and formulated APIs to medicines. The presence of these unwanted chemicals even in small amounts may influence the efficacy and safety of the pharmaceutical products. (26)

- **Dissolution**

  Tablet Dissolution is a standardized method for measuring the rate of drug release from a dosage form. Place the stated volume of the dissolution medium in the vessel assemble the apparatus; equilibrate the dissolution medium to 37 ± 0.5 ° C. Place one tablet or one capsule in the apparatus and immediately operate the apparatus at the rate specified in the individual monograph. Within a time interval specified, withdraw a specimen from a zone midway between the surface of the dissolution medium.

- Dissolution testing of an enteric coated dosage form consists of two phases. First dissolution is performed in an acidic medium (0.1 N HCl) that mimics the conditions in the stomach. Subsequently the same dosage is taken to a buffered dissolution medium (e.g. pH 6.8 phosphate buffer) to simulate the environment in the intestine. (12)

- **Residual solvent**

  Residual solvents are typically determined using chromatographic techniques such as gas chromatography. If only Class 3 solvents are present, a nonspecific method such as loss on drying may be used. (13)

- **Stability**

  Stability testing is required to demonstrate that a pharmaceutical product meets its acceptance criteria throughout its shelf life and to gain regulatory approval for commercialization. The purpose of stability testing is to provide

evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions. In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use. (27)

Table 6

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

***** It is up to the applicant to decide whether long term stability studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH

** If 30°C ± 2°C/65% RH ± 5% RH is the long term condition, there is no intermediate condition

LITERATURE REVIEW

4. LITERATURE REVIEW

4.1 REVIEW OF WORK DONE

J. S. Boateng (31) et al has prepared solvent-cast films from three polymers, carboxymethylcellulose (CMC), sodium alginate (SA), and xanthan gum, by drying the polymeric gels in air. Three methods, (a) passive hydration, (b) vortex hydration with heating, and (c) cold hydration, were investigated to determine the most effective means of preparing gels for each of the three polymers. Different drying conditions [relative humidity - RH (6-52%) and temperature (3-45°C)] were investigated to determine the effect of drying rate on the films prepared by drying the polymeric gels. The tensile properties of the CMC films were determined by stretching dumbbell-shaped films to breaking point, using a Texture Analyzer. Glycerol was used as a plasticizer, and its effects on the drying rate, physical appearance, and tensile properties of the resulting films were investigated. Vortex hydration with heating was the method of choice for preparing gels of SA and CMC, and cold hydration for xanthan gels. Drying rates increased with low glycerol content, high temperature, and low relative humidity. The residual water content of the films increased with increasing glycerol content and high relative humidity and decreased at higher temperatures. Generally, temperature affected the drying rate to a greater extent than relative humidity. Glycerol significantly affected the toughness (increased) and rigidity (decreased) of CMC films. CMC films prepared at 45°C and 6% RH produced suitable films at the fastest rate while films containing equal quantities of glycerol and CMC possessed an ideal balance between flexibility and rigidity.

R Hyppolaa (32) et al has prepared ethyl cellulose films plasticized with 0, 10 and 20% of five different plasticizers. The films were cast into teflon molds from ethanol solution. The plasticizers used were: dibutyl sebacate, triethyl citrate, triacetin, Myvacet (acetylated monoglycerides) and diethyl phthalate. The physical properties of the films were evaluated using thermal analysis, tensile testing, porosimetry, scanning electron microscopy and hot stage microscopy. The results reported are glass transition temperature, tensile stress, percentage elongation at break, elastic modulus,

total volume of pores, total surface area of pores and mean and median diameters of pores. On the basis of tensile tests and thermal analysis, dibutyl sebacate and MyvacetE were found to be the two most efficient plasticizers for ethyl cellulose films cast from ethanol solution.

S Obara (33) et al has investigated a spray method for the preparation of free films from aqueous polymeric dispersions. Free films were prepared from aqueous dispersions of methacrylic acid.ethyl methacrylate copolymer (Eudragit L 30D). hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), and ethyl cellulose (EC) by a spray method and a cast method, and their mechanical properties and reproducibility were investigated. Uniform films were obtained from the dispersions of Eudragit L 30D, HPMCAS, and EC by the spray method, but films could not be formed by spraying the CAP dispersion. The tensile strength, elongation, and elastic modulus of the sprayed Eudragit L 30D films were similar to the properties of the cast films, and good reproducibility was obtained from both methods. Marked within-run variation in the mechanical properties was observed for the cast HPMCAS and CAP films, which could be due to a settling of the solid particles during the drying step. The variation in the mechanical properties of the sprayed HPMCAS films was lower and the tensile strength significantly higher than that of the cast films. There were also significant differences in tensile strength and elongation of EC films between products of the two methods. The results indicated that the spray method used to prepare the free films from aqueous polymeric dispersions provided uniform films with consistent and reproducible properties.

L A. Felton (34) et al has determined certain properties of the polymer films may be as a method to evaluate coating formulations, substrate variables, and processing conditions. Author also described experimental techniques to assess various properties of both free and applied films, including water vapor and oxygen permeability, as well as thermal, mechanical, and adhesive characteristics. Methods to investigate interfacial interactions were also presented.

S Missaghi (35) et al have evaluated the nature of film formation on tablets with different compositions, using con-focal laser scanning microscopy (CLSM), and to measure film adhesion via the application of a novel “magnet probe test.” Three

excipients, microcrystalline cellulose (MCC), spray-dried lactose monohydrate, and dibasic calcium phos-phate dihydrate, were individually blended with 0.5% magnesium stearate, as a lubricant, and 2.5% tetracycline HCl, as a fluorescent marker, and were compressed using a Carver press. Tablets were coated with a solution consisting of 7% hydroxypropyl methylcellulose (HPMC) phthalate (HP-55), and 0.5% cetyl alcohol in acetone and isopropanol (11:9). The nature of polymer interaction with the tablets and coating was evaluated using CLSM and a designed magnet probe test. CLSM images clearly showed coating efficiency, thickness, and uniformity of film formation, and the extent of drug migration into the film at the coating interfaces of tablets. Among the excipients, MCC demonstrated the best interface for both film formation and uniformity in thickness relative to lactose monohydrate and dibasic calcium phosphate dihydrate. The detachment force of the coating layers from the tablet surfaces, as measured with the developed magnet probe test, was in the order of MCC > lactose monohydrate > dibasic calcium phosphate dihydrate. It was also shown that the designed magnet probe test provides reliable and reproducible results when used for measurement of film adhesion and bonding strength.

H C. Haas (36) et al have investigated the properties of ethyl cellulose films prepared by casting on glass from a limited number of different solvents. It was appeared that the solvent power of a given solvent for ethyl cellulose may be the prime factor which determines film properties in essentially amorphous polymers of this type. It has been found that thermodynamically poorer solvents for ethyl cellulose lead to films of higher birefringence, higher densities, lower brittle-point temperatures, and in general greater toughness. Modulus of flexure and the softening point appear to be relatively independent of solvent composition. A simple theory has been proposed to correlate solvent power and cross-section birefringence. More random modifications of ethyl cellulose films have been obtained by annealing glass casts. These annealed films have lower moduli and lower brittle-point temperatures, and the long-range high birefringence of glass casts has disappeared. An exceedingly low brittle-point temperature has been obtained by annealing films cast from benzene on glass. Essentially isotropic films prepared on a non rigid surface, i.e. mercury, also have lower moduli than glass casts, and a considerable change in the stress-elongation

curve has been observed, a decrease in yield stress and tensile strength being accompanied by more than a twofold increase in elongation. The noticeable effect of solvent composition on film properties when films are prepared on rigid casting surfaces largely disappeared when films were prepared on mercury. Lower brittle-point temperatures appear to be associated with the more isotropic films obtained by annealing or by casting on mercury.

N H. Parikh (37) et al have prepared free films of two commercially available formulations of aqueous ethylcellulose dispersion differing only in plasticizer content (Surelease/E-7-7050 without silica and E-7-7060 containing dibutyl sebacate and glyceryl tricaprylate/caprate as plasticizers, respectively) and coalesced at temperatures ranging between 30 and 70°C. Mechanical properties of these films were measured using tensile stress analysis. Three mechanical parameters, namely, tensile strength, work of failure, and elastic modulus, were computed from the load-time profiles of these films. The results showed that the tensile strength and elastic modulus values of the films cast from both formulations increased with the corresponding increase in coalescence temperature up to 60°C, beyond which no significant differences were observed. In the case of work of failure, however, the difference between the two formulations was observed above 60°C. The films cast from Surelease/E-7-7050 formulation without silica (dibutyl sebacate as the plasticizer) were relatively softer than those from Surelease/E-7-7060 formulation (glyceryl tricaprylate/caprate as the plasticizer). At coalescence temperatures above 50°C, the films cast from both formulations exhibited temperature-dependent plastic deformation.

S Obara (38) et al have reported a novel method for the preparation of free films from aqueous polymeric dispersions by a spray technique. The apparatus included a spray gun, rotary drum and a temperature controlling system. The influence of spray rate and processing temperature on the mechanical properties of free films prepared from aqueous dispersions of Eudragit© L 30D-55, and L 100-55 (methacrylic acid-ethyl acrylate copolymer), Shin-Etsu AQOAT® (hydroxypropyl methylcellulose acetate succinate), Aquateric® (cellulose acetate phthalate) and Aquacoat® (ethyl cellulose), plasticized with triethyl citrate, was investigated. The processing

temperature was monitored using a telemetric system. Reproducible free films were obtained from the five polymers using this apparatus. The tensile strength and elongation of films of the two Eudragit® latex dispersions, having a minimum film formation temperature (MFT) less than 20°C, were not influenced by spray rate or processing temperature between 30 and 40°C. The mechanical values of free films from Shin-Etsu AQOAT® were significantly decreased at a slower spray rate, but processing temperature did not affect film properties. This polymeric dispersion contained larger particles than the acrylic dispersions and the free films had a low MFT. The Aquateric® dispersion, having a high MFT, contained larger particles than the acrylic latexes and produced films at high spray rates and slow drying conditions. The drying temperature significantly influenced the elongation properties of the films. The mean tensile strength of free films from Aquacoat®, high-MFT latex, was slightly higher at higher processing temperature, but this was not significant. The spray rate did not alter the mechanical properties of films prepared from this pseudo latex.

4.2 POLYMER PROFILE (16)

1. Hydroxy propyl methylcellulose (HPMC)

Nonproprietary Names

• BP: Hypromellose

• JP: Hydroxypropylmethylcellulose

• PhEur: Hypromellosum

• USP: Hypromellose

Synonyms

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

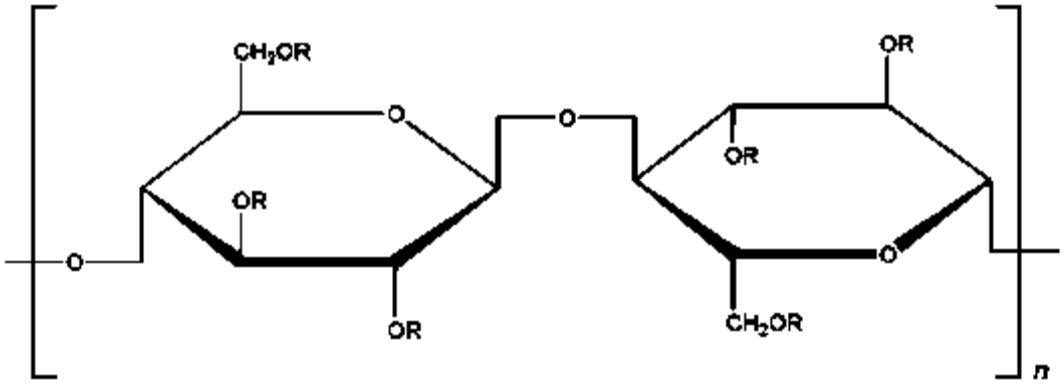
Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

Empirical Formula and Molecular Weight

The PhEur 2005 describes hypromellose as a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hypromellose defined in the USP 28 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH_2CH (OH) CH_3), calculated on a dried basis. It contains methoxy and hydroxypropoxy groups. Molecular weight is approximately 10,000–1,500,000. The JP 2001 includes three separate monographs for hypromellose: hydroxypropylmethylcellulose 2208, 2906, and 2910, respectively.

Structural Formula



where R is H, CH_3, or $CH_3CH(OH)CH_2$

Functional Category

- Coating agent
- Film-former
- Rate-controlling polymer for sustained release
- Stabilizing agent
- Suspending agent
- Tablet binder
- Viscosity-increasing agent

Applications in Pharmaceutical Formulation or Technology

- Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes.
- High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.
- Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are

used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Examples of film coating materials that are commercially available include *AnyCoat C*, *Spectracel*, and *Pharmacoat*.

- Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.
- Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.
- In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

Solubility:

Soluble in cold water, practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Specific gravity:

1.26

Viscosity (dynamic):

A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous Hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions

Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage. However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative: when hypromellose is used as a viscosity increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, Hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

2. Hypromellose Phthalate

Nonproprietary Names

• BP: Hypromellose phthalate

• JP: Hydroxypropylmethylcellulose phthalate

• PhEur: Hypromellosi phthalas

• USPNF: Hypromellose phthalate

Synonyms

Cellulose phthalate hydroxypropyl methyl ether; HPMCP; hydroxypropyl methylcellulose benzene-1, 2-dicarboxylate; 2-hydroxypropyl methylcellulose phthalate; methyl hydroxyl propyl cellulose phthalate.

Chemical Name and CAS Registry Number

Cellulose, hydrogen 1, 2-benzenedicarboxylate, 2-hydroxypropyl methyl ether [9050-31-1]

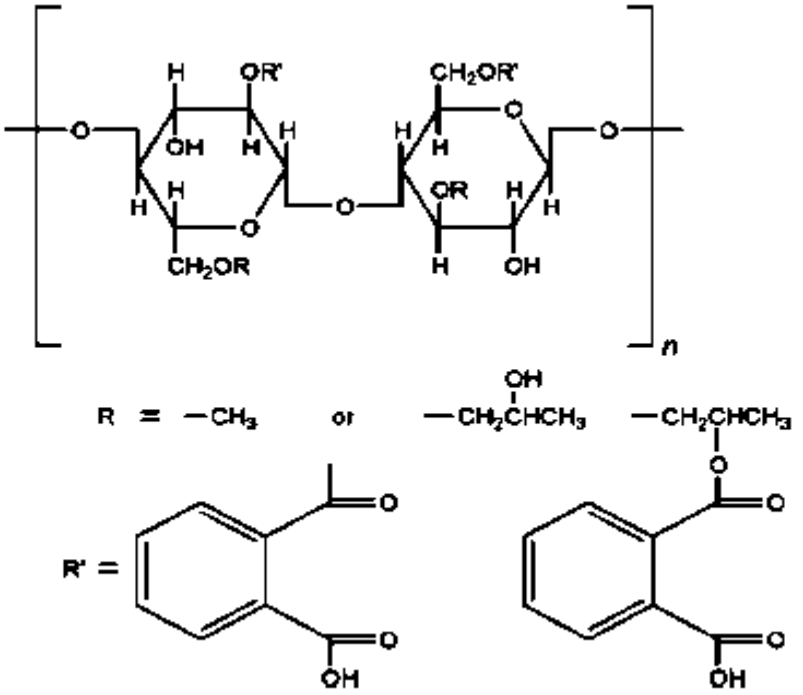
Empirical Formula and Molecular Weight

Hypromellose phthalate is cellulose in which some of the hydroxyl groups are replaced with methyl ethers, 2-hydroxypropyl ethers, or phthalyl esters. Several different types of hypromellose phthalate are commercially available with molecular weights in the range 20 000–200 000. Typical average values are 80 000–130 000.

Table 7: Molecular weight of various grades of HPMC Phthalate

Grades	**HP – 50**	**HP – 55**	**HP – 55S**
Mol. weight	84,000	78,000	1,32,000

Structural Formula



Functional Category: Coating agent

Applications in Pharmaceutical Formulation or Technology

- Hypromellose phthalate is widely used in oral pharmaceutical formulations as an enteric coating material for tablets or granules. Hypromellose phthalate is insoluble in gastric fluid but will swell and dissolve rapidly in the upper intestine. Generally, concentrations of 5–10% of hypromellose phthalate are employed with the material being dissolved in either a dichloromethane: ethanol (50: 50) or an ethanol: water (80: 20) solvent mixture.
- Hypromellose phthalate can normally be applied to tablets and granules without the addition of a plasticizer or other film formers, using established coating techniques. However, the addition of a small amount of plasticizer or water can avoid film cracking problems; many commonly used plasticizers, such as diacetin, triacetin, diethyl and dibutyl phthalate, castor oil, acetyl

monoglyceride, and polyethylene glycols, are compatible with hypromellose phthalate. Tablets coated with hypromellose phthalate disintegrate more rapidly than tablets coated with cellulose acetate phthalate.

- Hypromellose phthalate can be applied to tablet surfaces using a dispersion of the micronized hypromellose phthalate powder in an aqueous dispersion of a suitable plasticizer such as triacetin, triethyl citrate, or diethyl tartrate along with a wetting agent.
- Hypromellose phthalate may be used alone or in combination with other soluble or insoluble binders in the preparation of granules with sustained drug-release properties; the release rate is pH-dependent. Since hypromellose phthalate is tasteless and insoluble in saliva, it can also be used as a coating to mask the unpleasant taste of some tablet formulations.
- Hypromellose phthalate has also been co-precipitated with a poorly soluble drug to improve dissolution characteristics.

Description

Hypromellose phthalate occurs as white to slightly off-white, free-flowing flakes or as a granular powder. It is odorless or with a slightly acidic odor and has a barely detectable taste.

Melting point: 150°C

Glass transition temperature: Glass transition temperature is 137°C for HP-50 and 133°C for HP-55.

Moisture content:

Hypromellose phthalate is hygroscopic; it takes up 2–5% of moisture at ambient temperature and humidity conditions.

Solubility:

Readily soluble in a mixture of acetone and methyl or ethyl alcohol (1: 1), in a mixture of methyl alcohol and dichloromethane (1: 1), and in aqueous alkali. Practically insoluble in water, dehydrated alcohol and very slightly soluble in acetone.

The solubility of the *HP-50* and *HP-55* grades, in various solvents and solvent mixtures, are shown in table

Table 8:

SOLVENT	**HP 50**	**HP 55**
Acetone	S/I	S
Acetone: ethanol (1:1)	S/S	S
Acetone: methanol	S	S
Acetone: 2 propanol	S/S	S
Acetone: water	S	S
Acetone: dichloromethane	S/I	S
Ethyl acetate : methanol	S	S
Ethyl acetate : ethanol	S/S	S
Ethyl acetate : 2 propanol	S/I	S
Dichloromethane	S/I	S/I
Dichloromethane : ethanol	S	S
Dichloromethane : methanol	S	S
Dichloromethane : 2-propanol	S/S	S
Ethanol (95%)	S/I	S/I
Methanol	S/I	S/I
Propan-2-ol	X	S/I

S = SOLUBLE, CLEAR SOLUTION

S/S = SLIGHTLY SOLUBLE, CLOUDY SOLUTION

S/I = SWELLS BUT INSOLUBLE

X = INSOLUBLE

Stability and Storage Conditions

Hypromellose phthalate is chemically and physically stable at ambient temperature for at least 3–4 years and for 2–3 months at 40°C and 75% relative humidity. It is stable on exposure to UV light for up to 3 months at 25°C and 70% relative humidity. Drums stored in a cool, dry place should be brought to room temperature before opening to prevent condensation of moisture on inside surfaces. After 10 days at 60°C and 100% relative humidity, 8–9% of carbyoxybenzoyl group were hydrolyzed. In general, hypromellose phthalate is more stable than cellulose acetate phthalate. At ambient storage conditions, hypromellose phthalate is not susceptible to microbial attack.

Incompatibilities

Incompatible with strong oxidizing agents. Splitting of film coatings has been reported rarely, most notably with coated tablets that contain microcrystalline cellulose and calcium carboxymethylcellulose. Film splitting has also occurred when a mixture of acetone: propan-2-ol or dichloromethane: propan-2-ol has been used as the coating solvent, or when coatings have been applied in conditions of low temperature and humidity. However, film splitting may be avoided by careful selection of formulation composition, including solvent, by use of a higher molecular weight grade of polymer, or by suitable selection of plasticizer. The addition of more than about 10% titanium dioxide to a coating solution of hypromellose phthalate, which is used to produce a colored film coating, may result in coating with decreased elasticity and resistance to gastric fluid.

3. ETHYL CELLULOSE

Nonproprietary Names

• BP: Ethylcellulose

• PhEur: Ethylcellulosum

• USPNF: Ethylcellulose

Synonyms

Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

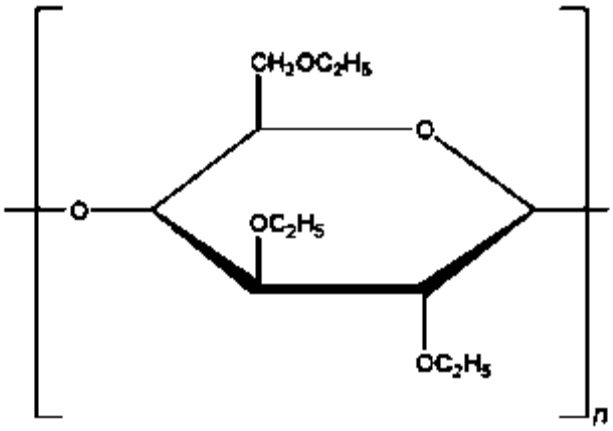
Chemical Name and CAS Registry Number

Cellulose ethyl ether [9004-57-3]

Empirical Formula and Molecular Weight

Ethyl cellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}O_6$ ($C_{12}H_{22}O_5$) *nC12H23O5* where *n* can vary to provide a wide variety of molecular weights. Ethyl cellulose, an ethyl ether of cellulose, is a long-chain polymer of β- anhydroglucose units joined together by acetal linkages.

Structural Formula



Functional Category

- Coating agent
- Flavoring fixative
- Tablet binder
- Tablet filler
- Viscosity-increasing agent

Applications in Pharmaceutical Formulation or Technology

- Ethyl cellulose is widely used in oral and topical pharmaceutical formulations; the main use of ethyl cellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethyl cellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethyl cellulose as a matrix former.

- Ethyl cellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethyl cellulose grades tend to produce stronger and more durable films. Ethyl cellulose films may be modified to alter their solubility, by the addition of hypromellose or a plasticizer; An aqueous polymer dispersion (or latex) of ethyl cellulose such as *Aquacoat ECD* (FMC Biopolymer) or *Surelease* (Colorcon) may also be used to produce ethyl cellulose films without the need for organic solvents.

- Drug release through ethyl cellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those instances, aqueous ethyl cellulose dispersions are generally used to coat granules or pellets. Ethyl cellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression.

- High-viscosity grades of ethyl cellulose are used in drug microencapsulation. Release of a drug from an ethyl cellulose microcapsule is a function of the microcapsule wall thickness and surface area.

- In tablet formulations, ethyl cellulose may additionally be employed as a binder, the ethyl cellulose being blended dry or wet-granulated with a solvent such as ethanol (95%). Ethyl cellulose produces hard tablets with low friability, although they may demonstrate poor dissolution.

- Ethyl cellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances.

- In topical formulations, ethyl cellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used. Ethyl cellulose has been studied as a stabilizer for emulsions.

- Ethyl cellulose is additionally used in cosmetics and food products.

Description

Ethyl cellulose is a tasteless, free-flowing, and white to light tan-colored powder.

Glass transition temperature:

129–133°C

Moisture content:

Ethyl cellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily.

Solubility:

Ethyl cellulose is practically insoluble in glycerin, propylene glycol, and water. Ethyl cellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%).

Ethyl cellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

Specific gravity:
1.12–1.15 g/cm^3

Viscosity:

The viscosity of ethyl cellulose is measured typically at 25°C using 5% w/v ethyl cellulose dissolved in a solvent blend of 80% toluene: 20% ethanol (w/w). They may be used to produce 5% w/v solutions in organic solvent blends with viscosities nominally ranging from 7 to 100 mPa s (7–100 cP). Specific Ethyl cellulose grades, or blends of different grades, may be used to obtain solutions of a desired viscosity. Solutions of higher viscosity tend to be composed of longer polymer chains and produce strong and durable films. The viscosity of an Ethyl cellulose solution increases with an increase in Ethyl cellulose concentration; e.g. the viscosity of a 5% w/v solution of *Ethocel Standard 4 Premium* is 4 mPa s (4 cP) and of a 25% w/v solution of the same Ethyl cellulose grade is 850 mPa s (850 cP). Solutions with a lower viscosity may be obtained by incorporating a higher percentage (30–40%) of a low-molecular-weight aliphatic alcohol such as ethanol, butanol, propan-2-ol, or *n*-butanol with toluene. The viscosity of such solutions depends almost entirely on the alcohol content and is independent of toluene.

Stability and Storage Conditions

Ethyl cellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters. Ethyl cellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230–340 nm range. Ethyl cellulose should be stored at a temperature not exceeding 32°C (90°F) in a dry area away from all sources of heat.

Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

4. Polymethacrylates

Nonproprietary Names

• **BP**: Methacrylic acid–ethyl acrylate copolymer (1: 1)

• **PhEur**: Acidum methacrylicum et ethylis acrylas polymerisatum 1: 1

Acidum methacrylicum et ethylis acrylas polymerisatum 1: 1 dispersio 30 per centum

Acidum methacrylicum et methylis methacrylas polymerisatum 1: 1

Acidum methacrylicum et methylis methacrylas polymerisatum 1: 2

Copolymerum methacrylatis butylati basicum

Polyacrylatis dispersion 30 per centum

• **USPNF**: Ammonio methacrylate copolymer

Methacrylic acid copolymer

Methacrylic acid copolymer dispersion

Synonyms

Acryl-EZE; Acryl-EZE MP; Eastacryl 30D; Eudragit; Kollicoat MAE 30 D; Kollicoat MAE 30 DP; polymeric methacrylates.

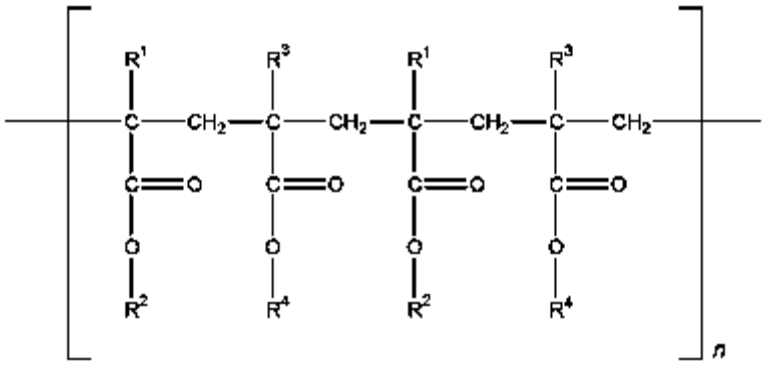
Table 9: Chemical Name and CAS Registry Number of Polymethacrylates

Chemical name	Trade name	CAS number	Applications
Poly(butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate) 1 : 2 : 1	Eudragit E100 Eudragit E12.5 Eudragit EPO	[24938-16-7]	Film coating
Poly(ethyl acrylate, methyl methacrylate) 2 : 1	Eudragit NE30 D Eudragit NE40 D	[9010-88-2]	Sustained release, tablet matrix
Poly(methacrylic acid, methyl methacrylate) 1 : 1	Eudragit L100 Eudragit L12.5 Eudragit L12.5 P	[25806-15-1]	Enteric coating
Poly(methacrylic acid, ethyl acrylate) 1 : 1	Eudragit L 30D-55 Eudragit L100-55	[25212-88-8]	
Poly(methacrylic acid, methyl methacrylate) 1 : 2	Eudragit S100 Eudragit S12.5 Eudragit S12.5 P	[25086-15-1]	Enteric coating
Poly(methyl acrylate, methyl methacrylate, methacrylic acid) 7: 3:1	Eudragit FS 30D	[26936-24-3]	Enteric coating
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.2	Eudragit RL100 Eudragit RLPO Eudragit RL30 D Eudragit RL12.5 Eudragit RD100	[33434-24-1]	Sustained release
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1	Eudragit RS100 Eudragit RSPO Eudragit RS30 D Eudragit RS12.5	[33434-24-1]	Sustained release

Empirical Formula and Molecular Weight

- The PhEur 2005 describes methacrylic acid–ethyl acrylate copolymer (1: 1) as a copolymer of methacrylic acid and ethyl acrylate having a mean relative molecular mass of about 250, 000. The ratio of carboxylic groups to ester groups is about 1: 1. It may contain suitable surfactants such as sodium dodecyl sulfate or polysorbate 80.
- Methacrylic acid–methyl methacrylate copolymer (1 : 1) is described in the PhEur 2005 as a copolymer of methacrylic acid and methyl methacrylate having a mean relative molecular mass of about 135 000. The ratio of carboxylic acid to ester groups is about 1: 1. A further monograph in the PhEur 2005 describes methacrylic acid–methyl methacrylate copolymer (1: 2), where the ratio of carboxylic acid to ester groups is about 1: 2.
- The PhEur 2005 describes basic butylated methyacrylate copolymer as a copolymer of (2-dimethylaminoethyl) methacrylate, butyl methyacrylate, and methyl methacrylate having a mean relative molecular mass of about 150 000. The ratio of (2-dimethylaminoethyl) methacrylate groups to butyl methyacrylate and methyl methacrylate groups is about 2: 1:1. Polyacrylate dispersion (30 per cent) is described in the PhEur 2005 as a dispersion in water of a copolymer of ethyl acrylate and methyl methacrylate having a mean relative molecular mass of about 800 000. It may contain a suitable emulsifier.
- The USPNF 23 describes methacrylic acid copolymer as a fully polymerized copolymer of methacrylic acid and an acrylic or methacrylic ester. Three types of copolymers, namely Type A, Type B, and Type C, are defined in the monograph. They vary in their methacrylic acid content and solution viscosity. Type C may contain suitable surface-active agents. Two additional polymers, Type A (*Eudragit RL*) and Type B (*Eudragit RS*), also referred to as ammonio methacrylate copolymers, consisting of fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, are also described in the USPNF 23. A further monograph for an aqueous dispersion of Type C methacrylic acid copolymer is also defined; typically, the molecular weight of the polymer is ≥100 000.

Structural Formula



For Eudragit E:

R1, R3 = CH_3

R2 = $CH_2CH_2N\ (CH_3)_2$

R4 = CH_3, C_4H_9

For Eudragit L and Eudragit S:

R1, R3 = CH_3

R2 = H

R4 = CH_3

For Eudragit FS:

R1 = H

R2 = H, CH_3

R3 = CH_3

R 4 = CH_3

For Eudragit RL and Eudragit RS:

R1 = H, CH_3

R2 = CH_3, C_2H_5

R3 = CH_3

R4 = $CH_2CH_2N\ (CH_3)_3^+\ Cl^-$

For Eudragit NE 30 D and Eudragit NE 40 D:

R1, R3 = H, CH_3

R2, R4 = CH_3, C_2H_5

Table 10: COMPARISION OF PROPERTIES OF DIFFERENT GRADES OF EUDRAGIT

Type	Supply form	Recommended solvents or diluents	Solubility/permeability
Eudragit E12.5	Organic solution	Acetone, alcohols	Soluble in gastric fluid to pH 5
Eudragit E100	Granules	Acetone, alcohols	Soluble in gastric fluid to pH 5
Eudragit EPO	Powder	Acetone, alcohols	Soluble in gastric fluid to pH 5
Eudragit L12.5 P	Organic solution	Acetone, alcohols	Soluble in intestinal fluid from pH 6
Eudragit L12.5	Organic solution	Acetone, alcohols	Soluble in intestinal fluid from pH 6
Eudragit L100	Powder	Acetone, alcohols	Soluble in intestinal fluid from pH 6
Eudragit L100-55	Powder	Acetone, alcohols	Soluble in intestinal fluid from pH 5.5
Eudragit L30 D-55	Aqueous dispersion	Water	Soluble in intestinal fluid from pH 5.5
Eudragit S12.5 P	Organic solution	Acetone, alcohols	Soluble in intestinal fluid from pH 7
Eudragit S12.5	Organic solution	Acetone, alcohols	Soluble in intestinal fluid from pH 7
Eudragit S100	Powder	Acetone, alcohols	Soluble in intestinal fluid from pH 7
Eudragit FS 30D	Aqueous dispersion	Water	Soluble in intestinal fluid from pH 7
Eudragit RL 12.5	Organic solution	Acetone, alcohols	High permeability
Eudragit RL 100	Granules	Acetone, alcohols	High permeability
Eudragit RL PO	Powder	Acetone, alcohols	High permeability
Eudragit RL 30 D	Aqueous dispersion	Water	High permeability
Eudragit RS 12.5	Organic solution	Acetone, alcohols	Low permeability
Eudragit RS 100	Granules	Acetone, alcohols	Low permeability
Eudragit RS PO	Powder	Acetone, alcohols	Low permeability
Eudragit RS 30 D	Aqueous dispersion	Water	Low permeability

Table 11: Solubility of commercially available polymethacrylates in various solvents

Type	Acetone & alcohol	MDC	Ethyl acetate	1 N HCl	1 N NaOH	Water
Eudragit E 12.5	M	M	M	M	-	-
Eudragit E 100	S	S	S	-	-	I
Eudragit L 12.5P	M	M	M	-	M	P
Eudragit L 12.5	M	M	M	-	M	P
Eudragit L 100 – 55	S	I	I	-	S	I
Eudragit L 100	S	I	I	-	S	I
Eudragit L 30 D – 55	M	-	-	M	-	-
Eudragit S 12.5 P	M	M	M	—	M	P
Eudragit S 12.5	M	M	M	—	M	P
Eudragit S 100	S	I	I	—	S	I
Eudragit RL 12.5	M	M	M	—	—	M
Eudragit RL 100	S	S	S	—	—	I
Eudragit RL PO	S	S	S	—	I	I
Eudragit RL 30 D	M	M	M	—	I	M
Eudragit RS 12.5	M	M	M	—	—	M
Eudragit RS 100	S	S	S	—	—	I
Eudragit RS PO	S	S	S	—	I	I
Eudragit RS 30 D	M	M	M	—	I	M

S = SOLUBLE, I = INSOLUBLE, M = MISCIBLE, P = PRECIPITATES

Functional Category:

- Film former;
- Tablet binder;
- Tablet diluent.

Viscosity (dynamic):

• 3–12 mPa s for *Eudragit E*;

• ≤50 mPa s for *Eudragit NE 30D*;

• 50–200 mPa s for *Eudragit L* and *S*;

• ≤20 mPa s for *Eudragit FS 30D*;

• ≤15 mPa s for *Eudragit L 30 D-55*;

• 100–200 mPa s for *Eudragit L 100-55*;

• ≤15 mPa s for *Eudragit RL* and *RS*;

• ≤200 mPa s for *Eudragit RL* and *RS 30D*;

Stability and Storage Conditions

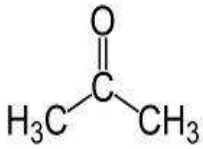
Dry powder polymer forms are stable at temperatures less than 30°C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can readily be broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30°C. Dispersions are sensitive to extreme temperatures and phase separation occurs below 0°C. Dispersions should therefore be stored at temperatures between 5 and 25°C and are stable for at least 18 months after shipping from the manufacturer's warehouse if stored in a tightly closed container at the above conditions.

Incompatibilities

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature; For example, dispersions of *Eudragit L 30 D*, *RL 30 D*, *L 100-55*, and *RS 30 D* are incompatible with magnesium stearate.

4.3 ALTERNATIVE SOLVENT PROFILE (16)

1. ACETONE

CHEMICAL NAME:	2- propanone
SYNONYMS:	Dimethyl formaldehyde, dimethyl ketone, β keto propane
MOL.FORMULA:	C_3H_6O
STRUCTURAL FORMULA:	
MOL.WEIGHT:	58.08
CAS NO.:	67 – 64 – 1
DESCRIPTION:	Colorless, volatile, flammable, transparent liquid with a sweetish odor & pungent sweetish taste
BOILING POINT:	56.2 °C
FLASH POINT:	- 20 °C
SOLUBILITY:	Miscible with water, DMF, choloroform. Freely soluble in ethanol (95%)
VAPOUR PRESSURE:	185 mmHg at 20 °C

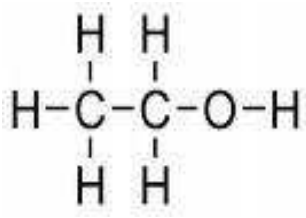
2. ETHANOL

CHEMICAL NAME: Ethanol

SYNONYMS: Ethyl alcohol, ethyl hydroxide, methyl carbinol

MOL.FORMULA: C_2H_6O

STRUCTURAL FORMULA:



MOL.WEIGHT: 46.07

CAS NO.: 64 – 17 – 5

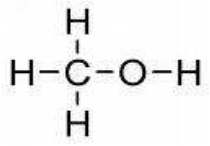
DESCRIPTION: Clear, Colorless, volatile, flammable, mobile liquid with a slight characteristic odor & burning taste

BOILING POINT: 78.15 °C

FLASH POINT: 14 °C

SOLUBILITY: Miscible with water, glycerin, chloroform, ether

3. METHANOL

CHEMICAL NAME:	Methanol
SYNONYMS:	Methyl alcohol, carbinol
MOL.FORMULA:	CH_4O
STRUCTURAL FORMULA:	
MOL.WEIGHT:	32.04
CAS NO.:	67 – 56 – 1
DESCRIPTION:	Clear, Colorless, volatile, flammable, poisonous, mobile liquid
BOILING POINT:	64.7 °C
FLASH POINT:	12 °C
SOLUBILITY:	Miscible with water, ethanol, benzene, Ketone, ether and most other organic solvents

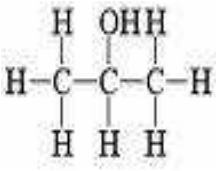
4. ISOPROPYL ALCOHOL

CHEMICAL NAME: Propan – 2 – ol

SYNONYMS: Isopropanol, IPA, 2 – propanol, dimethyl carbinol

MOL.FORMULA: C_3H_8O

STRUCTURAL FORMULA:



MOL.WEIGHT: 60.1

CAS NO.: 67 – 63 – 0

DESCRIPTION: Clear, colorless, mobile ,volatile, flammable liquid with a characteristic spirituous odor, slight bitter taste

BOILING POINT: 82.4 °C

FLASH POINT: 11.7 °C

VAPOUR PRESSURE: 32.4 mmHg at 20 °C

SOLUBILITY: Miscible with benzene, chloroform, ethanol, ether, glycerin and water

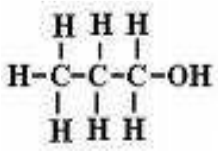
5. PROPANOL

CHEMICAL NAME: Propan – 1 – ol

SYNONYMS: propanol, n – propanol, propyl alcohol

MOL.FORMULA: C_3H_8O

STRUCTURAL FORMULA:



MOL.WEIGHT: 60.1

CAS NO.: 71 – 23 – 8

DESCRIPTION: Liquid, alcoholic and slightly stupefying odor

BOILING POINT: 97.2 °C

FLASH POINT: 15 °C

SOLUBILITY: Miscible with ethanol (95%), ether and water

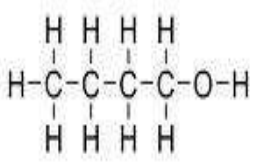
6. n- BUTYL ALCOHOL

CHEMICAL NAME: Butan – 1 – ol

SYNONYMS: Butyl alcohol, 1 – butanol, propyl carbinol

MOL.FORMULA: $C_4H_{10}O$

STRUCTURAL FORMULA:



MOL.WEIGHT: 74.12

CAS NO.: 71 – 36 – 3

DESCRIPTION: Colorless liquid

BOILING POINT: 117 – 118 °C

FLASH POINT: 36 – 38 °C

SOLUBILITY: Miscible with ethanol, ether and many other organic solvents

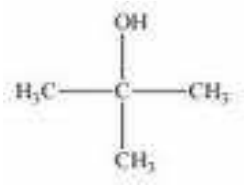
7. Tert- BUTYL ALCOHOL

CHEMICAL NAME: 2-Methylpropan-2-ol

SYNONYMS: 2 – methyl – 2 – propanol , trimethyl carbinol

MOL.FORMULA: $C_4H_{10}O$

STRUCTURAL FORMULA:



MOL.WEIGHT: 74.12

CAS NO.: 75 – 65 – 0

DESCRIPTION: Colorless liquid or white solid, depending on the ambient temperature

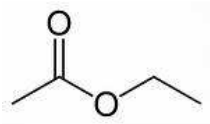
BOILING POINT: 82.41 °C

MELTING POINT: 25.6 °C

FLASH POINT: 11.1 °C

SOLUBILITY: Miscible with ethanol, ether and many other organic solvents

8. ETHYL ACETATE

CHEMICAL NAME:	Ethyl acetate
SYNONYMS:	Ethyl ethanoate, acetic ester, acetic acid ethyl ester
MOL.FORMULA:	$C_4H_8O_2$
STRUCTURAL FORMULA:	
MOL.WEIGHT:	88.1
CAS NO.:	141– 78 – 6
DESCRIPTION:	Clear, colorless, flammable volatile liquid with a pleasant fruity fragrant & slightly acetous odor
BOILING POINT:	77 °C
FLASH POINT:	- 5.0 °C
SOLUBILITY:	Soluble in 1 in 10 part of water at lower temperature than at higher temperature. Miscible with acetone, chloroform, DCM, ethanol and ether

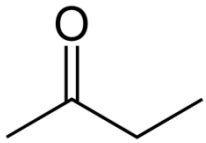
9. METHYL ETHYL KETONE

CHEMICAL NAME: Methyl ethyl ketone

SYNONYMS: 2 butanone, ethyl methyl ketone, MEK, 2 – oxobutane

MOL.FORMULA: C_4H_8O

STRUCTURAL FORMULA:



MOL.WEIGHT: 72.11

CAS NO.: 78 – 93 – 3

DESCRIPTION: Flammable liquid with acetone like odor

BOILING POINT: 79.6 °C

FLASH POINT: - 6.0 °C

SOLUBILITY: Soluble in ~ 4 parts of water, less soluble at higher temperature, Miscible with alcohol, ether, benzene

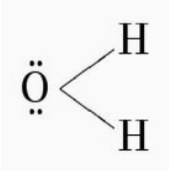
10. WATER

CHEMICAL NAME: Water

SYNONYMS: Aqua, hydrogen oxide

MOL.FORMULA: H_2O

STRUCTURAL FORMULA:



MOL.WEIGHT: 18.02

CAS NO.: 7732 – 18 – 5

DESCRIPTION: Clear, colorless, odorless & tasteless liquid

BOILING POINT: 100 °C

SURFACE TENSION: 71.97 dynes/ cm at 25 °C

SOLUBILITY: Miscible with most polar solvents

EXPERIMENTAL WORK

5. EXPERIMENTAL WORK

5.1 MATERIALS AND EQUIPMENTS:

Table 12: List of Materials

SR. No.	Name of Material	Mfr.	Function
1.	Microcrystalline cellulose pH 102	FMC	Diluent
2.	PVP K 30	ISP	Binder
3.	Directly compressible lactose DCL 11	DMV	Directly compressible diluents
4.	Magnesium stearate	Ferro	Lubricant
5.	Hydroxyl propyl methyl cellulose phthalate	Shin -Etsu	Enteric coating polymer
6.	Hypromellose 6cps	Shin-Etsu	Film coating polymer
7.	Ethyl cellulose 10 cps	Hercules Lab ltd	Film forming agent
8.	Eudragit RSPO	Evonik Rohm	Film forming agent
9.	Polyethylene glycol 400	Clarient	Plasticizer
10.	Polyethylene glycol 6000	Clarient	Plasticizer
11.	Tri ethyl citrate	Vertellus	Plasticizer
12.	Diethyl phthalate	Indo - NIP	Plasticizer
13.	Acetone	Finar	Solvent
14.	Isopropyl alcohol	Finar	Solvent
15.	Methanol	Finar	Solvent
16.	Methylene dichloride	Finar	Solvent
17.	Talc	Luzenac	Lubricant
18.	Titanium dioxide	KronosG	Opacifying agent
19.	Iron oxide yellow	Sensient	Colorant
20.	Iron oxide black	Sensient	Colorant
21.	Mercury	Rankem	Surface for film casting

Table 13: List of Equipments

SR. No.	Equipment	Manufactured by
1	Disintegration test apparatus	Electrolab
2	Vibrator Shifter	CIP, Samtech
3	Conta Blender	Allen Brandly
4	Tablet hardness tester	Erweka
5	Weighing balance	Mettler Toledo, Sartorius
6	Rotary tablet compression machine	Cadmach
7	Roche friability tester	Electrolab
8	Colloid mill	CIP
9	Mechanical stirrer	Remi
10	Tablet coating machine	Neocota
11	Hot air oven	EIE Instrument
12	Viscometer	Brookfield
13	Digital tensiometer	Servo control system
14	Dial vernier caliper	Mitutoyo

5.2 EVALUATION OF SOLUBILITY OF FILM FORMING AGENTS

5.2.1 EVALUATION OF SOLUBILITY OF HPMC PHTHALATE (HP 55)

Procedure:

250 ml clean glass beaker was taken. In it 100 ml of solvent/solvent mixture was (wherever applicable) added and was kept on stirring. 0.45 gm (10% w/w of dry polymer) of Diethyl phthalate (DEP) was added as a plasticizer during stirring. It was stirred well for 5 min. Then 4.55 gm of hydroxy propyl methylcellulose phthalate (HP 55) was added slowly and stirred till complete dissolution of the polymer. This procedure is to be followed for all solvent/solvent mixture. The observations are enclosed below in table no 14

SOLVENT	OBSERVATION	REMARKS
Acetone	Dissolved within 5 min, clear, transparent solution was formed	Although polymer dissolved completely, there are chances of spray drying of the material as well as of explosion as acetone evaporates very fast and has low flash point. It is not a good choice to use acetone alone as a coating solvent, therefore not used further.
Acetone: IPA (90: 10)	Dissolved within 5 min, clear, transparent solution was formed	Solution prepared using (90: 10) Acetone: IPA has same properties as solution containing 40:60 Therefore, 40:60 Acetone: IPA was selected for film casting to reduce the amount of acetone.
Acetone: IPA (40:60)		
Acetone: water (90: 10)	Dissolved within 5 min. clear, transparent solution was formed	Both the solutions have same properties, therefore 70: 30 Acetone: Water was selected for film casting to reduce the amount of acetone
Acetone: water (70: 30)		

Acetone: water (60: 40)	Not dissolved, lump formation was observed, which did not dissolved in solvent system even after 30 min of stirring	As amount of water increases solubility of polymer decreases in solvent system, this resulted in a lump formation. As polymer was not soluble in solvent system, not selected for film casting
IPA : MDC (60: 40)	20 min of stirring was required for solubilization. Clear, transparent solution was obtained.	Used as a reference to compare the film properties formed from other non halogenated solvent

RESULT & DISCUSSION

- Solution of HPMCP (grade HP55) in all the solvent system tried was found clear, transparent and of low viscosity. Time required for solubilization varies according to solvent system; highest time was required in IPA: MDC.
- HP 55 got dissolved in Acetone: IPA in different ratios starting from 90:10 to 40: 60. As there is no significant difference in solution properties between Acetone: IPA 90: 10 and 40:60, Acetone: IPA 40: 60 was chosen for casting a film.
- HP 55 got dissolved in Acetone: water in different ratios starting from 90: 10 to 70:30. Below 70: 30, lump formation of polymer was observed, which did not get dissolve in solvent system even after 30 min of stirring. Hence acetone: water 70: 30 was chosen for casting of film.
- Methanol: acetone 60: 40 was selected just to check if any significant difference is observed during the film casting or not.
- IPA: MDC is the reference halogenated solvent system used to which other non halogenated solvent systems are to be compared.

5.2.2 EVALUATION OF SOLUBILITY OF ETHYL CELLULOSE (10 cps)

Procedure:

250 ml clean glass beaker was taken. In it 100 ml of solvent/solvent mixture was (wherever applicable) added and was kept on stirring. 0.45 gm (10% w/w of dry polymer) of Triethyl citrate (TEC) was added as a plasticizer during stirring. It was stirred well for 5 min. Then 4.55 gm of Ethyl cellulose 10 cps was added slowly and stirred till complete dissolution of the polymer. This procedure is to be followed for all solvent/solvent mixture. The observations are enclosed below in table no 15

SOLVENT	OBSERVATION	REMARKS
Acetone	Dissolved in acetone but solution remained hazy	Although polymer dissolved completely, there are chances of spray drying of the material as well as of explosion as acetone evaporates very fast and has low lash point. It is not a good choice for the coating solvent, Therefore not used further.
Methanol	Dissolved but solution remained hazy more hazy then acetone	Haziness was observed in the solution, alone methanol can not be used
Methanol : Acetone (35:65)	Hazy, translucent solution	From three different ratios it was observed that haziness decreases as amount of acetone increases, but there was no significant difference observed between 30:70 and 20:80 ratios. Therefore 30:70 ratio was selected for casting a film
Methanol : Acetone (30:70)	Less hazy then 35:65	
Methanol : Acetone (20:80)	Same as 30:70	

SOLVENT	OBSERVATION	REMARKS
IPA : Acetone (35:65)	Hazy, translucent solution	From three different ratios it was observed that haziness decreases as amount of acetone increases, but there was no significant difference observed between 30:70 and 20:80 ratios. Therefore 30:70 ratio was selected for casting a film
IPA : Acetone (30:70)	Less hazy then 35:65	
IPA : Acetone (20:80)	Same as 30:70	
IPA : MDC (50:50)	Clear, transparent solution	Due to higher solubility in MDC clear, transparent solution was formed

RESULT & DISCUSSION

- Solution of Ethyl Cellulose 10 cps in all the solvent system checked were varies in clarity, transparency and viscosity.
- EC got dissolved in Acetone alone and in various ratios of Acetone: IPA. Transparency of the solution increases as amount of acetone increases. Although some haziness was observed in all the solutions, it was lower in IPA: Acetone in 30: 70 ratios. In higher ratio no significant difference in haziness and other properties was observed. So IPA: Acetone in 30: 70 ratios was selected for the casting of film.
- EC also got dissolved in methanol either alone or in combination with Acetone. Although it formed clear solution in methanol, more haziness was observed in methanol then acetone. Some amount of haziness was observed in all the solutions but it was lower in Methanol: Acetone in 30: 70 ratios. In higher ratio no significant difference in haziness and other properties was observed. So Methanol: Acetone in 30: 70 ratios was selected for the casting of film.
- IPA: MDC is the reference halogenated solvent system used to which other non halogenated solvent systems are to be compared.

5.2.3 EVALUATION OF SOLUBILITY OF HPMC (6 cps)

Procedure:

250 ml clean glass beaker was taken. In it 100 ml of solvent/solvent mixture was (wherever applicable) added and was kept on stirring. 0.45 gm (10% w/w of dry polymer) of Polyethylene glycol 6000 (PEG 6000) was added as a plasticizer during stirring. It was stirred well for 5 min. then 4.55 gm of Hydroxypropylmethylcellulose (HPMC) 6 cps was added slowly and stirred till complete dissolution of the polymer. This procedure is to be followed for all solvent/solvent mixture. The observations are enclosed below in table no 16

SOLVENT	OBSERVATION	REMARKS
Acetone	Not soluble	Some amount of water is required for the solubilization of HPMC, therefore alone acetone can not be used
Water	Clear, transparent, viscous solution	Completely soluble in water, viscosity of solution was also high compare to other solvent system
Acetone: Water (80:20)	Hazy, translucent solution	As amount of water increases, haziness decreases and transparency increases. Therefore acetone: water in 50:50 ratio was used for the casting of the film
Acetone: Water (50:50)	Clear, transparent solution	
IPA: Water (80:20)	Hazy, translucent solution	As amount of water increases, haziness decreases and transparency increases. So IPA: water in 50:50 ratio was used for the casting of the film
IPA: Water (50:50)	Clear, transparent solution	
IPA: Acetone (50:50)	Remain insoluble	Not used for film casting, as polymer is insoluble in solvent system
IPA: MDC (50:50)	Clear, transparent, viscous solution	Used as a reference to compare the film properties formed from other non halogenated solvent

RESULT & DISCUSSION

- Solution of HPMC (2910 6 cps) in all the solvent system tried were varies in clarity, transparency and viscosity.
- HPMC remained insoluble in both Acetone and combination of Acetone: IPA.
- HPMC got dissolved in Acetone: water in different ratios. It was observed that transparency of the solution increases as amount of water increases in the solvent system. So acetone: water 50: 50 was chosen for the casting of the film.
- HPMC got dissolved in IPA: water in different ratios. It was observed that transparency of the solution increases as amount of water increases in the solvent system. So IPA: water 50: 50 was chosen for the casting of the film.
- IPA: MDC is the original solvent system to which other solvent systems are to be compared. Clear, transparent solution was formed with IPA: MDC solvent system.
- HPMC has highest solubility in water, get easily dissolved in water and formed clear, transparent solution.

5.2.4 EVALUATION OF SOLUBILITY OF AMMONIO METHACRYLATE COPOLYMER B (EUDRAGIT RSPO)

Procedure:

250 ml clean glass beaker was taken.100 ml of solvent/solvent mixture was (wherever applicable) added and was kept on stirring. 0.45 gm (10% w/w of dry polymer) of Polyethylene glycol 400 (PEG 400) was added as a plasticizer during stirring. It was stirred well for 5 min. Then 4.55 gm of Eudragit RSPO (E RSPO) was added slowly and stirred till complete dissolution of the polymer. This procedure is to be followed for all solvent/solvent mixture. The observations are enclosed below in table no 17

SOLVENT	OBSERVATION	REMARKS
IPA: Acetone (50:50)	Dissolved readily, clear, transparent solution	In all the solvent system tried, solution characteristics remain same. All solutions were clear, transparent and of low viscosity
Methanol: Acetone (50: 50)	Dissolved readily, clear, transparent solution	
IPA: MDC (50:50)	Dissolved readily, solution was clear, transparent	

RESULT & DISCUSSION

- Solution of ammonio methacrylate copolymer B (Eudragit RSPO) in all the solvent system tried was almost same in clarity, transparency and viscosity.
- E RSPO got dissolved in Acetone: IPA, Acetone: Methanol in 50: 50 ratios.
- IPA: MDC is the reference halogenated solvent system used to which other non halogenated solvent systems are to be compared.

5.3 DETERMINATION OF VISCOSITY FOR FILM FORMING AGENTS

Viscosity of different film forming agents in different solvent system was measured and compared to the original solvent system. Viscosity measurement was done using Brookfield LV (DV I prime) instrument spindle no 61 at 100 RPM.

Procedure:

- 300 ml solution having 5% concentration of polymer in various solvent systems was prepared in 500 ml clean glass beaker.
- Appropriate spindle i.e. spindle no 61 was attached to the viscometer.
- The spindle was made to descend slowly into the beaker containing solution. RPM of the spindle was set such that maximum torque was obtained.
- The dial reading on the viscometer showed the viscosity of the solution in cps, which was noted down.
- This procedure is to be followed for all film forming agents.
- The observations are enclosed below.

Table 18: VISCOSITY OF VARIOUS FILM FORMING AGENTS IN DIFFERENT SOLVENT SYSTEM

POLYMER	SOLVENT SYSTEM	VISCOSITY (cps)
HPMCP (HP 55)	IPA: MDC (60:40)	10.2
	IPA: ACETONE (60:40)	9.12
	ACETONE: WATER (70:30)	10.48
	ACETONE: METHANOL (60:40)	8.94
ETHYL CELLULOSE 10 CPS	IPA: MDC (50:50)	11.4
	IPA: ACETONE (30:70)	9.4
	ACETONE: METHANOL (30:70)	9.1
HPMC 6 CPS	IPA: MDC (50:50)	37.6
	IPA: WATER (50:50)	56.7
	ACETONE: WATER (50:50)	30.3
	WATER	23.1
EUDRAGIT RSPO	IPA: MDC (50:50)	4.26
	IPA: ACETONE (50:50)	3.72
	ACETONE: METHANOL (50:50)	3.30

DISSCUSION:

- Solution of 5% HPMCP (HP 55) in different solvent system shows almost same viscosity. All solutions were of low viscosity. Higher viscosity was observed in Acetone: water (70:30) solvent system.
- Solution of 5% ethyl cellulose (10 cps) in different solvent system shows almost same viscosity. All solutions were of low viscosity. Higher viscosity was observed in IPA: MDC (50:50) solvent system.
- Solution of 5% HPMC (6 cps) in different solvent system shows variable viscosity. It was observed that viscosity increases from aqueous to non aqueous to hydro alcoholic solvent system. Lowest viscosity was observed in polymer solution having water as a solvent, while highest viscosity was observed in IPA: WATER solvent system.
- Solution of 5% Eudragit RSPO in different solvent system shows almost same viscosity. All solutions were of low viscosity. Higher viscosity was observed in IPA: MDC (50:50) solvent system.

5.4 FILM CASTING TRIALS FOR FILM FORMING AGENTS

5.4.1 FILM CASTING TRIALS FOR HPMC PHTHALATE (HP 55)

Film casting was done either of these two methods

1) Film casting using Glass mould
2) Film casting using Mercury metal

Film casting using glass mould

Procedure:

- HP 55 and plasticizer DEP (10% w/w of polymer) were dissolved in solvent mixture at a concentration of 5% w/w.
- 15 gm of solution was poured into leveled square glass moulds and covered with inverted funnels to prevent solvent removal by convection.
- Glass plate moulds were kept in an oven at 50° C temperature for 24 hours.
- After removal films were evaluated for mechanical and physical properties.

BATCH NO	SOLVENT SYSTEM	APPEARANCE
A 1	IPA:MDC (60:40)	Clear, transparent film with somewhat rough texture
A 2	IPA:ACETONE (60:40)	Clear, transparent film with smooth texture
A 3	METHANOL:ACETONE (60:40)	Clear, transparent, film with smooth texture
A 4	WATER:ACETONE (70:30)	Film was not formed, may be due to the precipitation of the polymer

Table 19: EVALUATION OF THE FILMS

BATCH NO	SOLVENT SYSTEM	THICKNESS (mm)	TENSILE STRENGTH (N/cm^2)	% ELONGATION	FOLDING ENDURANCE
A 1	IPA:MDC (60:40)	0.040 ± 0.007	1.861±0.04	6.67%	93
A 2	IPA:ACETONE (60:40)	0.036 ± 0.005	3.512 ± 0.061	6.67%	174
A 3	METHANOL: ACETONE (60:40)	0.048 ± 0.004	1.981 ± 0.060	6.67%	156

COMPARISON OF TENSILE STRENGTH

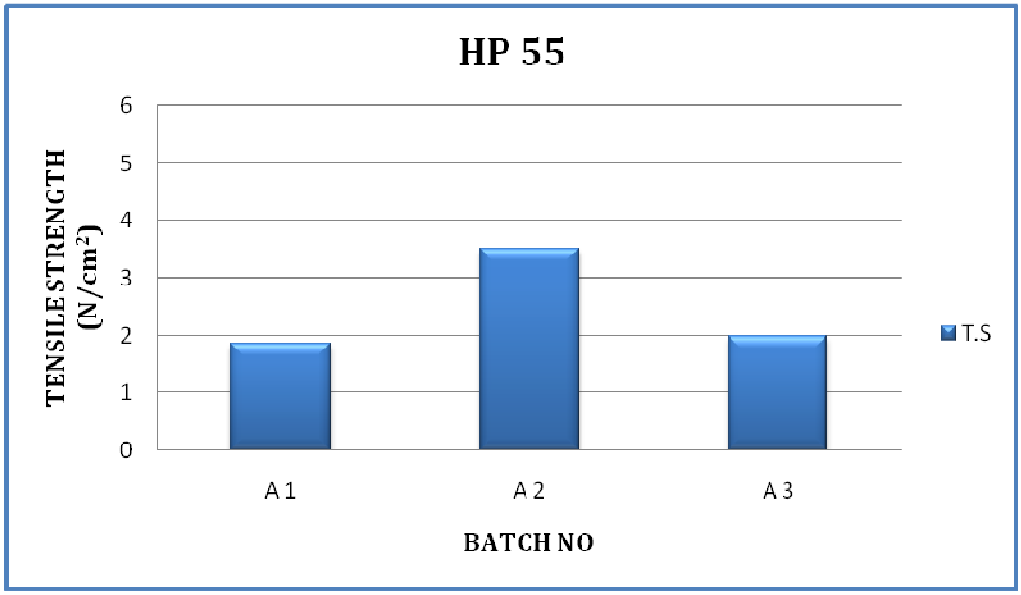


Figure 1

COMPARISON OF FOLDING ENDURANCE

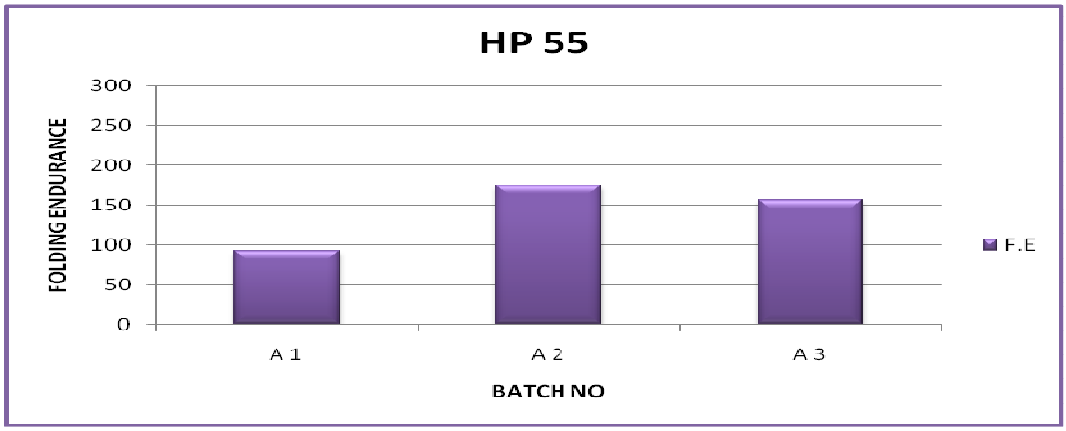


Figure 2

RESULT & DISCUSSION

- From all the solvent system used for film casting it was observed that film was not formed in the Acetone: water system. The precipitation of polymer was observed on the glass mould. This is may be due to the rapid evaporation of acetone in which polymer has higher solubility.
- All films were clear and transparent. Film formed from IPA: MDC has some rough texture while from IPA: Acetone has smooth texture. Film formed from Methanol: Acetone was difficult to remove from the mould. All the films formed were evaluated for the mechanical properties. Tensile strength of films was observed in this order. **IPA: Acetone (60: 40) > Methanol: Acetone (60: 40) > IPA: MDC (60: 40).** Folding endurance was also observed in the same manner i.e. **IPA: Acetone (60: 40) > Methanol: Acetone (60: 40) > IPA: MDC (60: 40).** % Elongation was found same for all the films which may be due to the same amount of same plasticizer in all the films. Negligible variations were observed in the thickness of the films.
- Based upon data of physical appearance, tensile strength, % elongation and folding endurance casted films of HPMCP (HP 55) using IPA: Acetone (60:40) system shows comparatively better results than original IPA: MDC system. Therefore can be used as a replacement of IPA: MDC system.

5.4.2 FILM CASTING TRIALS FOR ETHYL CELLULOSE (10 cps)

Film Casting using Glass moulds

Procedure:

- EC (10 cps) and plasticizer TEC (10 % w/w of polymer) were dissolved in solvent mixture at a concentration of 5 % w/w.
- 15 gm of solution was poured into leveled square glass moulds and covered with inverted funnels to prevent solvent removal by convection,
- Glass plate moulds were kept in an oven at 50° C temperature for 24 hours.
- After removal films were evaluated for mechanical and physical properties.

BATCH NO	SOLVENT SYSTEM	APPEARANCE
B 1	IPA: MDC (50 : 50)	Clear, transparent brittle films with smooth texture
B 2	IPA:ACETONE (30:70)	
B 3	METHANOL:ACETONE (30:70)	

Table 20: EVALUATION OF THE FILMS

BATCH NO	SOLVENT SYSTEM	THICKNESS (mm)	TENSILE STRENGTH (N/cm^2)	% ELONGATION	FOLDING ENDURANCE
B 1	IPA: MDC (50 : 50)	0.044 ± 0.005	0.98 ± 0.0307	6.67%	37
B 2	IPA:ACETONE (30:70)	0.032 ± 0.004	2.109 ± 0.040	6.67%	58
B 3	METHANOL: ACETONE (30:70)	0.060 ± 0.010	0.493± 0.024	6.67%	18

COMPARISON OF THE TENSILE STRENGTH

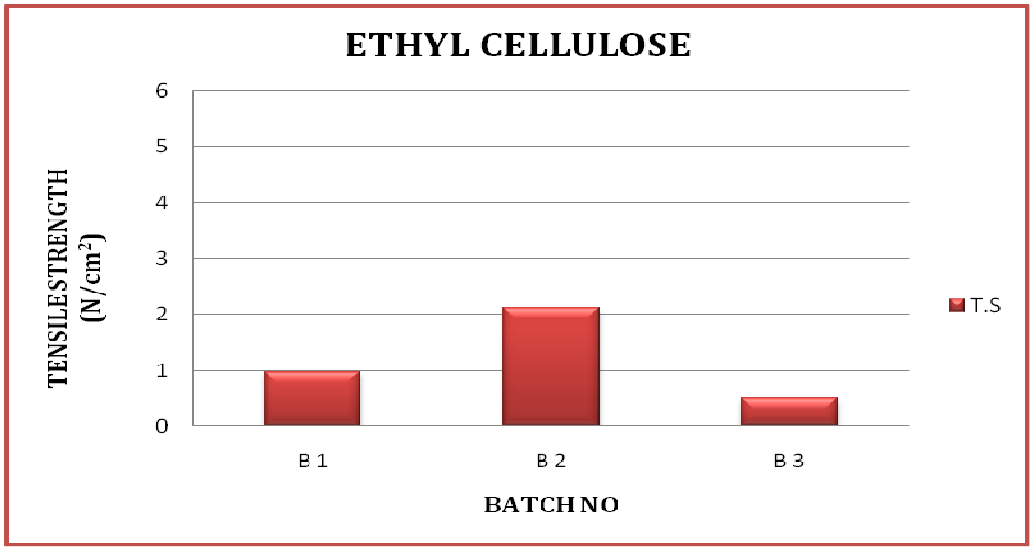


Figure 3

COMPARISON OF THE FOLDING ENDURANCE

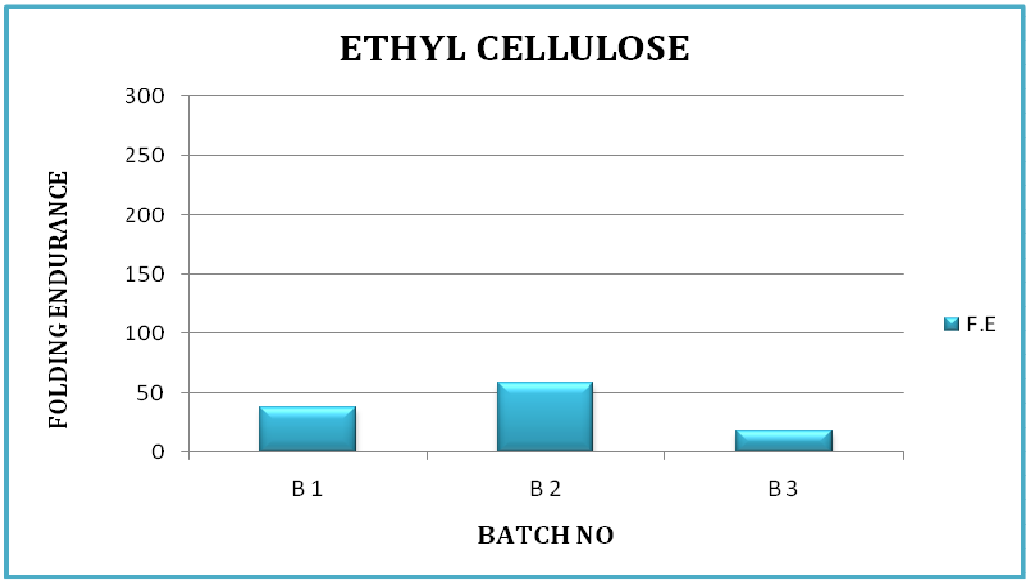


Figure 4

RESULT & DISCUSSION

- From all the solvent system used for film casting it was observed that films formed were brittle in all the solvent system. Although solution of IPA: Acetone and Methanol: Acetone was hazy, films formed were clear and transparent. Film formed from Methanol: Acetone was difficult to remove from the mould.
- All the films formed were evaluated for the mechanical properties. Tensile strength of films was observed in this order **IPA: Acetone (30: 70) > IPA: MDC (50: 50) > Methanol: Acetone (30: 70).** Folding endurance was also observed in the same manner i.e. **IPA: Acetone (30: 70) > IPA: MDC (50: 50) > Methanol: Acetone (30: 70).** % Elongation was found same for all the films which may be due to the presence of the same amount of same plasticizer in all the films. Negligible variations were observed in the thickness of the films.
- Based upon data of physical appearance, tensile strength, % elongation and folding endurance casted films of Ethyl Cellulose using IPA: Acetone (30:70) system shows comparatively better results than original IPA: MDC system. Therefore can be used as a replacement of IPA: MDC system.

5.4.3 FILM CASTING TRIALS FOR HPMC (6 cps)

Film casting using glass mould

Procedure:

- HPMC (6 cps) and plasticizer PEG 6000 (10 % w/w of polymer) were dissolved in solvent mixture at a concentration of 5 % w/w.
- 15 gm of solution was poured into leveled square glass moulds and covered with inverted funnels to prevent solvent removal by convection,
- Glass plate moulds were kept in an oven at 50° C temperature for 24 hours.
- After removal films were evaluated for mechanical and physical properties.

BATCH NO	SOLVENT SYSTEM	APPEARANCE
C 1	IPA: MDC (50 : 50)	Clear, transparent, smooth films
C 2	IPA : WATER (50:50)	
C 3	ACETONE : WATER (50:50)	
C 4	WATER	

Table 21: EVALUATION OF THE FILMS

BATCH NO	SOLVENT SYSTEM	THICKNESS (mm)	TENSILE STRENGTH (N/cm^2)	% ELONGATION	FOLDING ENDURANCE
C 1	IPA: MDC (50 : 50)	0.060 ± 0.012	5.612 ± 0.023	13.33%	213
C 2	IPA : WATER (50:50)	0.046 ± 0.005	5.555 ± 0.117	13.33%	252
C 3	ACETONE : WATER (50:50)	0.052 ± 0.004	5.381± 0.019	13.33%	201
C 4	WATER	0.058 ± 0.008	3.953± 0.041	13.33%	169

COMPARISON OF TENSILE STRENGTH

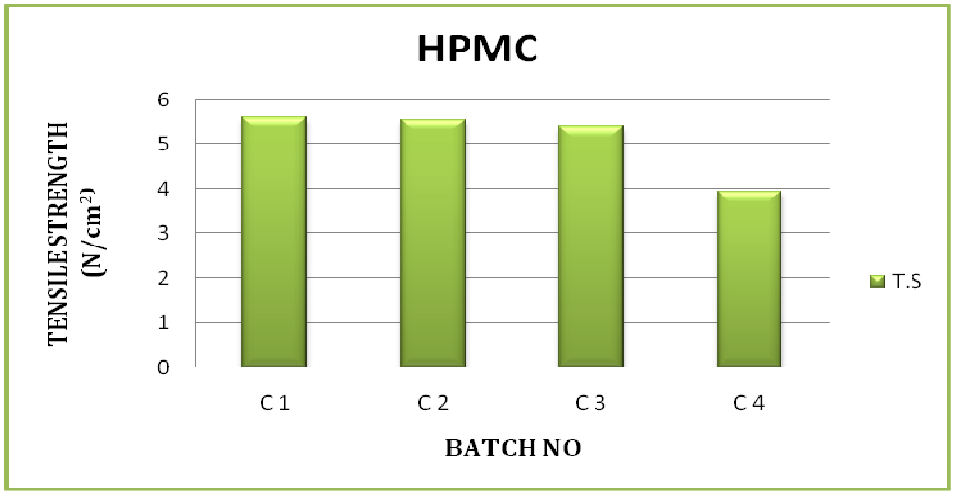


Figure 5

COMPARISON OF FOLDING ENDURANCE

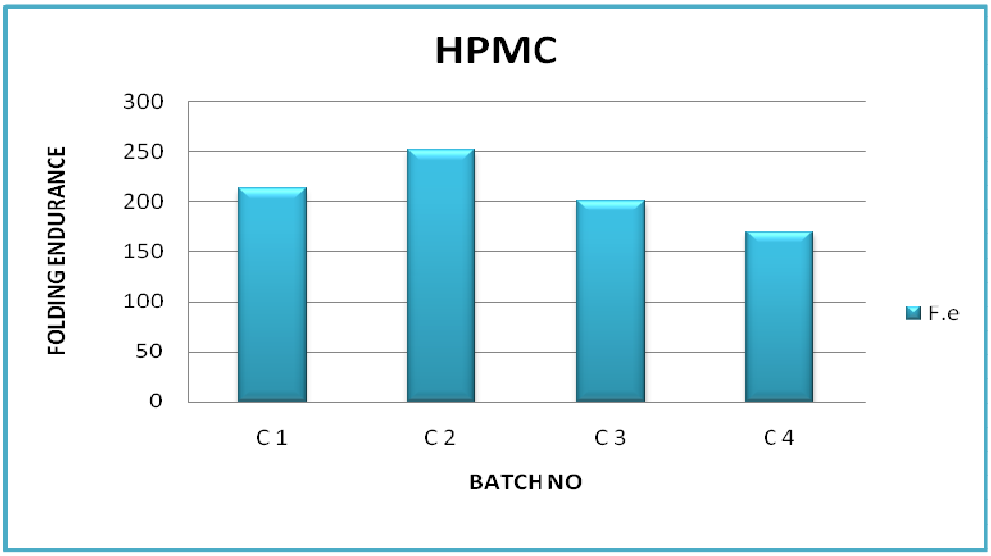


Figure 6

RESULT & DISCUSSION

- All films formed were clear, transparent and easily removable from the moulds. All the films formed were evaluated for the mechanical properties. Tensile strength of films was observed in this order. **IPA: MDC (50: 50) > IPA: Water (50: 50) > Acetone: Water (50: 50) > Water.** Folding endurance was observed in this manner **IPA: Water (50: 50) > IPA: MDC (50: 50) > Acetone: Water (50: 50) > Water**. % Elongation was found same for all the films which may be due to the same amount of same plasticizer in all the films. Negligible variations were observed in the thickness of the films.
- Based upon data of physical appearance, tensile strength, % elongation and folding endurance casted films of HPMC using IPA: Water (50:50) system shows comparatively better results than original IPA: MDC system. Therefore can be used as a replacement of IPA: MDC system.

5.4.4 FILM CASTING TRIALS FOR AMMONIO METHACRYLATE COPOLYMER B (EUDRAGIT RSPO)

Film casting using glass mould

Procedure:

- Eudragit RSPO and plasticizer PEG 400 were dissolved in solvent system.
- 15 gm of solution was poured into leveled square glass moulds and covered with inverted funnels to prevent solvent removal by convection,
- Glass plate moulds were kept in an oven at 50° C temperature for 24 hours.
- After removal films were evaluated for mechanical and physical properties.

TRIAL	OBSERVATION	REMARKS
Total solid content 5% **Plasticizer 10% w/w of polymer** **Solvent system** **IPA:Acetone (50:50)** **Methanol: Acetone (50: 50)** **IPA: MDC (50:50)**	Films were not able to remove from the glass moulds	This may be due to sticky nature of polymer and higher adhesion force
Total solid content 7.5% **Plasticizer 10% w/w of polymer** **Solvent system** **IPA:Acetone (50:50)** **Methanol: Acetone (50: 50)** **IPA: MDC (50:50)**	Films were not able to remove from the glass moulds	Solid content of the solution was increased from 5% to 7.5% , but film was not able to remove from the mould
Total solid content 7.5% **Plasticizer 20% w/w of polymer** **Solvent system** **IPA:Acetone (50:50)** **Methanol: Acetone (50: 50)** **IPA: MDC (50:50)**	Films were not able to remove from the glass moulds	Plasticizer content was increased from 10% to 20% but film was not able to separate from the mould

TRIAL	OBSERVATION	REMARKS
Total solid content 7.5% **Plasticizer 30% w/w of polymer** **Solvent system** **IPA:Acetone (50:50)** **Methanol: Acetone (50: 50)** **IPA: MDC (50:50)**	Films were not able to remove from the glass moulds	Plasticizer content was further increased to 30% but film was not able to remove from the mould
Film was casted on aluminum foil **Total solid content 5% E RSPO** **Plasticizer 10% w/w of polymer** **Solvent system** **IPA:Acetone (50:50)**	Film was not able to remove from the aluminum foil	Film casting solution was poured into petri dish covered with aluminum foil but it does not have any effect on film separation

RESULT & DISCUSSION

- Films were not able to remove from the mould in the trial containing E RSPO 5%, E RSPO 7.5% with the plasticizer content of 10 %, therefore films with higher plasticizer content 20%, 30% were tried but films were not able to remove from the mould, inspite of higher % of plasticizer was used. This may be due to higher adhesion force of the polymer
- Another trial was tried with pouring a solution on glass Petri plate covered with aluminum foil, but film was not able to separate from the foil.
- Films formed from all these trials were very sticky, can not be removed from the mould. There fore other method of film casting using mercury metal was used

FILM CASTING USING MERCURY METAL

Procedure:

- Eudragit RSPO and plasticizer PEG 400 were dissolved in solvent system.
- Petri plate having diameter of 5 cm was taken. Mercury was filled into the petri plate till uniform layer was formed.
- Required amount of solution of the Eudragit RSPO was poured onto the layer of mercury.
- Petri plate was covered with inverted funnels to prevent solvent removal by convection.
- Petri plate was kept in an oven at 40° C temperature for 24 hours.
- After removal films were evaluated for mechanical and physical properties.

Table 22: EVALUATION OF THE FILMS

BATCH NO	SOLVENT SYSTEM	THICKNESS (mm)	TENSILE STRENGTH (N/cm^2)	% ELONGATION	FOLDING ENDURANCE
D 1	IPA: MDC (50: 50)	0.338 ± 0.023	2.306 ± 0.011	36.66 %	124
D 2	IPA: ACETONE (50: 50)	0.326±0.015	2.770 ± 0.022	36.66 %	189
D 3	METHANOL: ACETONE (50: 50)	0.348±0.008	2.438 ± 0.016	36.66 %	146

COMPARISON OF TENSILE STRENGTH

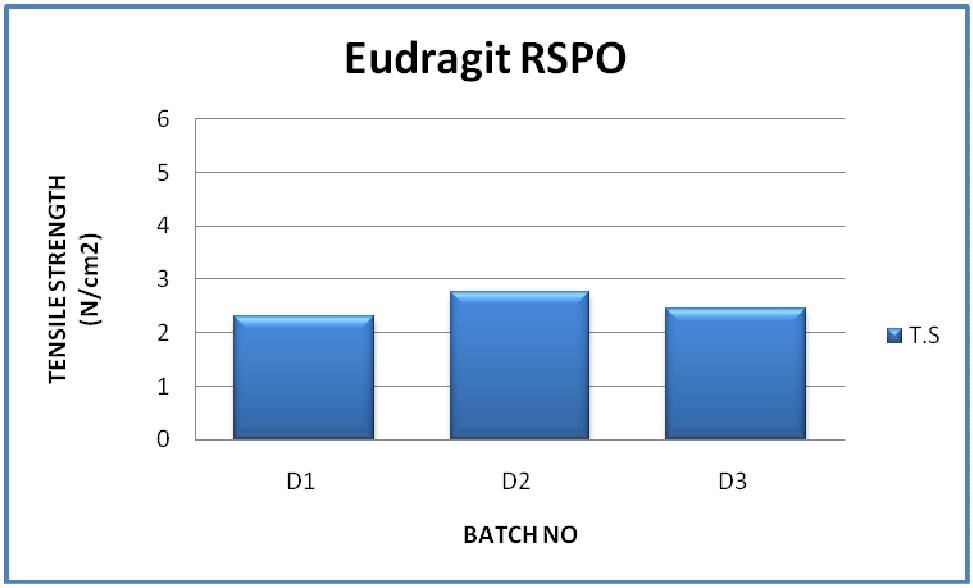


Figure 7

COMPARISON OF FOLDING ENDURANCE

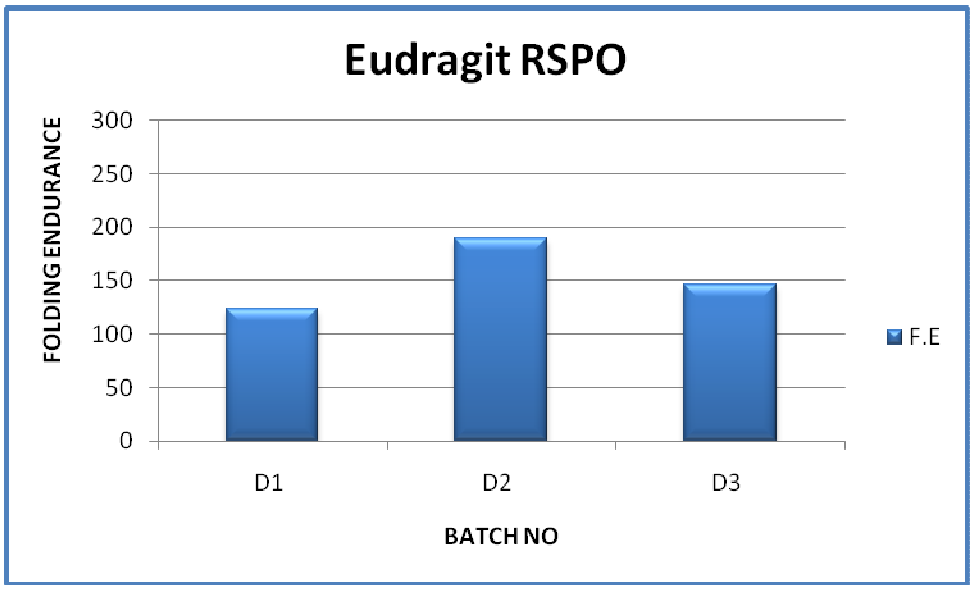


Figure 8

RESULT & DISCUSSION

- All films formed were clear, transparent and easily removable from the surface of mercury. All the films formed were evaluated for the mechanical properties. Tensile strength of films was observed in this order. **IPA: Acetone (50: 50) > Methanol: Acetone (50: 50) >IPA: MDC (50: 50).** Folding endurance was observed in this manner **IPA: Acetone (50: 50) > Methanol: Acetone (50: 50) >IPA: MDC (50: 50).**
- % elongation was found higher for all the films which may be due to the effect of plasticizer i.e. PEG 400. % Elongation was found same for all the films which may be due to the same amount of same plasticizer in all the films. Negligible variations were observed in the thickness of the films.
- Based upon data of physical appearance, tensile strength, % elongation and folding endurance casted films of Eudragit RSPO using IPA: Acetone (50: 50) system shows comparatively better results than original IPA: MDC system. Therefore can be used as a replacement of IPA: MDC system.

5.5 COATING TRIALS FOR FILM FORMING AGENTS USING ORIGINAL AND ALTERNATE SOLVENT SYSTEM

Table 23: COMPOSITION OF TABLET

Ingredients	mg/ tablet
Lactose DCL 11	204
MCC 102	90
PVP K 30	4.5
Magnesium Stearate	1.5

Total tablet weight: 300 mg

PROCEDURE:

- All ingredients were weighed accurately
- Lactose DCL 11, MCC 102, PVP K 30 were mixed and passed through 40# sieve.
- Magnesium stearate was passed from 60# sieve. It was mixed to the above mixture and blended in genson blender for 10 min at 16 RPM.
- Prepared RFC was compressed in 16 station tablet compression machine using 9 mm Round, SC, PL/PL punches.

Table 24: EVALUATION OF THE UNCOATED TABLETS

Average weight	300.4 mg
Thickness	4.72 mm
Hardness	80.80 N
Diameter	8.99 mm
Friability	0.01%
D.T	14.25 seconds

5.5.1 COATING TRIALS FOR HPMC PHTHALATE (HP 55)

5.5.1.1 COATING TRIALS FOR HPMC PHTHALATE USING IPA: MDC

Table 25: COMPOSITION OF COATING SOLUTION FOR BATCH HPIM 1

Ingredients	mg/ tablet	Qty/batch 4000 tablets (gm)
HP 55	5.80	23.2
Talc	0.568	2.272
Titanium dioxide	0.595	2.380
Diethyl phthalate	0.580	2.320
Yellow iron oxide	0.077	0.308
Black iron oxide	0.030	0.120
MDC	-	204
IPA	-	306
Total	7.65	30.6

Total solid content: 6%

Weight gain – 2.5%

PREPARATION OF COATING SOLUTION:

Procedure:

- All ingredients were weighed accurately
- IPA and MDC were mixed
- 60% of solvent was transferred in separate container, in which HP 55 and DEP were dissolved with continuous stirring
- Talc, TiO_2 and colorants were milled with remaining 40% solvent for 20 minutes in colloid mill and transferred to step 3 with continuous stirring.

PROCESS PARAMETERS FOR BATCH HPIM 1

Inlet temperature: 45 - 47° C

Exhaust temperature: 31- 33° C

Atomization pressure: 1.75 bars

Pan Speed: 3 – 5 RPM

Spray Rate: 12 – 13 gm/ min

Pan size: 1 kg

Pan load: 500 gm

Remark: coating was found satisfactory, some whiteness was found on the surface of the tablets. Tablets were further evaluated for the enteric strength and other physical parameters

5.5.1.2 COATING TRIALS FOR HPMC PHTHALATE (HP 55) USING IPA: ACETONE

Table 26: COMPOSITION OF COATING SOLUTION FOR BATCH HPIA 1

Ingredients	Mg/ tablet	Qty/batch 4000 tablets (gm)
HP 55	5.80	23.2
Talc	0.568	2.272
Titanium dioxide	0.595	2.380
Diethyl phthalate	0.580	2.320
Yellow iron oxide	0.077	0.308
Black iron oxide	0.030	0.120
Acetone	-	204
IPA	-	306
Total	7.65	30.6

Total solid content: 6%

Weight gain – 2.5%

PREPARATION OF COATING SOLUTION:

Procedure:

- All ingredients were weighed accurately
- IPA and Acetone were mixed
- 60% of solvent was transferred in separate container, in which HP 55 and DEP were dissolved with continuous stirring
- Talc, TiO_2 and colorants were milled with remaining 40% solvent for 20 minutes in colloid mill and transferred to step 3 with continuous stirring.

PROCESS PARAMETERS FOR BATCH HPIA 1

Inlet temperature: 34 - 40° C

Exhaust temperature: 29 - 35° C

Atomization pressure: 1.75 bars

Pan Speed: 3 – 5 RPM

Spray Rate: 13 – 14 gm/ min

Pan size: 1 kg

Pan load: 500 gm

Remarks:

At inlet temperature 40° C spray drying of the acetone was observed, so temperature was lowered up to 34° C. Coating was found satisfactory, whiteness was found on the surface of the tablets. Tablets were further evaluated for the enteric strength and other physical parameters.

5.5.1.3 COATING TRIALS FOR HPMC PHTHALATE (HP 55) USING ACETONE: WATER

Table 27: COMPOSITION OF COATING SOLUTION FOR BATCH HPAW 1

Ingredients	Mg/ tablet	Qty/batch 4000 tablets (gm)
HP 55	5.80	23.2
Talc	0.568	2.272
Titanium dioxide	0.595	2.380
Diethyl phthalate	0.580	2.320
Yellow iron oxide	0.077	0.308
Black iron oxide	0.030	0.120
Acetone	-	357
Water	-	153
Total	7.65	30.6

Total solid content: 6%

Weight gain – 2.5%

PREPARATION OF COATING SOLUTION:

Procedure:

- All ingredients were weighed accurately
- Acetone and Water were mixed
- 60% of solvent was transferred in separate container, in which HP 55 and DEP were dissolved with continuous stirring
- Talc, TiO_2 and colorants were milled with remaining 40% solvent for 20 minutes in colloid mill and transferred to step 3 with continuous stirring.

PROCESS PARAMETERS FOR BATCH HPAW 1

Inlet temperature: 40° C - 50° C

Exhaust temperature: 34 – 38 ° C

Atomization pressure: 1.75 bars

Pan Speed: 3 – 5 RPM

Spray Rate: 4 – 6 gm/ min

Pan size: 1 kg

Pan load: 500 gm

Remark:

Initially inlet temperature set was low i.e. 40 ° C, therefore acetone was dried but water took some time for drying. So inlet temperature was gradually increased up to 50° C. Due to rise in temperature acetone dried before reach to tablets. This was resulted in spray drying of the tablets. Over dried surface of tablet was observed. So process was stopped and tablets were not evaluated further.

5.5.1.4 COATING TRIALS FOR HPMC PHTHALATE (HP 55) USING ACETONE: METHANOL

Table 28: COMPOSITION OF COATING SOLUTION FOR BATCH HPAM 1

Ingredients	Mg/ tablet	Qty/batch 4000 tablets (gm)
HP 55	5.80	23.2
Talc	0.568	2.272
Titanium dioxide	0.595	2.380
Diethyl Phthalate	0.580	2.320
Yellow iron oxide	0.077	0.308
Black iron oxide	0.030	0.120
Acetone	-	204
Methanol	-	306
Total	7.65	30.6

Total solid content: 6%

Weight gain – 2.5%

PREPARATION OF COATING SOLUTION:

Procedure:

- All ingredients were weighed accurately
- Acetone and Methanol were mixed
- 60% of solvent was transferred in separate container, in which HP 55 and DEP were dissolved with continuous stirring
- Talc, TiO_2 and colorants were milled with remaining 40% solvent for 20 minutes in colloid mill and transferred to step 3 with continuous stirring.

PROCESS PARAMETERS FOR BATCH HPAM 1

Inlet temperature: 34 - 36° C

Exhaust temperature: 29 - 31° C

Atomization pressure: 1.75 bars

Pan Speed: 3 – 5 RPM

Spray Rate: 13 – 14 gm/ min

Pan size: 1 kg

Pan load: 500 gm

Remark: coating was found satisfactory, some whiteness was found on the surface of the tablets. Tablets were further evaluated for the enteric strength and other physical parameters

Table 29: EVALUATION OF THE COATED TABLET

PARAMETERS	UNCOATED	SEAL COATED	HPIM 1 (IPA: MDC)	HPIA 1 (IPA: ACETONE)	HPAM 1 (ACETONE: METHANOL)
WEIGHT	300.4 mg	306.4 mg	316.7 mg	315.6 mg	317.7 mg
THICKNESS	4.72 mm	4.82 mm	4.88 mm	4.88 mm	4.89 mm
DIAMETER	8.99 mm	9.04 mm	9.13 mm	9.10 mm	9.09 mm
HARDNESS	80.80 N	115.8 N	195.80 N	197.80 N	165.20 N
ENTERIC STRENGTH **0.1 N HCl** (900 ml for 2 hours in D.T apparatus) **pH 6.8 phosphate buffer** (900 ml in D.T apparatus)	N/A	N/A	Tablet remain intact, no swelling, no erosion After 3 min tablet start to swell, enteric coat was removed after 5 min.	Tablet remain intact, no swelling, no erosion After 3 min tablet start to swell, enteric coat was removed after 5 min.	Tablet remain intact, no swelling, no erosion After 3 min tablet start to swell, enteric coat was removed after 5 min.

RESULT & DISCUSSION:

It was observed all physical parameters including hardness were higher in enteric coated tablets. Tablets remain intact in 0.1 N HCl for 2 hours, when 0.1 N HCl was replaced with pH 6.8 phosphate buffer tablet start to swell and enteric coat was removed after 5 min. This phenomenon was observed in all different solvent system. So overall we can conclude that alternate systems have same characteristics as reference IPA: MDC system.

5.5.2 COATING TRIALS FOR HPMC (6cps)

5.5.2.1 COATING TRIALS FOR HPMC (6cps) USING IPA: MDC

Table 30: COMPOSITION OF COATING SOLUTION FOR BATCH HIM 1

Ingredients	mg/ tablet	Qty/batch 5000 tablets (gm)
HPMC 6 cps	6.00	30.00
Talc	0.75	3.75
Titanium dioxide	1.65	8.25
Polyethylene glycol 6000	0.60	3.00
MDC	-	450.00
IPA	-	450.00
Total	9 .00	45.00

Total solid content: 5 %

% Weight gain – 3%

PREPARATION OF COATING SOLUTION:

Procedure:

- All ingredients were weighed accurately
- IPA and MDC were mixed
- 60% of solvent was transferred in separate container, in which HPMC 6 cps and PEG 6000 were dissolved with continuous stirring
- Talc and TiO_2 were milled with remaining 40% solvent for 20 minutes in colloid mill and transferred to step 3 with continuous stirring.

PROCESS PARAMETERS FOR BATCH HIM 1

Inlet temperature: 45 - 47° C

Exhaust temperature: 31 - 33° C

Atomization pressure: 1.75 bars

Pan Speed: 3 – 5 RPM

Spray Rate: 12 – 13 gm/ min

Pan size: 1 kg

Pan load: 500 gm

Remark: coating was found satisfactory, shiny white tablet surface was observed. Tablets were further evaluated for disintegration time and other physical parameters

5.5.2.2 COATING TRIALS FOR HPMC (6cps) USING IPA: WATER

Table 31: COMPOSITION OF COATING SOLUTION FOR BATCH HIW 1

Ingredients	mg/ tablet	Qty/batch 5000 tablets (gm)
HPMC 6 cps	6.00	30.00
Talc	0.75	3.75
Titanium dioxide	1.65	8.25
Polyethylene glycol 6000	0.60	3.00
Water	-	450
IPA	-	450
Total	9 .00	45.00

Total solid content: 5 %

Weight gain- 3%

PREPARATION OF COATING SOLUTION:

Procedure:

- All ingredients were weighed accurately
- IPA and Water were mixed
- 60% of solvent was transferred in separate container, in which HPMC 6 cps and PEG 6000 were dissolved with continuous stirring
- Talc and TiO_2 were milled with remaining 40% solvent for 20 minutes in colloid mill and transferred to step 3 with continuous stirring.

PROCESS PARAMETERS FOR BATCH HIW 1

Inlet temperature: 49 - 51 ° C

Exhaust temperature: 33 - 35° C

Atomization pressure: 1.75 bars

Pan Speed: 3 – 5 RPM

Spray Rate: 5 – 6 gm/ min

Pan size: 1 kg

Pan load: 500 gm

Remark: coating was found satisfactory, shiny white tablet surface was observed. Tablets were further evaluated for disintegration time and other physical parameters

5.5.2.3COATING TRIALS FOR HPMC (6cps) USING WATER

Table 32: COMPOSITION OF COATING SOLUTION FOR BATCH HW 1

Ingredients	mg/ tablet	Qty/batch 5000 tablets (gm)
HPMC 6 cps	6.00	30.00
Talc	0.75	3.75
Titanium dioxide	1.65	8.25
Polyethylene glycol 6000	0.60	3.00
Water	-	900
Total	9 .00	45.00

Total solid content: 5 %

Weight gain – 3%

PREPARATION OF COATING SOLUTION:

Procedure:

- All ingredients were weighed accurately
- 60% of water was transferred in separate container, in which HPMC 6 cps and PEG 6000 were dissolved with continuous stirring
- Talc and TiO_2 were milled with remaining 40% water for 20 minutes in colloid mill and transferred to step 3 with continuous stirring.

PROCESS PARAMETERS FOR BATCH HW 1

Inlet temperature: 58 – 60 ° C

Exhaust temperature: 35 – 38 ° C

Atomization pressure: 1.75 bars

Pan Speed: 3 – 5 RPM

Spray Rate: 4 – 6 gm/ min

Pan size: 1 kg

Pan load: 500 gm

Remark: coating was found satisfactory, shiny white tablet surface was observed. Tablets were further evaluated for disintegration time and other physical parameters

Table 33: EVALUATION OF THE COATED TABLET

PARAMETERS	UNCOATED TABLET	HIM 1 (IPA:MDC)	HIW 1 (IPA:WATER)	HW 1 (WATER)
WEIGHT	300.4 mg	309.1 mg	309.2	309.7 mg
THICKNESS	4.42 mm	4.46 mm	4.47 mm	4.50 mm
DIAMETER	9.02 mm	9.07 mm	9.06 mm	9.09 mm
HARDNESS	185.40 N	229.40 N	261 N	259.40 N
D.T	14.25 min	16.30 min	17.45 min	17 min

RESULT & DISCUSSION

It was observed that all physical parameters including disintegration time were higher in HPMC coated tablets. Disintegration time of uncoated tablet was found to be 14.25 min, while that of coated tablet was 16.30 min, 17.45 min, 17 min for solvent system containing IPA: MDC, IPA: WATER, WATER respectively. Parameters of tablets containing alternate solvent are comparable with that of reference system.

SUMMARY AND CONCLUSION

6. SUMMARY AND CONCLUSION

Halogenated solvents are commonly used in manufacturing and laboratory processes. Their use in the industry represents a large entry of these chemicals into the environment, resulting in widespread dissemination and often times undesirable conditions. Several of the halogenated solvents have, for some time, been associated with human carcinogenesis. These substances can pose major problems when they are released into the environment, and reducing their use can consequently reduce the health and environmental threats associated with them. Hence it was decided to bring together research efforts in the quest to find "green" replacements for halogenated solvents and to direct efforts to change solvent system based on halogenated solvent to non halogenated solvents to protect the environment and health as well as industrial safety without changing the product composition.

Initially various products were selected in which Methylene dichloride was used either in the granulation or in the coating process. Based upon regulatory, health and environmental aspects, solubility characteristics of the polymer used and by conducting the series of trials, alternate solvents were selected. Solution properties of the alternate solvent system i.e. appearance, viscosity were compared to that of reference system. Film forming properties of the polymers in these alternate solvents were also checked by conducting film casting trials and were compared to the reference system. Films were evaluated for physical and mechanical properties like appearance, thickness, tensile strength, % elongation and folding endurance and results of both the system were compared. Selected alternate solvents were further tried in coating system. By conducting various trials tablets were coated with reference as well as alternate system and evaluated further for physical parameters.

For HPMC Phthalate (HP 55) alternate solvents selected were IPA: Acetone (60:40), Methanol: Acetone (60:40) and Acetone: water (70: 30). All the alternative solvents have almost same viscosities. It was observed from the mechanical properties of films that films having IPA: Acetone solvent system have better tensile strength and folding endurance then reference IPA: MDC system. These alternate systems were further used in the coating trials. HPMC Phthalate (HP 55) coated tablets were also checked

for enteric strength and various other physical parameters like weight gain, thickness, hardness, diameter etc. From the results of the various physical parameters it was observed that results of IPA: Acetone system was comparable with reference halogenated system i.e. IPA: MDC. Hence we can replace the reference halogenated system IPA: MDC with the safer alternative solvent system IPA: Acetone for HPMC Phthalate (HP 55).

For Ethyl cellulose (10 cps) alternate solvents selected were IPA: Acetone (30:70), Methanol: Acetone (30:70). All the alternative solvents have almost same viscosities. It was observed from the mechanical properties of films that films having IPA: Acetone solvent system have better tensile strength and folding endurance then reference IPA: MDC system. Hence we can replace the reference halogenated system IPA: MDC with the safer alternative solvent system IPA: Acetone for ethyl cellulose.

For HPMC (6 cps) alternate solvents selected were IPA: Water (50:50), Acetone: water (50: 50) and water. Viscosity of IPA: Water system was higher then other system. From the mechanical properties of films it was observed that films having IPA: Water solvent system have better tensile strength and folding endurance then reference IPA: MDC system. These alternate systems were further used in the coating trials. HPMC coated tablets were also checked for various other physical parameters like weight gain, thickness, hardness, diameter etc. From the results of the various physical parameters it was observed that results of IPA: water system was comparable with reference halogenated system i.e. IPA: MDC. Hence we can replace the reference halogenated system IPA: MDC with the safer alternative solvent system IPA: Acetone for HPMC (6 cps).

For Eudragit RSPO alternate solvents selected were IPA: Acetone (50:50) and Methanol: Acetone (50: 50). All the alternative solvents have almost same viscosities as reference IPA: MDC system. Due to higher adhesion force films were difficult to remove from the glass mould therefore other method of film casting i.e. film casting on mercury metal was tried. From the mechanical properties of films it was observed that films having IPA: Acetone solvent system have better tensile strength and folding endurance then reference IPA: MDC system. Hence we can replace the reference

halogenated system IPA: MDC with the safer alternative solvent system IPA: Acetone for Eudragit RSPO.

For hydrogenated castor oil other alternative solvents are not available and as it does not form the film, film casting study was not performed. In such case alternate approach like hot melt granulation can be use.

Preliminary trials and feasibility for all polymers in alternate solvent system were checked, but before implementing these solvents further suitability in actual products and stability studies are necessary.

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SUMMARY

Halogenated solvents are commonly used in manufacturing and laboratory processes. Their use in the industry represents a large entry of these chemicals into the environment, resulting in widespread dissemination and often times undesirable conditions. Several of the halogenated solvents have, for some time, been associated with human carcinogenesis. These substances can pose major problems when they are released into the environment, and reducing their use can consequently reduce the health and environmental threats associated with them. Hence it was decided to bring together research efforts in the quest to find "green" replacements for halogenated solvents and to direct efforts to change solvent system based on halogenated solvent to non halogenated solvents to protect the environment and health as well as industrial safety without changing the product composition.

Initially various products were selected in which Methylene dichloride was used either in the granulation or in the coating process. Based upon regulatory, health and environmental aspects, solubility characteristics of the polymer used and by conducting the series of trials, alternate solvents were selected. Solution properties of the alternate solvent system i.e. appearance, viscosity were compared to that of reference system. Film forming properties of the polymers in these alternate solvents were also checked by conducting film casting trials and were compared to the reference system. Films were evaluated for physical and mechanical properties like appearance, thickness, tensile strength, % elongation and folding endurance and results of both the system were compared. Selected alternate solvents were further tried in coating system. By conducting various trials tablets were coated with reference as well as alternate system and evaluated further for physical parameters.

For HPMC Phthalate (HP 55) alternate solvents selected were IPA: Acetone (60:40), Methanol: Acetone (60:40) and Acetone: water (70: 30). All the alternative solvents have almost same viscosities. It was observed from the mechanical properties of films that films having IPA: Acetone solvent system have better tensile strength and folding endurance then reference IPA: MDC system. These alternate systems were further used in the coating trials. HPMC Phthalate (HP 55) coated tablets were also checked for enteric strength and various other physical parameters like weight gain, thickness, hardness, diameter etc. From the results of the various

physical parameters it was observed that results of IPA: Acetone system was comparable with reference halogenated system i.e. IPA: MDC. Hence we can replace the reference halogenated system IPA: MDC with the safer alternative solvent system IPA: Acetone for HPMC Phthalate (HP 55).

For Ethyl cellulose (10 cps) alternate solvents selected were IPA: Acetone (30:70), Methanol: Acetone (30:70). All the alternative solvents have almost same viscosities. It was observed from the mechanical properties of films that films having IPA: Acetone solvent system have better tensile strength and folding endurance then reference IPA: MDC system. Hence we can replace the reference halogenated system IPA: MDC with the safer alternative solvent system IPA: Acetone for ethyl cellulose.

For HPMC (6 cps) alternate solvents selected were IPA: Water (50:50), Acetone: water (50: 50) and water. Viscosity of IPA: Water system was higher then other system. From the mechanical properties of films it was observed that films having IPA: Water solvent system have better tensile strength and folding endurance then reference IPA: MDC system. These alternate systems were further used in the coating trials. HPMC coated tablets were also checked for various other physical parameters like weight gain, thickness, hardness, diameter etc. From the results of the various physical parameters it was observed that results of IPA: water system was comparable with reference halogenated system i.e. IPA: MDC. Hence we can replace the reference halogenated system IPA: MDC with the safer alternative solvent system IPA: Acetone for HPMC (6 cps).

For Eudragit RSPO alternate solvents selected were IPA: Acetone (50:50) and Methanol: Acetone (50: 50). All the alternative solvents have almost same viscosities as reference IPA: MDC system. Due to higher adhesion force films were difficult to remove from the glass mould therefore other method of film casting i.e. film casting on mercury metal was tried. From the mechanical properties of films it was observed that films having IPA: Acetone solvent system have better tensile strength and folding endurance then reference IPA: MDC system. Hence we can replace the reference halogenated system IPA: MDC with the safer alternative solvent system IPA: Acetone for Eudragit RSPO.

For hydrogenated castor oil other alternative solvents are not available and as it does not form the film, film casting study was not performed. In such case alternate approach like hot melt granulation can be use.

Preliminary trials and feasibility for all polymers in alternate solvent system were checked, but before implementing these solvents further suitability in actual products and stability studies are necessary.