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Development of Sustained Release Ambroxol Hydrochloride by Pelletization

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Abstract:
The aim of the present study was to develop and characterize sustained release pellets of Ambroxol HCl using Ethyl cellulose 7cps and Ethyl cellulose 50cps.The pellets were prepared by Wurster process with EC 7cps in 0.5%w/w, 1%w/w and 1.5%w/w and EC 50cps at 2%w/w, 3.5%w/w and 5%w/w.Then the pellets were evaluated for bulk density, angle of repose and Carr's index. The pellets were characterized for particle size by sieving technology and particle surface, surface texture by SEM analysis. The in-vitro dissolution studies were carried out using 0.1N HCl for first 2hrs followed by phosphate buffer of pH 6.8 up to 24h with USP-II dissolution apparatus. The mean dissolution time was found to be increased by increasing Ethyl cellulose levels. From one way ANOVA it was found that the ratio of binary polymer mixture had significant ($p < 0.05$) effect on drug release. The data were fitted to various kinetic models. The data fitted well in both Higuchi and Hixon-crowl model.

Keywords:
Ambroxol hcl, Ethylcellulose, wurster process,angle of repose, carr'sindex, SEM anaysis, hcl, phosphate buffer, higuchi hixon crowl.

1.1. Novel Drug Delivery System

The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period of time. This is generally accomplished by attempting "zero-order" release from the dosage form. Zero-order release constitutes drug release from the dosage form which is independent of the amount of drug in the delivery system (i.e. a constant release rate). Sustained-release systems generally do not attain this type of release and usually try to mimic zero-order release by providing drug in a slow first-order fashion (i.e., concentration release dependent). Systems that are designated as prolonged release can aso be considered as attempts at achieving sustained-release delivery.

The term "Controlled- release drug product" has been used to describe various types of oral extended release rate dosage forms, including sustained release (sustained action), prolonged release (long action) and retarded release.

A modified- release dosage form is defined "as one for which the drug release characteristics of time course and location are chosen to accomplish therapeutic convenience.

Extended release delivery systems are divided into 4 categories

1. Delayed release
2. Controlled release
   a. Sustained release
   b. Prolonged release
3. Site- specific release
4. Receptor release

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1.2. Principle behind SR/CR drug release

Dissolution and diffusion controlled systems have classically been of primary importance in oral delivery of medication because of their relative ease of production and cost compared with other methods of sustained or controlled delivery. Most of these systems are solids, although a few liquids and suspension have been recently introduced.

The classifications of such systems are as follows

1. Diffusion controlled systems
2. Dissolution controlled system
3. Dissolution and Diffusion controlled system
4. Osmotically controlled system
5. Ion exchange systems

1.2.1 Diffusion Controlled Systems

Diffusion systems are characterized by the release rate being dependent on its diffusion through an inert membrane barrier. Usually this barrier is an insoluble polymer. In general two types of sub classes of diffusional systems are recognized they are

a. Reservoir devices
b. Matrix devices

a) Reservoir devices:

Reservoir devices are characterized by a core drug reservoir surrounded by a polymeric membrane.

The nature of the membrane determines the rate of release of drug from the system.

The process of diffusion is generally described by Ficks equations,

$$J = -D \, dc/dx$$

Where,

J = Flux (amount/area –time)

D = Diffusion co-efficient of drug in the membrane (area/time)

dc/dx = rate of exchange in concentration C, with respect to a distance X in the membrane.

b) Matrix Devices:

It contains of drug dispersed homogeneously throughout a polymer matrix. In this model, drug in the outside layer exposed to bath solution is dissolved first and then diffuses out of the matrix. Higuchi equation describes the rate of release of drug dispersed in an inert matrix system.

$$Dm/dh = C_o d_h - Cs/2$$

Where,

Dm = Change in the amount of drug released per unit area.

d_h = Change in the thickness of the zone of matrix that have been depleted of drug.

C_o = Total amount of drug in unit volume of matrix.

Cs = Saturated concentration of drug within the matrix.

1.2.2. Dissolution controlled Systems:

Drug with a slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by rate of dissolution. This being the case, SR preparations of drugs could be made by decreasing their dissolution rate. This includes preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving carrier. The dissolution process at steady state is described by Noyes-Whitney equation.

$$dc/dt = KDA (Cs-C) = DA (Cs-C)/h$$

Where,

dc/dt = Dissolution rate

K = Dissolution rate constant

Cs = Saturation solubility of the solid

C = Concentration of solute in bulk

h = Thickness of diffusion layer

Dissolution rate modifications:

Dissolution rate modifications include (a) Solubility, (b) Specific area, (c) Particle shape and surface structure,(d) dissolution conditions (contact of solid particles with the solvent) and (e) Crystallographic modification.

1.2.3. Dissolution and Diffusion Controlled release system:

Therapeutic systems will never dependent on only dissolution or only diffusion. In practice, the dominant mechanism for release will over shadow other processes enough to allow classification as either dissolution rate limited or diffusion controlled.

The mechanism of release from simple erodible slabs, cylinders and spheres has been described by Hopenberg as

$$Mt/M = 1 - (1 - Kot/Co\ a)n$$

Where,

n =2 for cylinder and

n = 1 for a slab

a = Radius of sphere or cylinder or 1/2 height of a slab

Mt = Mass of drug release at time t

M = Mass released infinite time

1.2.4. Osmotically controlled systems:

In this system the tablet was blended with osmotically active diluents by coating with a cellulose triacetate barrier which functions as a semi permeable membrane. A laser is used to form a precision orifice in the barrier, through which the drug is released due to development of osmotic pressure difference across the membrane, when this kept in water (or) medium.

1.2.5. Ion Exchange Systems:

These are salts of cationic or anionic exchange resins or insoluble complexes in which drug release results from exchange of bound drug ions that are normally present in GI fluids.

1.3 Pelletization

Pellets:

Pellets can be defined as small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5mm to 1.5mm, which are usually intended for oral administration, manufactured by the agglomerates of fine powders or granules of bulk drugs and Excipients using appropriate processing equipment12. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today.

Regardless of which manufacturing process is used, pellets have to meet the following requirements.

1. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.
2. The particle size range should be as narrow as possible. The optimum size of pellets for

pharmaceutical use is considered to be between 600 and 1000 m.

3. The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.

Advantages of Pellatization:

- Improved appearance of the product and the core is pharmaceutically elegant.
- Pelletization offers flexibility in dosage form design and development.
- Pellets are less susceptible to dose dumping.
- It reduces localized concentration of irritative drugs.
- It improves safety and efficacy of a drug.
- Pellets offer reduced variation in gastric emptying rate and transit time.
- Pellets disperse freely in G.I.T. and invariably maximize drug absorption and also reduce peak plasma fluctuation.
- Pellets ensure improved flow properties in formulation development.
- They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules.
- The most important reason for the wide acceptance of multiple unit products is the rapid increase in popularity of oral controlled release dosage forms. Controlled release oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time. With pellets, the above mentioned goals can be obtained through the application of coating materials (mainly different polymers), providing the desired function or through the formulation of matrix pellets to provide the desired effect
- The advantage of multiple unit products as a controlled release dosage form is believed to be their behavior in vivo because of their advantageous dispersion pattern in the gastrointestinal tract and their special size characteristics.

1.4 Methods Used for Pellets Preparation:

Methods for preparing pellets include

1.4.1 Compaction
1.4.2 Powder layering or Drug layering
1.4.3 Solution (or) Suspension layering

1.4.1 Compaction:

In the compaction techniques, extrusion and spheronization is the most popular method. Recently, however, melt pelletization has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer. Other pelletization methods such as globulation, balling and Compression are also used in development of pharmaceutical pellets although in a limited scale.

1.4.2 Powder layering:

Powder layering involves the deposition of successive layers of dry powders of drugs and excipients on preformed nuclei or cores with the help of binding liquids. As powder layering involves simultaneous application of binding agents and dry powders, hence it requires specialized equipments like spheronizer. The primary requirement in this process is that the product container should be solid walls with no perforation to avoid powder lose beneath the product chute before the powder is picked of by the wet mass of pellets that is being layered.

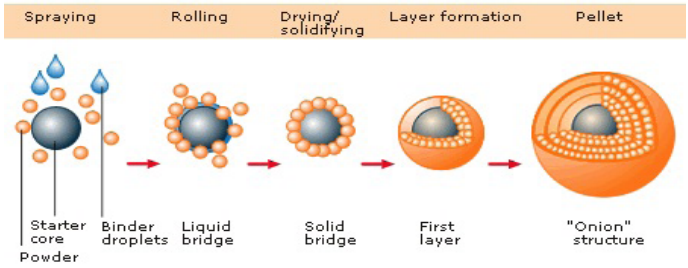

Fig.1: Powder Layering Process

1.4.3 Solution (or) Suspension layering:

Solution (or) Suspension layering involves the deposition of successive layers of solution or suspensions of drug substances and binder over the starter (or) non-pareil seeds, which is an inert material or crystals (or) granules of the same drug. In fact the coating process involved in general is applicable to solution or suspension layering technology. Consequently conventional coating pans, fluidized beds, centrifugal granulators, wurster coaters have been used successively to manufacture pellets by this method. The efficiency of the process and the quality of the pellets produced are in part related to the type of equipment used.

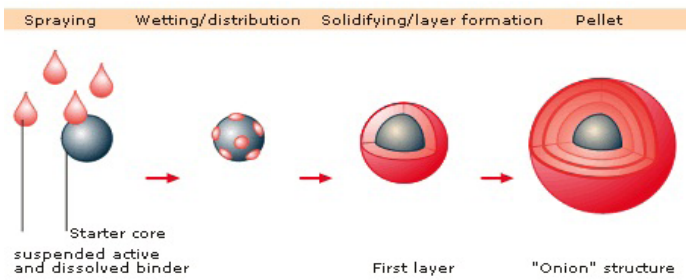

Fig.2: Suspention Layering Process

Pelletization by Extrusion and Spheronization:

The process involves first making the extrudes from the powder material and then converting the extrudes into beads using the spheronizer. The powder material could be any kind of powder (drug powder, ayurvedic powder, food ingredient powder, detergent powder, nuclear powder etc). Beads as fine as 0.6mm can be made.

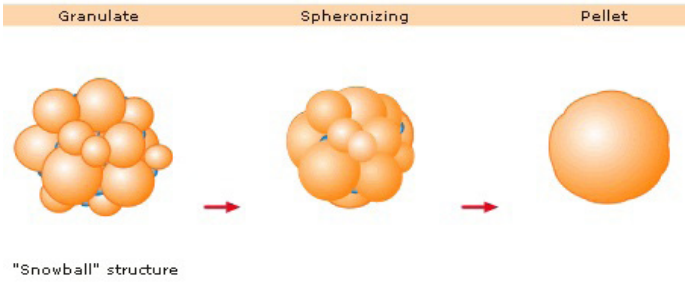

Fig.3: Granulate Spheronizing Process

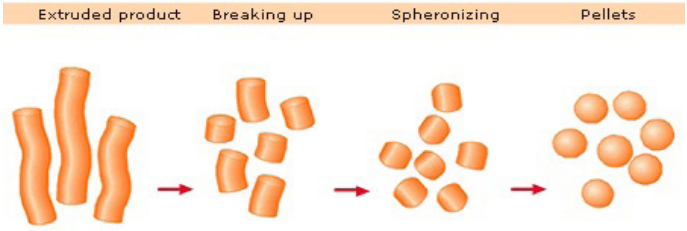

Fig.4: extruded product spheronizing process

Pellatization in Fluid Bed System:

Making uniform spherical pellets in the Fluid Bed System is possible only in the Tangential Spray Attachment or Roto-Processor attachment. The major advantage is that all the operations such as bead formation, bead drying and bead coating can be done in one machine. The top-spray attachment can be used for making granules and bottom spray attachment is used for coating.

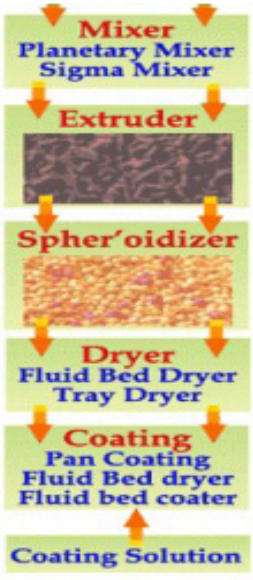

Fig.5: Diagrammatic representation for the entire process

Other Pellatization Methods:

Other pelletization methods such as globulation, cryopelletization, balling, and compression are also used, although a limited scale in the preparation of pharmaceutical pellets.

Globulation or droplet formation consists two related processes, spray drying and spray congealing.

Spray drying:

It is the process in which drugs in the suspension or solution without excipients are sprayed in to a hot stream to produce dry and morespherical particles. This process is commonly used for improving the dissolution rates.

Spray congealing:

It is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to produce spherical congealed pellets. Both immediate and controlled release pellets can be prepared in this process depending on the physiochemical properties of the ingredients and other formulation variables.

Cryopelletization:

It is a process in which the liquid formulation is converted in to solid spherical particles or pellets in the presence of liquid nitrogen as fixing medium. The shape depends up on the distance the droplet travel before contacting liquid nitrogen.

Compression:

It is one type of compaction technique for preparing pellets. Compacting mixtures or blends of active ingredients and excipients under pressure prepare pellets of definite sizes and shapes. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablets manufacturing.

Balling:

It is the pelletization process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixtures. The process consists of conversion of finely divided particles in to spherical particles upon the addition of appropriate amounts of liquid.

Excepients for Pellatization:

Formulation aids or excipients are added to pharmaceutical dosage forms mainly to produce sat-

isfactory delivery of the drug to the intended site, to impart favorable characteristics to the dosage form and to facilitate the manufacture of the product. Since pellets are intended to be administered orally, the excipients used in the pellet dosage forms are typically the same as those used in tablet or capsule formulations.

Sugar Spheres:

Sugar spheres contain not more than 92% of sugar, calculated on dry basis. The remainder consists of starch.

Table 1: Examples of commonly used excipients:

Filler	MCC, starch, sucrose, lactose, mannitol
Binder	Gelatin, HPC, HPMC, MC, PVP, sucrose, starch
Lubricant	Calcium stearate, glycerin, PEG, Mg. stearate
Separating agent	Kaolin, talc, silicon dioxide
Disintegrant	Alginates, croscarmellose sodium
pH adjuster	Citrate, phosphate, meglumine.
Surfactant	Polysorbate, SLS
Spheronization enhancer	MCC , sodium CMC
Glidant	Talc, starch, Mg stearate.
Release modifier	Ethyl cellulose, carnauba wax, shellac.

Table 2: Available Marketed Pellet Products:

PRODUCT	COMPANY
Bontril SR	Carnick laboratories, Inc
Brexin L.A	Savage Laboratories
Catazyme S	Organon Pharmaceuticals
Compazine	Smith Kline & French
Dilgard XL 180	Smith Kline & French
Elixophyline	Cipla Ltd
Fastin	Berlex Laboratories
Hispril	Berlex Laboratories
Ibugesic S.R 300	Cipla Ltd
Indocrin S.R	Merck Sharp & Dohme
Nicobid T.S	U.S. Vitamin
Ornade	Smith Kline & French
Omez	Dr. Reddy's Lab
Theobid S.R	Glaxo

Coating Equipments:

Most of the coating processes use three general types of equipments include

The standard coating pan:

The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand, the pan is rotated on its horizontal axis by a motor, the hot air is directed into the pan and onto the bed surface, and is exhausted by means of ducts positioned through the front of the pan .Coating solutions are applied by spraying the material on the bed surface.

The Perforated Coating pan:

Neocota is an updated automatic coating system for tablets and pellets. This model efficiently carries out the following operations: Aqueous film coating of tablets (or) pellets; Non-aqueous organic solvent based film coating of tablets (or) pellets; and enteric film coating of tablets (or) pellets.

The basic units of the system are Coating pan has perforations along its cylindrical portion. It is driven by a variable speed drive with a flame-proof motor. Supply of hot air and exhaust of drying air are arranged to facilitate the coating system through stainless steel plenums positioned on both sides of the perforated coating pan. The pan is enclosed in a cylindrical airtight housing provided with a suitable door and front glass window. This housing of pan with drive is a stainless steel cabinet accommodating the gearbox, AC variable drive, power panel, hot air unit, ex-haust unit and an air fitter.

Liquid spray system is complete with stainless steel liquid storage vessel, variable flow-rate liquid dosing pump, automatic spray gun, and inter-connecting flexible hoses.

The Fluidized bed coater:

The advantage of the Fluid Bed Systems is that not only coating but granulation and pellet formation is also possible in the same machine. Fluidized bed coating is a process that takes place inside a fluidized bed whereby a coat is introduced to cover the intended object in order to protect or modify its behavior. Particulate coating is a form of fluidized bed coating involving the coating of solid Particles inside the bed. In the process, a layer is deposited onto the surface of fluidized solid particles by spraying with a solution of the coating material. The fluidizing gas is also use to dry the deposited solution to form a coat on the surface of the particle. Fluidized beds are used for coating because of their high energy- and mass transfer. Fluidized beds for film coating can be divided into three groups:

- Top-spray
- Bottom-spray equipment

- Tangential-spray

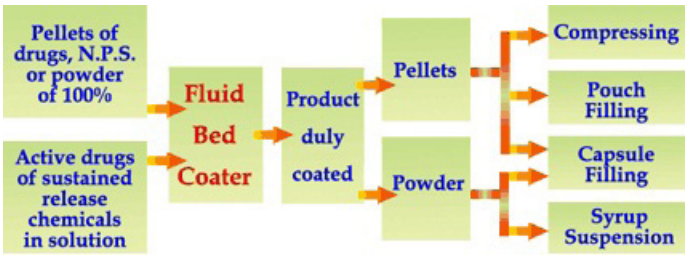

Fig.6: Fluid Bed Coating Flow Chart

Top spray:

The expansion chamber is lengthened to allow powder to remain fluidized longer and to move with a higher velocity, so that agglomeration is minimized. The expansion chamber is conically shaped to allow uniform deceleration of air stream. The filter housing is larger and designed to shake the fines back into the bed interrupting fluidization; this reduces agglomeration tendencies.

The nozzle is positioned low in the expansion chamber so that coating material impinge on the fluidized particle a short distance from the nozzle; this reduces droplet spray drying and provides for longer subsequent drying of the coated particles. The top spray coater has been used to apply aqueous and organic solvent based film coatings, controlled release coatings.

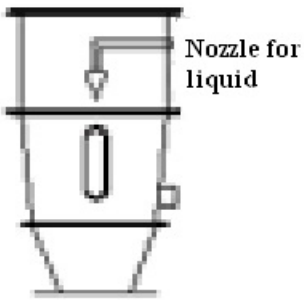

Fig.7: Top Sparying Method

Bottom Spray Coating (Wurster Process):

The wurster machine employs a cylindrical product container with a perforated plate. Inside the container a second cylinder (coating partition) which is raised slightly above the perforated plate, centered. Below this partition a spray nozzle used to dispense the coating solution. The perforated plate is designed with large holes in the area under the coating partition and smaller holes in the remainder of the plate, except for one ring of large holes at the perimeter. The design allows the substrate particles to be pneumatically transported upward through the coating partition, and downward outside this partition. Material passing through coating partition receives a layer of coating material, dries in the expansion chamber, and falls back in a semi fluidized state. The ring of large holes on the periphery of perforated plate prevents the accumulation of material at the container wall. It has been used for coating small particles, pellets and tablets.

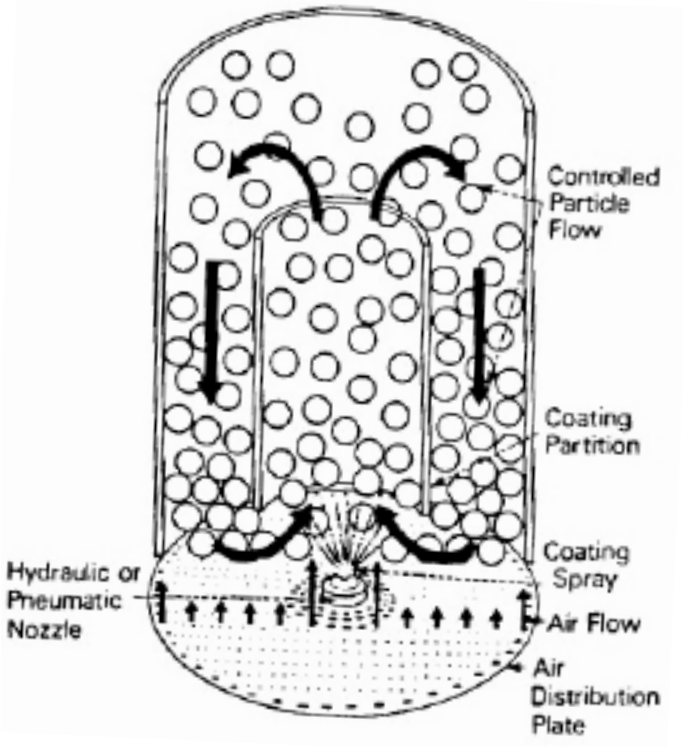

Fig.8: Wurster coating chamber

Table 3: Parameters Used in Bottom Spray Equipment

Inlet temperature	38-42°C
Product temperature	32-36°C
Exhaust temperature	32-38°C
Spray rate	8-12mg/min
Peristaltic pump	12-18 rpm

Tangential Spray (Rotating Disk Granulator):

These techniques have been extended for coating operations and combined with an expansion chamber to form the rotating disk granulator and coater fluid bed device. The basic design employs a rotating disk in the product container.

The disk can be moved up or down to create a variable slit opening between the outer perimeter of the disk and the sidewall of the container. Air is drawn into the product container through the slit under negative pressure. This fluidizes the material along the circumferential surface of the product container. At the same time the disk rotates at varying speeds and moves the product by the centrifugal force to the outer portions where it is lifted by the fluidizing air stream into the expansion chamber. As the material

decelerates, it descends to the center of the disk and repeats the same sequence.

The fluidization pattern is often described as a spiraling helix or rope-like pattern around the inside of the rotor chamber. Spray nozzles can be immersed in the bed of fluidized material and spray applied in tangential fashion with respect to the particle flow.

Fig.9: Rotating Disk Granulator

2. Materials and Methods

Table 4: List of Materials

Materials	Make
Ambroxol HCl	Lee Pharma, Hydrabad, India
Starch	Asaki Kayesi, Banglore, India
PVP K-90	International Fine Chemicals, Canada
Sugar spheres	Lee Pharma, Hydrabad, India
Isopropyl Alcohol	Sigma Aldrich (Chennai)
Ethyl Cellulose	Aqualon, Hydrabad, India
Methylene dichloride	Sigma Aldrich, Chennai, India
Talc	Colorcon, Chennai, India

Table 5: List of Equipments

Equipment	Make
Pulverizer	Bharatiya Equipments
Sifter	Karnavati Engineering
Double cone blender	Platinum Pharma Tech
Coating Pan	Millenium Industries
Tray Dryer	Thermo Control Systems
Magnetic Stirrer	Tarson
Fluidized bed coater	Palm glatt 3kg
pH meter	Digisum electronics
Peristaltic pump	Thermo labs
Dissolution test apparatus	Electrolab USP XXII
HPLC	Shimatzu
Disintegration test apparatus	Electrolab
Stability chambers	Thermo labs
Sieve# 12, 14, 16, 18, 40, 60, 100	Retsec

2.1 Methodology

Ambroxol hydrochloride sustained release pellets are prepared by wurster coating method using different excipients and polymers to release the drug slowly through an extend period of time. The method of preparation of Ambroxol HCl SR pellets involves in two steps, namely drug coating and polymer coating. In the drug coating process drug is coated as a suspension form to dummy pellets and dried and sieved. Drug coated pellets are coated with SR polymer to form SR pellets. These SR pellets are dried, sieved and send to quality control

2.1.1 Process Flow Chart:

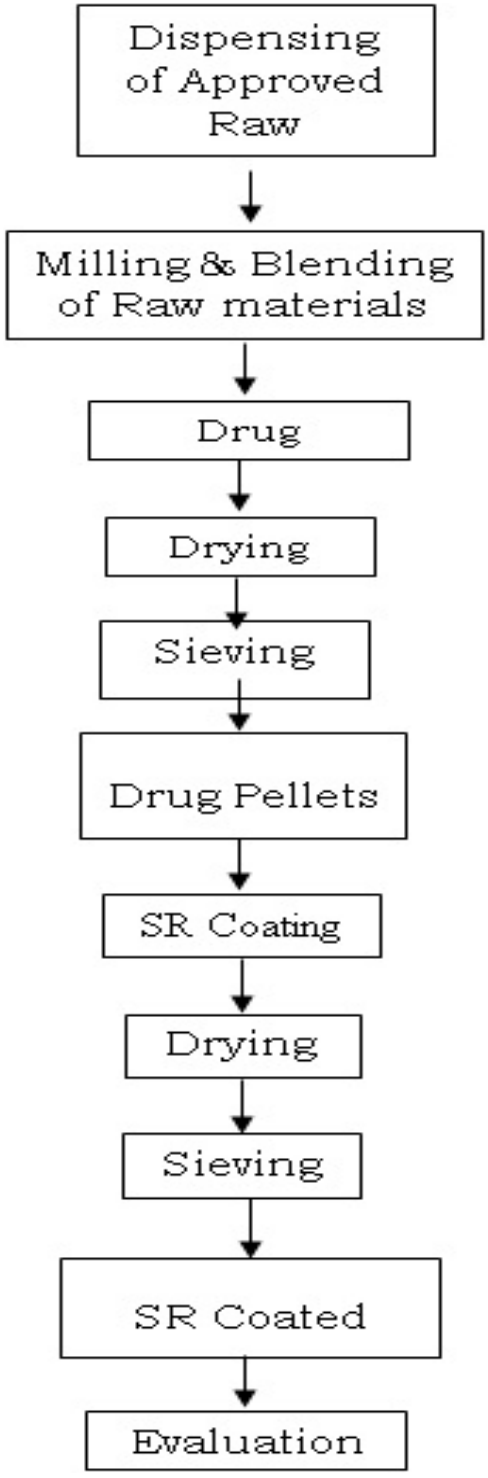

Fig 10: Process Flow Chart

2.2 Formulatin of Ambroxol Hydrochloride Sustained Release Pallets

In the present study 6 formulations of Ambroxol HCl SR pellets were prepared and the formulations composition was mentioned in the Table no. 3

Procedure for the Preparation of Ambroxol Hydrochloride Sustained Release Pallets

Step 1: Dispensing

Weigh the raw materials according to the manufacturing work order into double lined poly bags and affix dispensing labels with all details.

Step 2: Pulverization and Blending

Pulverize the Ambroxol HCL powder thoroughly and collect in double lined Polybags.
Sieve through #30 mesh by using sifter
Load the sifted material along with the starch in double cone blender and mix for 30 minutes.

Step 3: Drug Loading Solution Preparation

PVP K90 is dissolved in isopropyl alcohol under stirring

Step 4: Drug Loading

Load the non-pariel seeds into coating pan and wet it by spraying the Solution from step-3 and dust the blend powder till material stick to wet pellets, to form round spheres and repeat the operation till blend powder completes. Unload the drug pellets from the coating pan and load into tray drier for drying.

Table 6: In-Process Parameters for Sustained Release Coating

S.No	Process parameters	Range
1	Inlet temperature	38-420C
2	Product temperature	32-360C
3	CFC	800-2500
4	Atomization	1-3
5	Spray pressure(Barr)	3-4
6	Peristaltic pump speed	12-18rpm
7	Spray rate(mg/min)	8-12
8	Wruster height(mm)	20-60

Step 5: Drying and Sifting of Drug Coated Pellets

1. Initially dry the pellets under the current of air for 30min switch on the heaters and maintain temperature from 28°c-32°c. Dry the pellets till the moisture content of pellets reduce to 1.5%.
2. Shift the pellets from sieve#18mesh, collected the #25 mesh passing Sifting the #18 mesh passing through #25 mesh retained pellets and Labelled as 18/25 fraction pellets.

Step 6: Preparation of Sustained Release Coating Solution

1. Take isopropyl alcohol and methylene di chloride in a stainless steel container to this add TEC under stirring continuously.
2. To the above solution add ethyl cellulose by stirring
3. Filter the solution through nylon mesh to get a uniform solution.

Step 7: SR Coating

Load the drug pellets into Fluidized bed coater and spray the SR coating coating Solution by using Fluidized bed coater Maintain the required conditions in coater.

Step 8: Drying and Sifting for SR Coated Pellets

1. Initially dry the pellets under the current of air for 30min by using heaters and maintain temperature from 28°c-32°c. Dry the pellets till the moisture content of pellets reduce to 1.5%.
2. Sift the SR coated pellets from sieve #12 mesh, collect #12 mesh passings.sifting the #12 mesh passing through #16 mesh retained pellets and labeled as 12/16 fraction pellets.

Totally 6 Formulation trails were done using the same procedure. During all the stages of the manufacturing process, temperature and humidity was maintained at 25 ± 50C and 50 ± 10 % RH. To optimize the formulation, the capsules were assay by U.V Spectroscopic method and drug release study.

The formula of Trial 4 was optimized and selected for evaluation studies. By using the same formula as that of F4 batch that was taken for the stability study purpose.

Step 9: Filling:

Filling of the pellets into capsules by manually.

Loading of Ambroxol Hcl SR Pellets in Capsules:

Procedure:

1. Size'2' capsules were selected for capsule formulation
2. The pellets were loaded in hard gelatin capsules No-2 by manual filling because it is a lab scale batch.
3. Coated pellets were transferred into capsules by spreading it into equal quantities equivalent to 75 mg Ambroxol HCL .As per the above

procedure, drug loading was carried out for 6 trails.

3. Preformulation Studies:

Preformulation activities range from supporting discovery's identification of new active agents to characterizing physical properties necessary for the design of dosage form. Critical information provided during preformulation can enhance the rapid and successful introduction of new therapeutics entities for humans. Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage form.

3.1 A.P.I Characterization

3.1.1 Physical appearance:

A small quantity of Ambroxol HCl powder was taken in butter paper and viewed in well illuminated place. Finally the colour, odour and texture were observed.

3.1.2 Solubility:

A semi-quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute or vice versa. After each addition, the system vigorously shaken and examined visually for any undissolved solute particles. The solubility was expressed in terms of ratio of solute and solvent.

3.1.3 Determination of bulk density and tapped density:

It refers to a measurement to describe packing of particles and also used to determine the amount of drug that occupies the volume in mg/ml before tapping and after tapping an accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (Vo) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 100 taps and after that, the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density and tapped density were calculated using the following formula:

$$\textbf{Bulk density} = W / V_O$$

$$\textbf{Tapped density} = W / V_F$$

Where,

W = weight of the powder

V_O = initial volume

V_F = final volume

3.1.4. Compressibility index:

Compressibility was calculated from the powder density using the following formula:

$$\textbf{\% Compressibility} = \frac{Pt - PO}{Pt} \times 100$$

Where

P_t = Tapped density and

P_O = Bulk density

3.1.5 Melting point:

The melting point of Ambroxol HCl was found out by capillary method using programmable melting point apparatus.

3.2 Drug-Excepient Compatibility Studies:

Compatibility studies were carried out to study the possible interactions between AMBROXOL HCL and other inactive ingredients in the formulation.

Procedure:

The compatibility studies were carried out at 40oC/75% RH for 0,2 and 4 weeks and control samples were to be kept at 2-8oC. With respect to physical and chemical aspects, they were tested.

3.3 Evaluation Parameters of Sustained Release Coated Pellets

3.3.1 Physical Evaluation:

Angle of Repose:

Angle of repose is used to determine the flow properties of powders, pellets or granules. The method to find angle of repose is to pour the powder on a conical heap on a level, flat surface and measure the included angle with the horizontal.

$$\textbf{Tan } \theta = h/r$$

Where

h = height of the heap

r = Radius of the heap

Table 7: I.P limits

ANGLE OF REPOSE	POWDER FLOW
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very poor

Bulk Density:

Bulk density of a compound various substantially with the method of crystallization, milling or formulation. density is determined by pouring presieved granules into a graduated cylinder via a large funnel and measure the volume and weight.

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

Tapped Density:

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

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

Carr's Index:

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

$$CI = \frac{(TD\text{-}BD) \times 100}{TD}$$

Where
TD = Tapped density
BD = Bulk density

Moisture Content (Or) Water by Kf:

Take around 50ml of methanol in titration vessel of Karl Fischer titrator and titrate with Karl Fischer reagent to end point. In a dry mortar grind the pellets to fine powder .Weigh accurately about 0.5 g of the sample, transfer quickly to the titration vessel, stirr to dissolve and titrate with Karl Fischer reagent to end point.

Calculation:

$$\text{Moisture content} = \frac{V \times F \times 100}{\text{Weight of Sample in Mg}}$$

Where,
F = factor of Karl Fischer reagent.
V = volume in ml of Karl Fischer reagent consumed for sample titration

3.3.2 Chemical Evaluation:

Assay:

Standard preparation:

Weigh accurately about 75 mg of Ambroxol HCl working standard into 100 ml of volumetric flask add 50 ml of Methanol, sonicate and shake well and dilute to volume with Methanol. Mix well. Pipette 2 ml of this solution in to 100 ml volumetric flask dilute to volume with DM water and mix well.

Sample Preparation:

Weigh accurately about 75 mg drug equivalent pellets in a 100 ml volumetric flask, add 50 ml of Methanol, sonicate for 10 minutes. Cool and dilute to volume with Methanol. Filter the solution through what man filter paper. Then take 2 ml of filtrate into 100 ml volumetric flask. And dilute to volume with DM water.

Procedure:

Scan the solution of both standard and sample preparation against Blank preparation between 200 nm and 400 nm measure the absorbance for both standard and sample at 245 nm.

Calculation:

$$A = \frac{AT}{AS} \times \frac{WS}{100} \times \frac{2}{100} \times \frac{100}{WT} \times \frac{100}{2} \times P$$

AT = Absorbance of the sample preparation.
AS = Absorbance of the standard preparation.
WS = Weight of the standard taken in mg
WT = Weight of the sample taken in mg
P = Purity of the standard

Dissolution:

Apparatus	: USP APPARATUS II
Medium	: 0.1N HCl up to 1st two h, 6.8 pH Phosphate buffer for re maining hours
Sampling interval	: 1st h, 2nd h, 4th h, 8th h, 12th h and 24th h
Rpm	: 100
Temperature	: 37°C± 0.5°C

Procedure:

Weigh and transfer the pellets equivalent to 75mg of ambroxol individually in each of the 6 dissolution flasks, containing 900ml of 0.1N HCl. Previously adjust the temperature to37°C± 0.5°C. Collect the samples for first 2hrs and later replace the medium with phosphate buffer 6.8 and collect the samples for remaining 20hrs from a zone midway between the surface of the medium and the top of the rotating blade and not less than 1cm from the vessel wall and filter through 0.45µ membrane filter by discarding the first 5ml.The absorbance is measured at 245nm by using UV-spectrophotometer.

3.4 Stability Studies

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions, with the necessary

extrapolations to ensure the product over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product should be based on the knowledge of the behavior and properties of the drug substance and formal stability studies on the drug substance. Specification which is list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications, is addressed in ICH CS L6AS and IS6B.

3.4.1 Storage Conditions:

In general, a drug product should be evaluated under storage condition that tests its stability and if applicable, its sensitivity to moisture or potential for solvent loss. The long term testing should cover a minimum of 12 months study or at least three batches at the time of submission and should be continued for a period of sufficient time till it covers the proposed shelf life. Long term, accelerated and where appropriate, intermediate storage conditions for drug products are dtailed in below Table.

Table 8: Storage Conditions

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2 °C/ 60% 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

When significant change occurs at any time during 6 months testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria.

4. EXPERIMENTAL RESULTS

4.1 Preformulation Study of Active Pharmaceutical Ingredient:

Table 9: Preformulation Study of Active Pharmaceutical Ingredient

S.No	Characteristics	Results
1	Physical Appearance	A white (or) almost white powder, odourless.
2	Solubility	Sparingly soluble in water and soluble in Methanol, practically soluble in Methylene chloride.
3	Bulk density	0.75gm/ml
4	Tap density	0.89gm/ml
5	Compressibility index	15.73%
6	Melting point	235-2400C
7	Molecular weight	414.6.

4.2 Drug excipient compatibility studies:

Table 10: Drug excipient compatibility studies:

S. No	Composition Details	Observations						
		Storage Condition / Duration						
		Initial	40°C/ 75%RH			60°C		2-8°C
			1 M	2 M	3 M	15 D	30 D	3 M
1	Ambroxol HCL	A White colour powder	NCC	NCC	NCC	NCC	NCC	NCC
2	Ambroxol HCL and Sugar spheres (30 - 35 mesh)	A White colour Powder	NCC	NCC	NCC	NCC	NCC	NCC
3	Ambroxol HCL and starch	A White colour Powder	NCC	NCC	NCC	NCC	NCC	NCC
4	Ambroxol HCL and PVP K-90	A White colour Powder	NCC	NCC	NCC	NCC	NCC	NCC
5	Ambroxol HCL and ethyl cellulose	A White colour Powder	NCC	NCC	NCC	NCC	NCC	NCC

* NCC – No change in colour

4.3 Formulations of Ambroxol HCl SR Pellets

Table 11: Formulations of Ambroxol HCl SR Pellets

S. No	Ingredient (gm)	F1	F2	F3	F4	F5	F6
Drug Coating							
1	Ambroxol Hcl	20	20	20	20	20	20
2	Starch	10	10	10	10	10	10
3	Sugar Pellets	18	18	18	18	18	18
4	PVP K90	1.2	1.2	1.2	1.2	1.2	1.2
5	IPA (ml)	30	30	30	30	30	30
SR Coating							
6	EC 7cps	0.22	0.44	0.66	-	-	-
7	EC 50cps	-	-	-	0.98	1.7	2.46
8	IPA (ml)	0.17	0.17	0.17	0.17	0.17	0.17
9	MDC (ml)	50	50	50	50	50	50
10	TEC (ml)	17	17	17	17	17	17

4.4 Preformulation Characteristics

Table 12: Preformulation Characteristics

S. No	Formulations	Angle of Repose (°)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)
1	F1	25.7±0.09	0.74±0.14	0.86±0.45	13.95±0.71
2	F2	26.4±0.12	0.72±0.56	0.8±0.07	12.19±0.16
3	F3	28.9±0.52	0.69±0.31	0.87±0.13	20.68±0.20
4	F4	25.4±0.12	0.64±0.24	0.85±0.51	24.70±0.72
5	F5	24.3±0.41	0.75±0.56	0.89±0.13	15.73±0.63
6	F6	28.2±0.91	0.78±0.12	0.89±0.61	12.35±0.79

4.5 Chemical Evaluation

Table 13: Chemical Evaluation

S.No	Formulations	Moisture Content (%)	Assay (% w/w)
1	F1	2.2±0.30	97.62±0.12
2	F2	2.1±0.61	97.97±0.61
3	F3	2.2±0.17	97.81±0.72
4	F4	2.5±0.41	98.24±0.61
5	F5	2.5±0.16	98.62±0.83
6	F6	2.6±0.19	98.45±0.27

4.6 Dissolution Studies

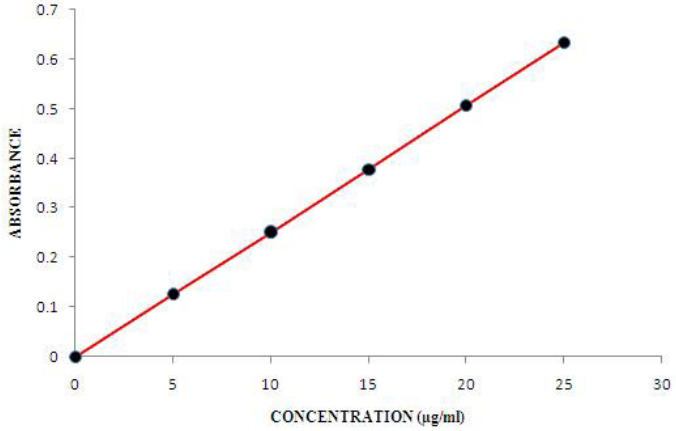

Fig 11: Standard Graph of Ambroxol HCl

λmax : 245
Medium : 6.8 pH Phosphate Buffer

Table 14: Dissolution Studies

S. No	Dissolution Time (h)	Percentage Drug Release (%)						
		F1	F2	F3	F4	F5	F6	Innovator
1	1	26.8	23.6	21.4	18.6	18.2	11.3	18.8
2	2	38.3	36.4	29.5	23.7	22.6	17.2	23.0
3	4	51.7	46.7	45.4	44.8	43.7	40.8	46.1
4	8	62.7	60.9	59.1	57.3	55.8	53.4	60.4
5	12	88.6	87.9	86.6	85.8	73.3	70.9	86.4
6	24	97.3	95.3	93.4	91.3	85.2	81.4	92.7

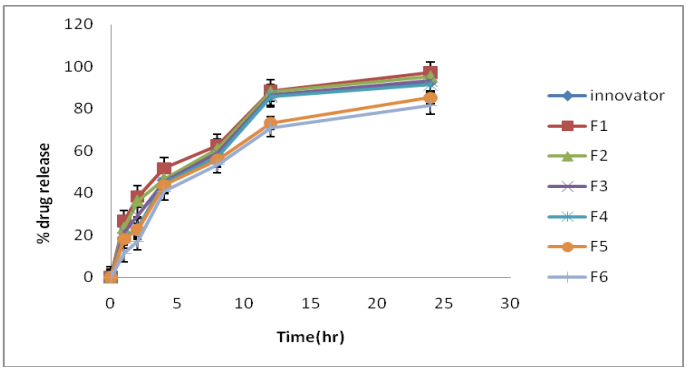

Fig 12: In-vitro Dissolution Profile of all Formulations

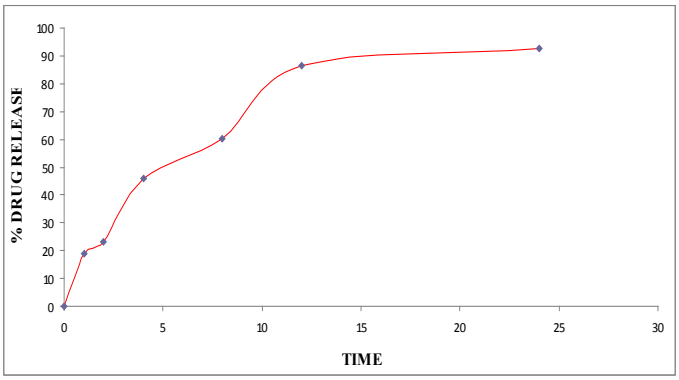

Fig 13: Dissolution Profile of Innovator

Mean Dissolution Time (MDT) Of The Formulations

Table 15: Mean Dissolution Time (MDT) Of the Formulations

S. No	Formulation	MDT (h)
1	F1	5.718
2	F2	5.774
3	F3	5.890
4	F4	5.906
5	F5	6.347
6	F6	6.448

Table 16: Comparison of Dissolution Profiles by Similarity Factors

Formulation	Difference Factor (f1)	Similarity Factor (f2)
F1	24	43
F2	13	57
F3	11	56
F4	**1**	**92**
F5	3	83
F6	16	52

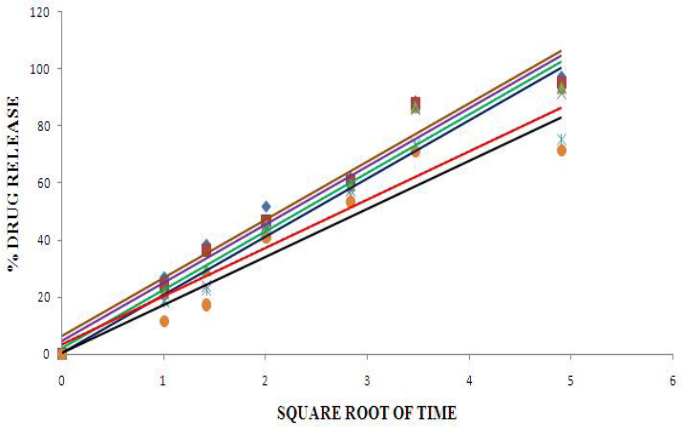

Fig 14: Curve fitting of Dissolution Study – Higuchi Model

Curve fitting of Dissolution Study – Hixon crowl Model

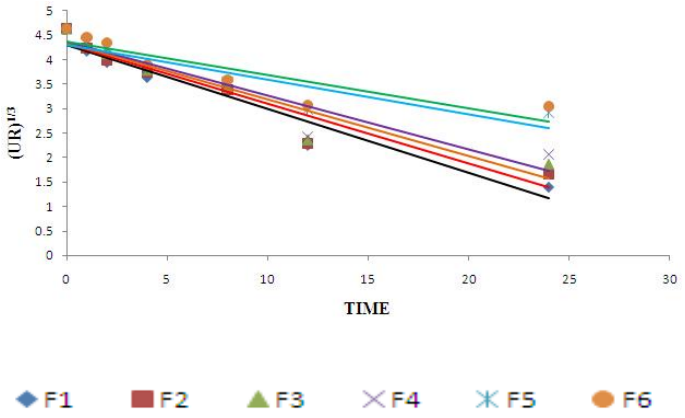

Fig 15: Curve fitting of Dissolution Study – Hixon crowl Model

5. DISCUSSION ON RESULTS

Ambroxol HCl acts as a mucolytic agent, which acts by stimulation of serous cells of tonsils of bronchial tubes. The aim of the present study was to formulate and evaluate the SR pellets of Ambroxol HCl.When preformulation studies were carried out, the colour of the drug loaded pellets was found almost white and round shape. FTIR studies showed no unaccountable extra peaks, which confirm the absence of chemical interaction between the drug and polymer (Fig.6).As the pellets were prepared by Wurster process only a little amount of moisture was expected. The loss on drying of pellets was determined as 2.5%w/w, which indicates that the layering processes as well as the raw materials were suitable to manufacture stable pellets having low moisture content, as moisture play vital role in case of pellets stability (Table 4.4). Flow properties of pellets were estimated by angle of repose. All the formulations, except F5 showed angle of repose within the range of 25-300, indicates that they had good flow property (Table4 .4). The friability of nuclei was 0.26% which is very well within the requirement (below 1%).Tapped density of pellets was found in range of 0.75 – 0.9gm/ml (Table4.4). These values were suitable to fill the pellets in empty hard gelatin capsule shell. Before coating the pellets size distribution was 710 - 850µ and after coating it was slightly increased (710 - 1250µ). For acceptable film coating, a narrow size distribution of pellets is a prerequisite. The size distribution effects the both the performance of the coating and release rate of the drug. SEM analysis was carried out and the photographs of pellets showed a uniform coating of SR polymer, the surface structure was appeared to be smooth (Fig.7).Thus the physical characteristics of the pellets prepared by wurster process was satisfactory and further studies were carried out with the sample.
The percentage drug content of drug was determined by extraction with methanol and analyzed by using UV-visible double beam spectrophotometer at 245nm after the proper dilution. All the formulations showed the percentage drug content of 100±5% (Table4.5).

After 12th h the percentage drug release from the formulations were 88.6%, 87.9%, 86.6%, 85.8%, 73.3%,70.9% for the formulations containing EC7cps 0.5%,1%,1.5% and EC50cps 2%,3.5% and 5% respectively (Table.6). The dissolution profile was shown in Fig.2 and mean dissolution time (MDT) of pellets were given in Table.7.The burst release of Ambroxol HCl from formulations with EC 50cps is comparatively lower than the one with EC 7cps, due to the fact that EC 50cps is more viscous and release retarding capacity is more when compared to EC 7cps.Formulation

F4 was identified to be the best as it matches well with the innovator (f2 = 92).

The release curve of best formulation fits better for First order kinetics (r2 = 0.99), Higuchi (r2 = 0.966) and Hixon crowl (r2 = 0.975) model equations. The regression values are given in Table.9.It implies that the release kinetics follows a First order non-fickian super case-II diffusion process. As it obeys Hixsoncrowel model the drug release may also be due to erosion process. The drug release mechanism from pellets is following both diffusion and erosion phenomenon.The statistical evaluation was performed by one way ANOVA and results were showed in Table.10. From the data it is evident that 'P' value is less than 0.05 in all formulations for 1h, 2h, 4h, 8h, 12h, 24h. Therefore it can be derived that the change in polymer ratio had significant effect on release of drug.

6. SUMMARY AND CONCLUSION

6.1 Summary

Cough is a protective reflex which helps to expel irritant matter from the respiratory tract. The respiratory mucosa contains cells bearing cilia which actively transport the locally produced mucous towards the throat from where it can be either coughed out or swallowed to keep the respiratory tract clean. Ambroxol HCl acts by stimulation of serous cells of tonsils of bronchial tubes, mucous membrane, increasing of mucous secretion content and changing of correlation of serous and mucous components of phlegm, breached under pathological process in lungs.

The present work aimed at developing SR pellets of Ambroxol HCl by Wurster process.FTIR studies showed no unacceptable extra peak which confirms the absence of chemical interaction between the drug and polymer. Angle of repose, tapped density, bulk density values for the formulations were within the range which indicates that pellets prepared by Wurster process were satisfactory for further studies. The percentage drug content of Ambroxol was determined by extraction with methanol and analyzed by using UV-visible spectrophotometer at 245nm. After 12th hour the percentage drug release from the formulations were 88.6%, 87.9%, 86.6%, 85.8%, 73.3%,70.9% for the formulations containing EC7cps 0.5%,1%,1.5% and EC50cps 2%,3.5% and 5% respectively. The dissolution profile was shown in Fig.2.The burst release of Ambroxol HCl from formulations with EC 50cps is comparatively lower than the one with EC 7cps, due to the fact that EC 50cps is more viscous and release retarding capacity is more when compared to EC 7cps.Formulation F4 was identified to be the best as it matches well with the innovator (f2 = 92). The release mechanism was explored and explained with higuchi and hixsoncrowel equations, which indicates that pellets followed diffusion and erosion mechanisms for drug release.

6.2 Conclusion

Accordingly, it can be concluded that the F4 (2%w/w EC 50cps) is robust one and the performance is less likely to be affected by the various factors studied. The formulations were kept at stability studies according to ICH guidelines for 3 months, which showed that all the formulations were stable.

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