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FORMULATION, DEVELOPMENT & EVALUATION OF NOVEL SUSTAINED RELEASE ORODISPERSIBLE TABLETS OF ROPINIROLE HCL BY SPRAY DRYING TECHNIQUE

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ABSTRACT

Ropinirole HCl, a dopamine agonist used in the Paarkinsonism in reatless legs syndrome (RLS) is a highly water soluble drug (133 mg/ml).It is generally generally available as a conventional solid oral dosage form which is a major problem for the patients undergoing the dopamine therapy. The Parkinsonism patients taking Ropinirole HCl conventional tablet cannot swallow the dosage form due to reduced muscular activity, unavailability of water, dryness of mouth and dysphagia. The frequency of administration of this dosage form is minimum thrice a day due to lower dose (upto 8 mg) and shorter half life (5 hrs), so the problem arises in the number of doses. To overcome both these problems the sustained release orodispersible tablet dosage form of Ropinirole HCl is developed which will deliver the drug over a longer period of time. Microspheres of Ropinirole HCl were prepared by spray drying technique using the combination of hydrophilic and lipophillic polymers i.e. HPMC-K1M and Eudragit RL100 & Eudragit RS100 in drug:polymer ratio 1:9.The ODTs were prepared by direct compression of mixture containing microspheres formula F12 using crospovidone as a superdisintegrants, lactose and sodium saccharine as a sweetener. The novel formulation of SR-ODT of Ropinirole HCl (F12) showed acceptable hardness (3.3 Kp), friability (0.84 %) and disintegration time (26 sec).The microsphere of Ropinirole HCl showed an increasing trend of entrapment efficiency and in-vitro drug release. The in vitro drug release study suggests

the sustained release of drug despite being highly water soluble.Scanning electron microscopy, differential scanning calorimetry and FT-IR study of the drug and formulation was carried out.

KEY WORDS: Parkinsonism, Restless legs syndrome, microspheres, spray drying, orodispersible tablet.

INTRODUCTION [1, 2]

Despite tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because of low cost of therapy, ease of administration, accurate dosage, self-medication, pain avoidance, versatility, leading to high levels of patient compliance. Tablets and capsules are the most popular dosage forms. But due to impaired swallowing ability, unavailability of water during travelling, dryness of mouth, many elderly patients find it difficult to take some conventional dosage forms such as tablets, capsules, and powders.This is seen to afflict nearly 35% of the general population. This disorder is also associated with a number of conditions like Parkinsonism [26]. In order to solve this problem and improve patient acceptance and compliance, the development of solid dosage forms that disintegrate rapidly or dissolve even when taken orally without water is being taken. Oral fast-disintegrating dosage forms (tablet or a capsule) are a relatively novel dosage technology that involves the rapid disintegration or dissolution of the dosage form into a solution or suspension in the mouth without the need for water.

Orally Disintegrating Tablet (ODT) [3, 4]

In 1998, the Centre of Drug Evaluation and Research (CDER) Nomenclature Standards Committee defined an orally disintegrating tablet (ODT) as ‘‘a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue’’ (US Food and Drug Administration). The European Pharmacopoeia defined orodispersible tablets as ‘‘uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed’’ (Council of Europe 2002). It is worth mentioning that to date; the United States Pharmacopoeia does not have a published definition for ODTs. Simply,it is a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15 s to 3 min.

Ideal Properties of ODT [4, 5]

An orally disintegrating tablet should

a. Not require water or other liquid to swallow.

b. Easily dissolve or disintegrate in saliva within a few seconds.

c. Have a pleasing taste.

d. Leave negligible or no residue in the mouth whenadministered.

Advantages of ODT [4, 5]

1. No need of water to swallow the tablet.
2. Can be easily administered to pediatric, elderly and mentallydisabled patients.
3. Free of risk of suffocation due to physical obstruction whenswallowed, thus offering improved safety.
4. Suitable for sustained/controlled release actives.

Limitations of ODT [4, 5]

1. The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
2. The tablets may leave unpleasant taste and/or grittiness in mouth if not formulatedproperly.
3. Fast dissolving tablet is hygroscopic in nature so must be keep in dry place.

Techniques used in the preparation of orally disintegrating tablets [6, 7]

Some of the new advanced technologies which are commonly being used in last few decades are summarized as:-

1. Freeze drying/Lyophilization
2. Molding
3. Direct Compression
4. Cotton Candy Process
5. Spray Drying
6. Sublimation
7. Mass Extrusion

Despite of successes of ODT formulations, there are currently no formulations that can deliver an API in a sustained manner, e.g., delivery for 12 h. Preparing ODTs with sustained-release properties is still a challenge. Because ODTs disintegrate or dissolve in the oral

cavity, one way to attain sustained-release from ODTs is to formulate the drug into a micro particulate system. ODT formulations with sustained release properties would bring new benefits that were not possible before. One of the controlled release mechanisms is micro particulate controlled drug delivery. Development of such dosage form will lead to overcome the drawback of conventional solid orals, inconvenience of dosing frequency as well as the problem of dysphagia in geriatrics. [27, 28]

SPRAY DRYING [8, 9, 10, 11]

Spray drying is a process by which highly porous, fine powders can be produced. It is one of the few important processes that can be used for the preparation of the microparticles ranging from 10-1000 µm. Spray drying is the continuous transformation of feed from a fluid state into dried particulate form by spraying the feed into a hot drying medium.

Three types of atomizers are commercially used. They are;

1. Rotary atomizer
2. Pressure nozzle
3. Two-fluid nozzle

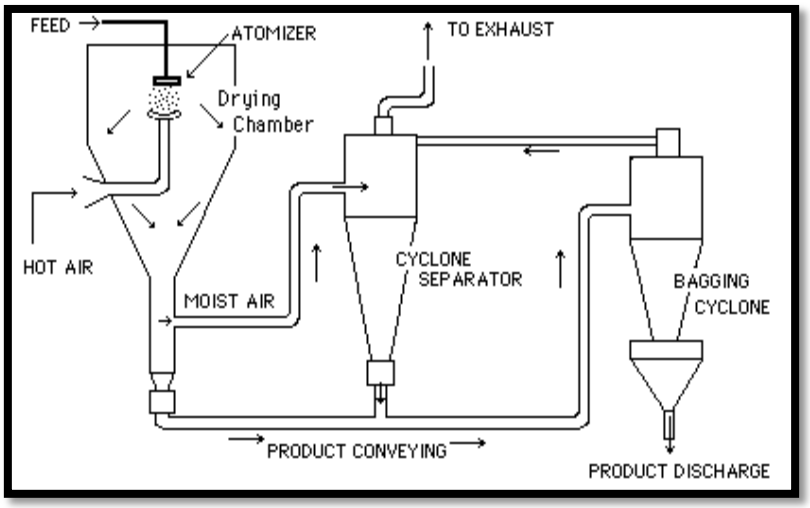


Fig.1 Laboratory Spray Dryer

Principle

Spray drying process mainly involves five steps

(i) Concentration: Feedstock is normally concentrated prior to introduction into the spray dryer.

(ii) Atomization: The atomization stage creates the optimum condition for evaporation to a dried product having the desired characteristics.

(iii) Droplet-air contact: In the chamber, atomized liquid is brought into contact with hot gas, resulting in the evaporation of 95% plus of the water contained in the droplets in a matter of a few seconds.

iv) Droplet drying: Moisture evaporation takes place in two stages-

a. **First stage**- There is sufficient moisture in the drop to replace the liquid evaporated at the surface and evaporation takes place at a relatively constant rate.
b. **Second stage**- It begins when there is no longer enough moisture to maintain saturated conditions at the droplet surface, causing a dried shell to form at the surface. Evaporation then depends on the diffusion of moisture through the shell, which is increasing in thickness.

(v) Separation: Cyclones, bag filters, and electrostatic precipitators may be used for the final separation stage. Wet Scrubbers are often used to purify and cool the air so that it can be released to atmosphere.

Parameters to be controlled

The pharmaceutical spray-dried products have important properties like
-Uniform Particle size,
-Nearly spherical regular particle shape,
- Excellent Flowability,
-Improved Compressibility,
-Low Bulk Density,
-Better Solubility,
-Reduced Moisture Content,
-Increased Thermal stability, and suitability for further applications.

Advantages of spray drying

1. It can be designed to virtually any capacity required. (Feed rates range from a few pounds per hour to over 100 tons per hour).
2. The actual spray drying process is very rapid, with the major portion of evaporation taking place in less than a few seconds.
3. Adaptable to fully automated control system that allows continuous monitoring and recording of very large number of process variables simultaneously.
4. Wide ranges of spray dryer designs are available to meet various product specifications.

5. It has few moving parts and careful selection of various components can result in a system having no moving parts in direct contact with the product, thereby reducing corrosion problems.
6. It can be used with both heat-resistant and heat sensitive products.

Applications

Many pharmaceutical and biochemical products are spray dried, including antibiotics, enzymes, vitamins, yeasts, vaccines, and plasma There are various applications of spray drying like microparticles formulation, granulation and tabletting, aerosol formulation, coating applications, dry emulsions and dry elixirs formulation. Spray drying technology can also be used for the preparation of orodispersible tablets containing microspheres of active ingredients.

SUSTAINED RELEASE OF A DRUG [7, 12]

There has been a remarkable increase in the interest in sustained release dosage form, due to prohibitive cost of developing new drug entities, discovery of the new polymers and improvement in efficiency and safety provided by these. SRDDS is a modified dosage form that prolongs the therapeutic activity of the drug. Accordingly, a prodrug or analogue modification of the drug sustains blood level is considered as sustained release system.

Advantages

1. Decreased local and systemic side effects.
2. Better drug utilization.
3. Decrease in total dose of the drug.
4. Prevents fluctuation of plasma drug concentration.
5. Better Bio-availability of the drug.
6. Improved efficiency in treatment.
7. Improved patient compliance.
8. Economy.

Disadvantages

1. Dose dumping.
2. Reduced potential for accurate dose adjustment.
3. Need for additional patient education.
4. Slow absorption may delay the onset of activity, but this is probably unimportant during multiple regimes.

INTRODUCTION TO MICROSPHERES AS DRUG DELIVERY SYSTEMS [5, 13]

The term microsphere describes a monolithic spherical structure with the drugs or therapeutic agent distributed throughout the matrix either as a molecular dispersion or as a dispersion of particles.

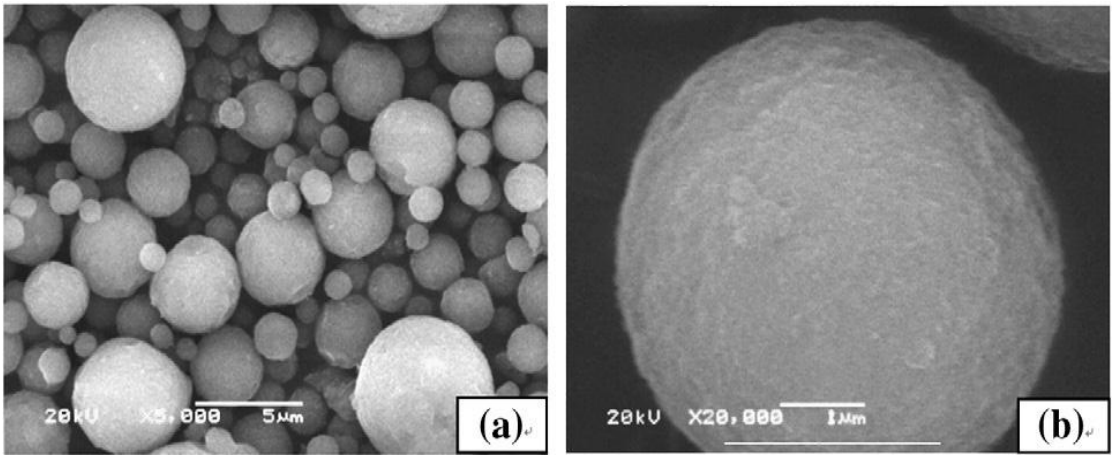


Fig.2 Microspheres

Micro-particles are the polymeric entities in the range of 1-1000µm.They cover two types of forms as Microcapsules which are micrometric reservoir systems and Microspheres which are micrometric matrix systems. Microspheres are essentially spherical in shape, whereas microcapsules may be spherical or non-spherical. Microparticles offer a method to deliver macromolecules by a variety of routes and effectively control the release of such drugs. They may also be used in the delivery of vaccines and molecules such as DNA for use in gene therapy. Microparticles offer effective protection of encapsulated agent against degradation (e.g. enzymatic), the possibility of controlled and local delivery of the drug over periods ranging from few hours to months, and easy administration. The optimum effect of many medical treatments is obtained by maintaining the drug concentration in the therapeutic range over a sustained period of time. This is especially true for highly potent drugs, such as anti-cancer drugs. Administration of the entire drug dose at once using conventional pharmaceutical dosage (e.g. tablets, bolus injection), the whole amount is rapidly released into the stomach, absorbed into the blood stream and distributed throughout the human body.

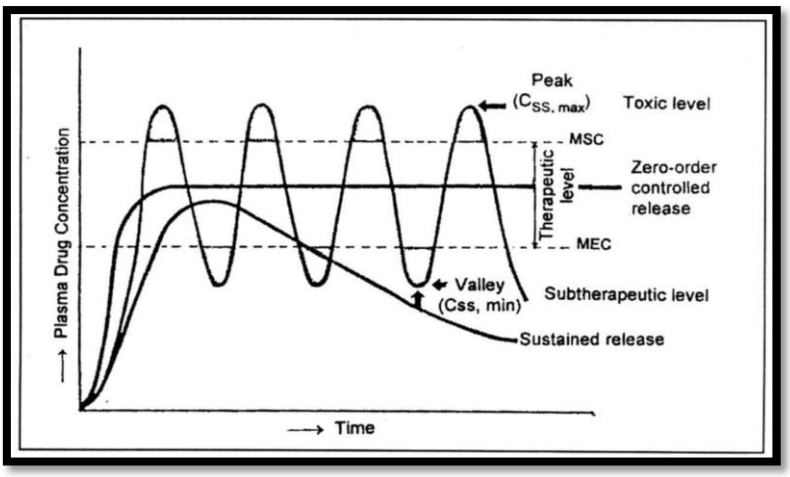


Fig.3: Concentration(c) vs. Time (t) profiles for conventional and controlled release drug delivery.

POLYMERS USED FOR MICROSPHERES [14]

Synthetic Polymers

Synthetic polymers are divided into two types.

a. Non-biodegradable polymers

e.g. Poly methyl methacrylate (PMMA), Glycidyl methacrylate, Epoxy polymers.

b. Biodegradable polymers

e.g. Lactides, Glycolides& their co polymers, Poly alkyl cyano acrylates, Poly anhydrides.

Natural polymers

Obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

Proteins: Albumin, Gelatin and Collagen.

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch.

Chemically modified carbohydrates:Poly(acryl)dextran.

TECHNIQUES FOR THE PREPARATION OF MICROSPHERES [10]

Preparation of microspheres should satisfy certain criteria

1. The ability to incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersability in aqueous vehicles for injection.
4. Release of active reagent with a good control over a wide time scale.

5. Biocompatibility with a controllable biodegradability and Susceptibility to chemical modification.

1. Solvent evaporation and extraction based processes:
   i. Single emulsion process
   ii. Double emulsion process
2. Phase separation-coacervation
3. Polymerization
4. Spray drying
5. Chemical and thermal cross-linking
6. Cross linking using a freeze-thaw technique

MATERIALS AND METHODS

MATERIALS

Ropinirole HCl was received as a gift sample from Ind-Swift Labs, Mohali (Punjab).

HPMC K15M was received as agift sample from Colorcon, Mumbai, Eudragit RL100 & Eudragit RS100 were received as gift samples from Evonik Degussa India Pvt.Ltd, Mumbai while other chemicals and solvents were procured from Loba Chemie, Mumbai as shown in **Table 3.** All materials used were of analytical grade as supplied by manufacturer.

METHODOLOGY

Preparation of Ropinirole HCl microspheres

Ropinirole HCl microspheres were prepared by spray drying technique as described elsewhere. Spray dryer (Labultima LU-222 Advanced) was used for the preparation of microspheres. Briefly, different amount of Eudragit RS100 and HPMC K15M was dissolved in 50 mL of mixture of dichloromethane and acetone in the ratio 1:1 by using a magnetic stirrer for all batches as shown in **Table 1** below. To this the required proportion of HPMC K15M was added and continued stirring until a uniform dispersion was ensured. The proportions of Eudragit RS100: HPMC K15M, Eudragit RS100:ERL100 and Eudragit RS100 alone were varied. The required quantity of Ropinirole HCl (4 mg) was kept constant and was dispersed in the polymer mixture. The polymeric solution was allowed to flow through the feed pipe at 1 mL/min. flow rate. The inlet and outlet temperatures were set.

Table 1: Formulations of Ropiniorle HCl Microspheres

Code	Ropinirole HCl(mg)	Drug:Eudragit RS100	Drug:Eudragit RS100+ERL100	Drug:Eudragit RS100+HPMC K15M
F1	4	1:3	-	-
F2	4	1:5	-	-
F3	4	1:7	-	-
F4	4	1:9	-	-
F5	4	-	1:2.5:0.5	-
F6	4	-	1:4:1	-
F7	4	-	1:5.5:1.5	-
F8	4	-	1:7:2	-
F9	4	-	-	1:2.5:0.5
F10	4	-	-	1:4:1
F11	4	-	-	1:5.5:1.5
F12	4	-	-	1:7:2

The spray drying conditions i.e inlet temperarure, outlet temperature and aspirator flow rate used for the formulations were constant. Inlet temperature was set to 75^0C and outlet temperature in the range 55 ^{0}C-60^{0}C.aspirator flow rate was set to 40 Nm^3/hr.

CHARACTERIZATION OF MICROSPHERES

1) Percentage yield

The percentage yield of different formulations was determined by weighing the microspheres after drying. The percentage yield was calculated as follows.

$$\textbf{Percentage yield} = \frac{\textbf{Practical yield}}{\textbf{Theoretical yield}} \quad \textbf{X 100}$$

as shown in **Table** 6.

2) Drug entrapment efficiency

The various batches of the microspheres were subjected to determination of drug entrapment efficiency. For each batch 50mg of microspheres were accurately weighed and crushed. The powdered microspheres were dissolved in (50ml) methanol. This solution was then filtered through Whatmann filter paper. After filtration, from this solution accurate quantity (1 ml) was taken and diluted up to 10 ml with methanol. Absorbance was measured against methanol as a blank. The percentage drug entrapment was calculated as follows.

$$\text{Percentage drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Shown in **Table 6.**

3) Percentage drug loading efficiency [15, 16, 17]

Percentage drug loading efficiency was determined by UV spectrophotometric method. Drug was extracted from the both the drug containing microspheres using methanol and the absorbance was measured using UV-visible.

$$\text{Percentage drug loading efficiency} = \frac{\text{Drug content in microspheres}}{\text{Weight of microspheres}} \times 100$$

as shown in **Table 6.**

DETERMINATION PRECOMPRESSION PARAMETERS

The flow properties were investigated by measuring the bulk and tapped density.

a) Bulk density

Measuring cylinder of capacity 10mL was taken and 10 gm of powder of all batches were weighed and passed through the sieves and filled into the cylinder and their volumes were noted down and bulk density was calculated. The formula used for calculation is as follow.

$$\textbf{Bulk density} = \frac{\textbf{Mass}}{\textbf{Volume}}$$

The results for bulk density are given in **Table 7.**

b) Tapped density

Measuring cylinder of capacity 10mL was taken and 10 gm of the powder of all batches were weighed and filled into the cylinder, volume of powder measured and noted then that cylinder was tapped about 300 times using bulk density apparatus and again volume of powder measured and tapped density of powder calculated by following formula.

$$\textbf{Tapped density} = \frac{\textbf{Mass of powder}}{\textbf{Tapped volume}}$$

The results for tapped density of material are given in **Table 7.**

c) Carr'sindex

Carr's index of the powder was determined for determination of flow of the powder, for the calculation of Carr's index it requires tapped density and bulk density. Relationship between type of flow and Carr's index are given in table no. 15. Formula for the calculation of the Carr's index is given below.

$$\text{Carr's index} = \frac{\text{Tapped density- Bulk density}}{\text{Tapped density}}$$

Table 2: Relationship between type of flow and their Carr's index

Carr's index	Type of flow
≤ 10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor

Results for the Carr's index of material were given in **Table 7.**

d) Hausner ratio

Hausnerratio gives information about flow ability of the powder, for the determination of the Hausner ratio it requires tapped density and bulk density. Table no. 16 shows relationship between Hausner ratio and type of flow.

Hausner ratio = tapped density / bulk density

Table 3: Relationship between Hausner ratio and type of flow.

Hausner ratio	Type of flow
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very very poor

e) Angle of repose

Angle of repose was determined according to USP 2007 method, funnel was taken and it is fixed at 1cm height on the stand. One cotton was placed at the orifice of the funnel and on that cotton a constant powder weight was placed. The cotton was removed and the diameter formed by powder and height formed by the pile of the powder was measured and angle of

repose was calculated from the following formula. Relationship between angle of repose and flow ability of powder is given in **Table 7.**

$$(\theta) = \tan^{-1} (h / r)$$

Where h = height formed by the pile of the powder.

R = diameter formed by powder.

Results for angle of repose of core are noted down in **Table 7.**

Table 4: Relationship between Angle of repose (θ) and flowability

Angle of repose	Type of flow
25-30	Excellent
31-35	Good
36-40	fair
41-45	Passable
46-55	Poor
56-65	Very poor
>66	Very very poor

FORMULATION OF ORODISPRESIBLE TABLETS OF PREPARED MICROSPHERES

Orodispersible tablets of Ropinirole HCl microspheres were prepared by direct compression technique using rotary tablet compression machine as described elsewhere. The microspheres were blended with the excipients like lactose monohydrate, crospovidone, magnesium stearate, sodium saccharin and talc. All formulations contained microspheres equivalent to 4 mg Ropinirole HCl. Also the level of superdisintegrant i.e. crospovidone was kept constant in all the formulations.

Table 5: Formulation of SR-ODTs

Code / Ingredients	F1	F2	F3	F4	F5	F6
Wt.of microsphere eq.to 4 mg Ropi.HCl	15.33	10.59	7.98	6.34	11.20	9.19
Crospovidone	15	15	15	15	15	15
Lactose monohydrate	115.17	119.21	122.52	124.16	119.3	121.31
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Sodium saccharin	3	3	3	3	3	3
Total weight	**150**	**150**	**150**	**150**	**150**	**150**

Code Ingredients	F7	F8	F9	F10	F11	F12
Wt. of microsphere eq. to 4 mg Ropi,HCl	8.36	6.76	13.67	10.02	8.22	6.24
Crospovidone	15	15	15	15	15	15
Lactose monohydrate	122.14	123.74	116.83	120.48	122.28	125.26
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Sodium saccharin	3	3	3	3	3	3
Total weight	**150**	**150**	**150**	**150**	**150**	**150**

All quantities in milligrams.

EVALUATION OF PREPARED SR-ODTs (POST COMPRESSION PARAMETERS)

a) **Hardness**: The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly.

b) **Friability:** Twenty tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dedusted, and reweighed. The percentage friability of the tablets was calculated using Equation.

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} * 100$$

c) In Vitro Disintegration time: The disintegration time of tablets is usually measured with the disintegration apparatus described in IP. A single tablet was put in the disintegration apparatus and the time required for the disintegration of the tablet was measured in seconds. The medium used for the disintegration was phosphate buffer pH 6.8. The results are given in **Table 8.**

d) Disintegration time in oral cavity: The in-vivo taste evaluation was carried out on healthy volunteers with sound organoleptic senses, with their prior consent. On placing the dosage form in the oral cavity, the disintegration time was noted after which it was further held in mouth for 60 sec by each volunteer, and the bitterness level was checked. After 60 sec, the disintegrated tablet was spitted out and the mouth was rinsed thoroughly with mineral water. Along with the taste evaluation, a simultaneous observation of mouth feel (grittiness or smoothness) and disintegration time noted to assess the quality of the product. The results are recorded in **Table 8** & **Figure 5**.

e) Uniformity of content. Five tablets were selected randomly and dissolved in 100 mL of 0.1 N HCl, stirred for 60 min, and filtered. One milliliter of the filtrate was diluted to 100 mL with 0.1 N HCl. Absorbance of this solution was measured at 250 nm using 0.1 N HCl as blank and content of Ropinirole HCl was estimated.

f) Wetting Time: A piece of tissue paper (12×10.75 cm) folded twice was placed in a Petri dish (internal diameter=9 cm) containing 10 ml of buffer solution simulating saliva, pH 6.8, and. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was recorded. Results of wetting time are given in **Table 8 & Fig5, 6..**

IN-VITRO RELEASE STUDIES

In-vitro release of Ropinirole HCl SR-ODTs was carried out at 50 rpm at 37^0C using the USP dissolution test apparatus Type-II (paddle). SR-ODTs containing weighed amounts of microspheres equivalent to 4 mg of drug were placed in dissolution jar. Dissolution medium used was 800 ml of 0.1 N HCI (pH 1.2) maintained at 37 ± 0.5°C and stirred at 50 rpm for 2 hrs. At predetermined time intervals of 1 hr, 5 ml of sample was withdrawn and replaced with equal amount of 0.1 N HCI (pH 1.2). After that dissolution medium was made upto 6.8 pH for next 10 hrs. The 5 ml withdrawn samples were filtered and suitably diluted with 0.1 N HCI and 6.8 pH buffer solution and analyzed spectrophotometrically. It is shown in **Table 9** and **Fig 8.**

ASSAY OF SR-ODT OF ROPINIROLE HCL

Five tablets of Ropinirole hydrochloride were weighed and powdered in glass mortar. Powder equivalent to 10 mg of the drug was transferred to 100 ml volumetric flask, dissolved in about 50ml distilled water and made up the volume to the mark with distilled water to obtain the concentration of 100 µg/ml. Aliquots of 0.5 to 3.5 ml portions of the standard solution were transferred to a series of calibrated 10 ml corning test tubes and the volume in each test tube was adjusted to 10 ml with distilled water. The absorbance of solutions was measured at 250 nm against reagent blank and calibration curve was constructed. Similarly absorbance of sample solution was measured and amount of Ropinirole hydrochloride in the tablet was determined by referring to the calibration curve. The assay results are shown in **Table 11.**

SCANNING ELECTRON MICROSCOPY (SEM) STUDY

SEM study of Ropinirole HCl microspheres was carried out to evaluate shape and surface characteristics. The results are shown in **Fig.10.**

FT-IR STUDY OF ROPINIROLE HCL MICROSPHERES

The infrared spectrum of the prepeaaed Ropinirole HCl microspheres formulation was drawn which clearly indicates the presence of drug in the formulation and helps to identify the drug. The results are shown in **Fig.11.**

KINETIC MODELING

In order to understand the kinetic and mechanism of drug release, the result of *in-vitro* drug release study of microspheres were fitted with various kinetic equation like zero order (equation 1) as cumulative % release vs. time, first order (equation 2)as log percentage of drug remaining to be released vs Time. Higuchi's model (equation 3) as cumulative % drug release vs square root of time. R^2 and K values were calculated for the linear curve obtained by regression analysis of the above plots. C = K0t …….. (1) Where k0 is the zero order rate constant expressed in units of concentration / time and t is time in hours. log C =log C0 - Kt/2.303 ……(2) Where C0 is the initial concentration of drugs, k is the first order constant, and t is time. Q = Kht1/2 …….. (3) Where Kh is Higuchi's square root of time kinetic drug release constant To understand the release mechanism *in-vitro* data was analyzed by Korsemeyer Peppas model (Equation 4) as log cumulative drug release vs. log time and the exponent 'n' was calculated through the slope of the straight line. $Mt / M\infty = bt^n$…….... (4) Where Mt is amount of drug release at time t, M∞ is the overall amount of the drug, b is constant, and n is the release exponent indicative of the drug release mechanism. If the exponent n = 0.5 or near, then the drug release mechanism is Fickian diffusion, and if n have value near 1.0 then it is non-Fickian diffusion and the results are shown in **Table and Fig**.

RESULTS AND DISCUSSION

Evaluation of Microsphere

Table 6: Evaluation of Microspheres

Code	Yield (%)	EE (%)	Loading efficiency (%)
F1	51.34	26.09	2.61
F2	53.12	37.76	3.80
F3	48.94	50.11	5.01
F4	51.00	63.08	6.31
F5	34.88	35.69	3.60
F6	47.67	43.51	4.35
F7	51.25	47.28	4.72
F8	50.00	59.10	5.91
F9	24.48	29.24	6.08
F10	46.66	39.9	3.99
F11	52.50	48.64	4.86
F12	49.00	64.07	6.41

The percentage yield of different batches was determined by weighing the microspheres after drying. The percentage yields of different formulation were in range of 24.48-53.12 %. The percentage yield of microspheres did not show remarkable change. The drug entrapment efficiency of different batches of microspheres of Eudragit RS100, Eudragit RL100 and HPMC K15M in methanol was found in the range of 26.09-64.07 %. The particle size of Ropinirole HCl microspheres using EudragitRS100: HPMC K15M and it was found to be 90 µm -130 µm. The drug loading efficiency of all batches was found to be 2.61 %- 6.41 % **(Table 6)**.

Higher practical yield was found for batch F12 formulation at the Eudragit RS100: HPMC K15M ratio 7:2. The entrapment efficiency was more (64.07%) at the Eudragit RS100: HPMC K15M ratio 7:2. **Fig.4**. Higher percentage of drug loading was obtained by increasing the amount of Eudragit RS100: HPMC K15M in water at 7:2 ratio (6.41%). The formulation F12 showed more % yield, more % entrapment efficiency, optimum particle size and more drug loading efficiency than others. **(Table 6, Fig 4.).**

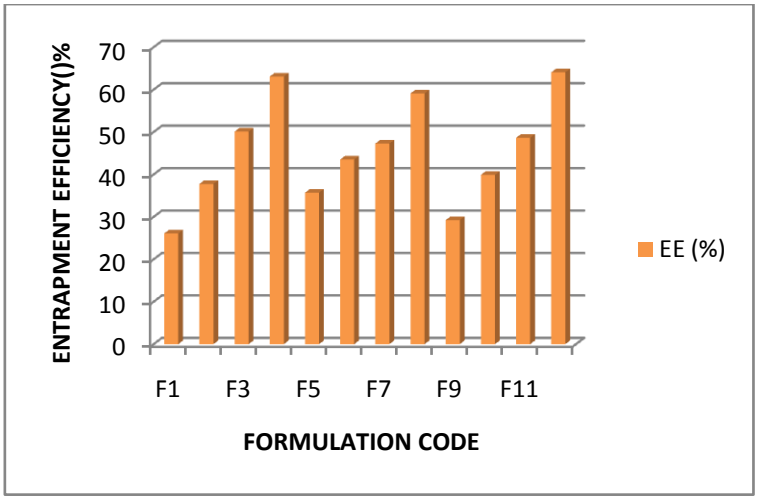


Fig 4: Percentage entrapment efficiency of Ropinirole HCl microspheres prepared by using ERL100, ERS100 & HPMC K15M at different concentrations & combinations.

DETERMINATION OF PRECOMPRESSION PARAMETERS FOR SUSTAINED RELEASE ORODISPERSIBLE TABLETS OF ROPINIROLE HCl

Table 7: Evaluation of precompression material.

Batch	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Hausner ratio	Carr's Index	Angle of Repose(Ɵ)
F1	0.67	0.77	1.149	12.98	30.21
F2	0.65	0.75	1.153	13.33	32.47
F3	0.66	0.76	1.151	13.15	31.63
F4	0.66	0.76	1.151	13.15	33.06
F5	0.66	0.75	1.151	12.00	32.13
F6	0.68	0.79	1.136	13.92	31.49
F7	0.67	0.76	1.134	11.84	34.15
F8	0.65	0.73	1.076	10.95	30.54
F9	0.64	0.73	1.140	12.32	32.30
F10	0.66	0.77	1.166	14.28	35.69
F11	0.67	0.78	1.164	14.10	33.51
F12	0.66	0.76	1.151	13.15	32.40

The precompression material for the preparation of SR-ODTs of Ropinirole HCl was evaluated for the parameters like bulk density, tapped density, Carr's compressibility index and Hausner ratio. The outcomes of these parameters are tabulated in the above table.

Bulk density of all the 12 batches was in the range of **0.64-0.68** gm/cm^3.

Tapped density was in the range of **0.73-0.78** gm/cm^3.

Carr's index was in the range of **10.95-14.28.**

Hausner ratio was in the range of **1.076-1.166.**

Angle of repose was also found in the prescribed range showing good flow characteristics. It was in the range **30.21-35.69.** Only the batch F10 exceeded the normal value of angle of repose. Carr's index in the range 11 to 15 shows good flow properties and Carr's index of all batches is in the range 11-15. Hnece these batches show good flow properties.
Hausner ratio of all the batches was in the range showing good flow properties. Hence selected for the compression.

EVALUATION OF SUSTAINED RELEASE ORODISPERSIBLE TABLETS FOR POST COMPRESSION PARAMETERS

Table 8: Technological characterization of tablets

Parameter / Code	Hardness (Kp)	Friability (%)	Wetting time(Sec.)	Disintegration time (Sec.)
F1	3.3	0.85	21	26
F2	3.2	0.87	20	24
F3	3.5	0.79	23	29
F4	3.5	0.81	22	28
F5	3.4	0.83	24	28
F6	3.5	0.80	24	30
F7	3.2	0.88	21	26
F8	3.3	0.86	21	27
F9	3.2	0.91	20	25
F10	3.5	0.80	22	29
F11	3.4	0.84	25	31
F12	3.3	0.84	21	26

Hardness was between 3.2-3.5 Kp. All the formulations also passed the friability limits which were within 0.79-0.91 % and below 1%. The wetting time is closely related to the disintegration time. There is a direct relationship between the wetting time and disintegration time, which is faster the wetting time, faster is the disintegration time. Wetting time is shown Figure 5, 6 .

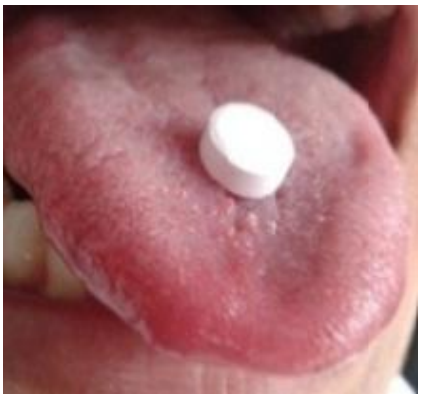
Fig 5: Before wetting

Fig 6: After wetting

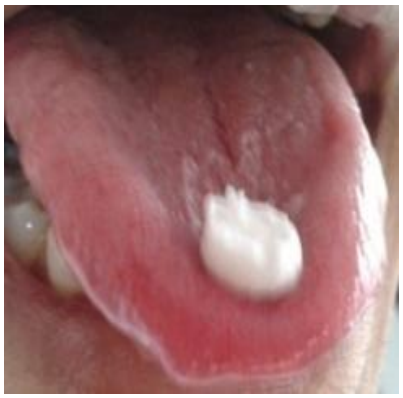
The disintegration time for all the batches was found to be within 24-31 seconds which is within acceptable limits. The in vivo disintegration time for the final formulation was taken in triplicate which was 30± 1 seconds.

The wetting time & disintegration time of F12 formulation was found to be 21 seconds & 26 seconds respectively.

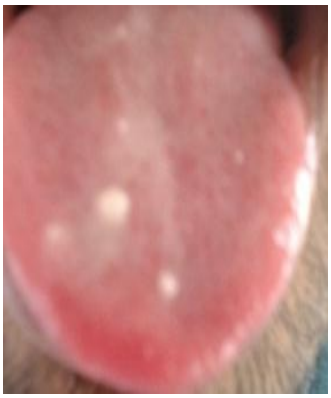
In Vivo study



Time: 0 seconds



Time: 18 seconds



Time: 29 seconds

Figure 7: In Vivo study of SR-ODT for mouth feel, taste and disintegrating time.

The in vivo study was conducted on human volunteer with their prior consent, to screen MDT for various parameters like mouth feel (smoothness or grittiness), disintegration time and taste of mouth dissolving tablet. From in vivo study conducted on human volunteer following results was found regarding:

1. Mouth feel: Test was carried out on human volunteer to check mouth feel (smoothness or grittiness) of ODT, it was found that ODT showed smooth mouth feel without any grittiness.

2. Disintegration time: The volunteer were asked for complete disintegration of ODT, and disintegration time for optimized formulation was found about 29 seconds.

4. **Taste:** The volunteer were also opinioned for taste of ODT, and volunteer sensed ODT to be sweet.

IN-VITRO DRUG RELEASE STUDY

Table 9: In Vitro % Cumulative Drug Release of SR-ODTs

Time(Hr)	Drug Release (%)					
	F1	F2	F3	F4	F5	F6
1	12.76	10.12	8.61	8.05	15.09	9.54
2	23.91	19.92	15.14	14.75	27.92	16.31
3	29.30	26.17	23.69	22.74	34.61	25.17
4	43.01	35.69	36.04	30.21	47.16	36.09
5	59.37	49.95	43.12	39.09	64.73	47.23
6	72.51	61.5	51.94	46.93	83.92	62.21
7	86.19	76.21	63.60	54.33	97.88	79.93
8	98.63	87.12	71.89	62.95		91.37
9		103.5	81.49	67.00		101.13
10			90.13	74.18		
11			99.03	81.11		
12				89.28		
13				101.23		

Time(Hr)	F7	F8	F9	F10	F11	F12
1	9.61	7.54	13.54	10.32	8.24	7.27
2	18.77	13.07	30.32	21.93	15.8	11.97
3	28.07	21.81	28.92	22.38	24.75	21.19
4	37.35	28.29	45.30	32.21	34.50	27.54
5	45.25	38.54	63.32	45.32	41.5	36.59
6	55.36	46.59	75.87	54.05	52.62	41.50
7	64.32	55.45	89.52	67.71	61.29	50.49
8	73.26	65.39	104.82	81.36	65.49	61.49
9	83.64	72.93		91.19	86.88	71.68
10	98.21	82.07		102.11	95.32	79.85
11		89.28			99.34	85.15
12		98.09				90.54
13						96.20
14						103.75

Polymer Eudragit RS100 and HPMC K15M are insoluble in water. Ropinirole HCl microspheres showed sustained release in pH 1.2 and pH 6.8 buffer solutions. Drug release of Ropinirole HCl microspheres was evaluated; at 1 Hr approximately 7.27% of the drug was released initially. Furthermore, drug release from the microspheres was sustained by the polymers. Eudragit RS100 is water insoluble polymer and it does not show pH dependency. As the ERS100 content was increased, the release of drug was decreased significantly and sustained the effect over 14 hours depending upon the ERS100 and HPMC K15M ratio. At the end of 14th hour drug release was found to be 103.75 % (F12) **Table 9**. The microspheres prepared by using ERS100 and HPMC K15M polymer ratio of 1:9 shows better sustained release of Ropinirole HCl than microspheres prepared using same ratios of ERL100:ERS100 & ERS100 alone. **Table 9** and **Fig 8**. The drug release of 'F4' and 'F8' was found to be 101.23 & 98.09 % at the end of 13 Hrs & 12 Hrs respectively as shown in **Table 9** and **Fig 8**.

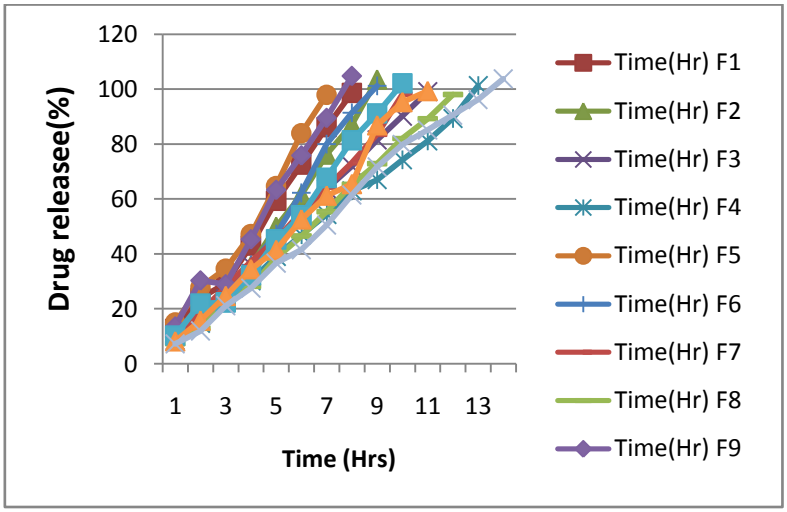


Fig 8: In- Vitro % CDR of Ropinirole HCl microspheres.

In vitro drug release study of Ropinirole HCl SR-ODT formulation F12 in triplicate

Table 10: In vitro drug release study of selected formulation.

	% DRUG RELEASE				
Time (Hrs)	**F12a**	**F12b**	**F12c**	**Avg.**	**SD**
1	7.27	8.91	8.11	8.106	0.835
2	11.97	12.41	12.62	12.33	0.331
3	21.19	20.17	19.97	20.44	0.654
4	27.54	27.09	27.73	27.45	0.328
5	36.59	37.17	37.02	36.92	0.301
6	41.50	42.15	41.29	41.64	0.448

7	50.49	52.28	51.78	51.51	0.923
8	58.49	57.78	57.26	57.84	0.617
9	66.68	67.34	67.09	67.03	0.333
10	73.85	74.01	74.94	74.26	0.588
11	82.07	81.73	82.11	81.97	0.208
12	89.54	90.23	90.01	89.92	0.352
13	96.20	97.18	96.31	96.56	0.536
14	103.75	102.97	101.43	102.71	1.18

The in vitro drug release of the selected formulation was repeated twice to study the reproducibility of the results. The sustained drug release was found to be reproducible in case of the selected SR-ODT formulation F12.

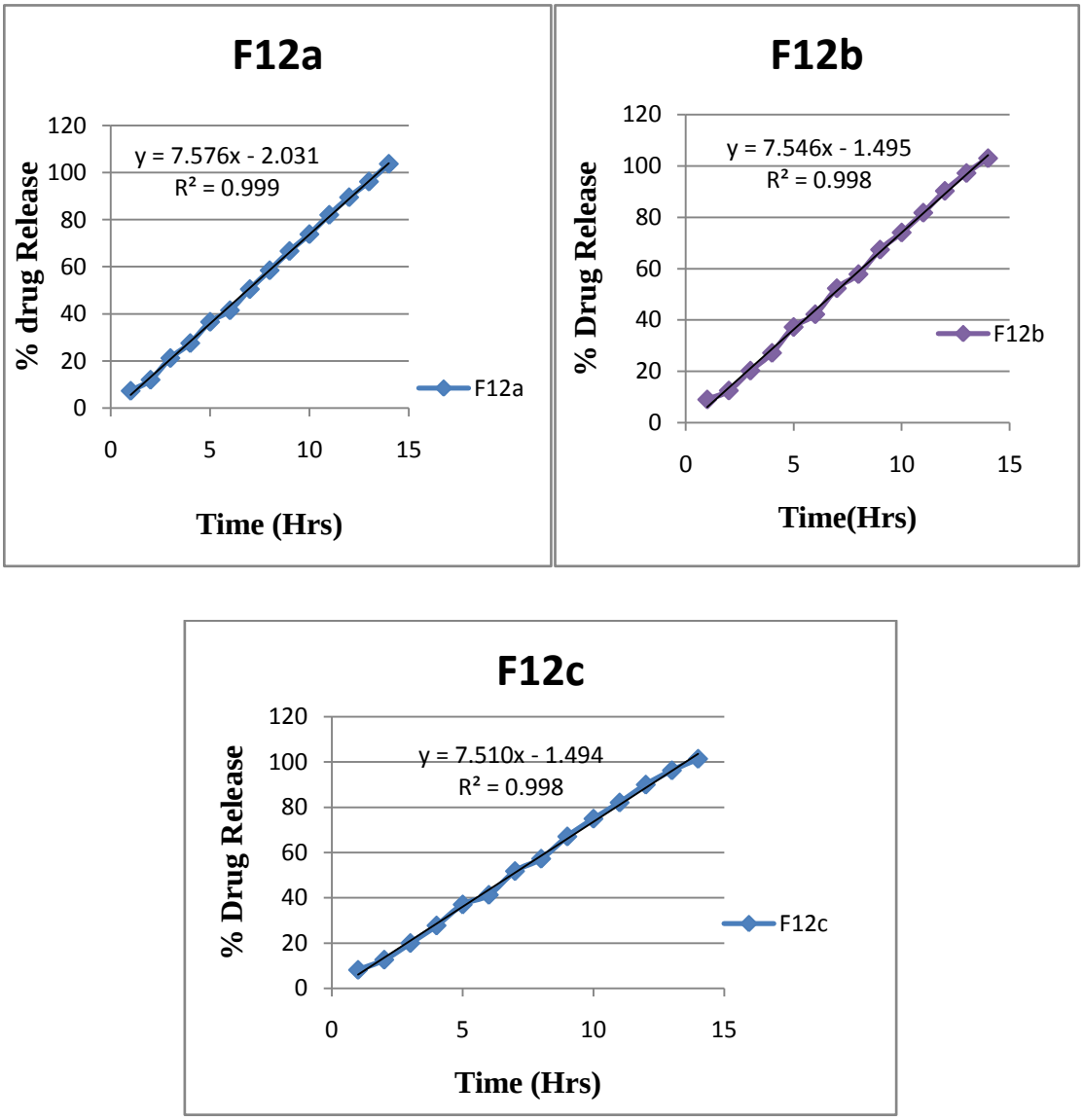


Fig 9: *In vitro* drug release of selected formulation (F12) in triplicate.

ASSAY OF ROPINIROLE HCL SUSTAINED RELEASE ORODISPERSIBLE TABLET (F12)

Table 11: Drug content of Ropinirole HCl SR-ODT

Drug content	Limit
98.75	NLT 98.7% and NMT 101.0%

SCANNING ELECTRON MICROSCOPIC ANALYSIS

Scanning Electron Microscopy of Ropinirole HCl microspheres showed spherical shape with no visible major surface irregularity. Few wrinkles were appeared at the surface and some crystal shape particles appeared as shown in **Fig** .

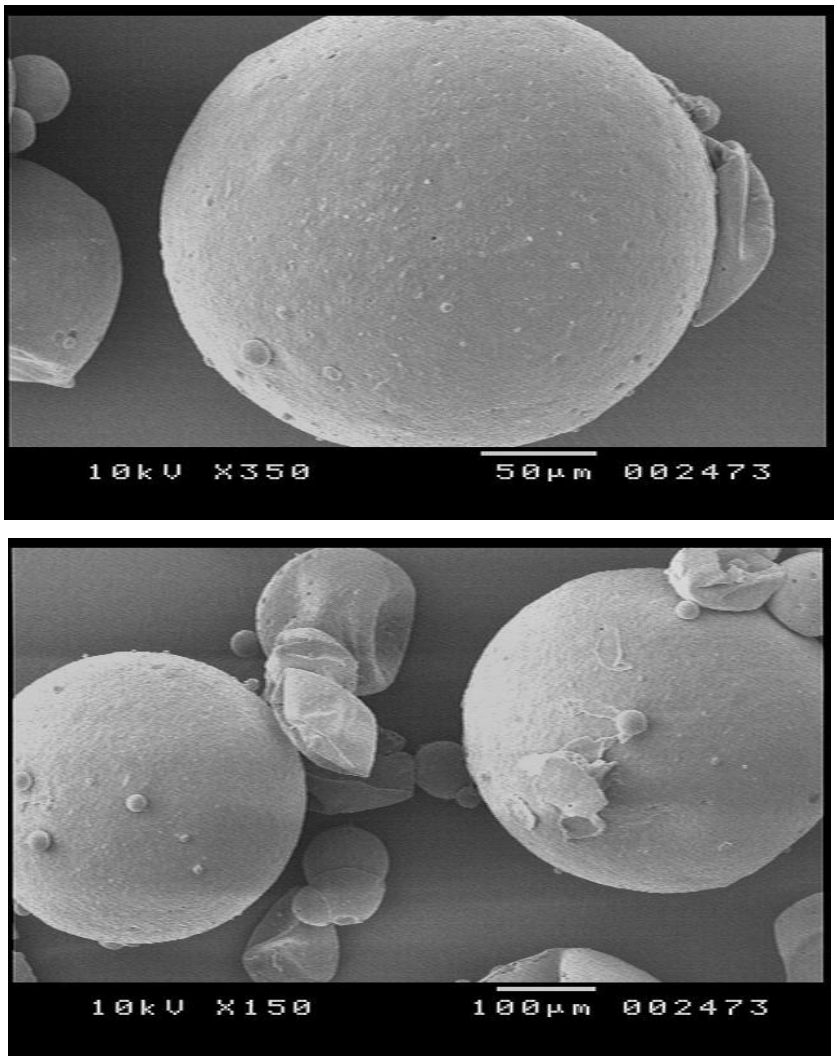


Fig 10: Scanning Electron Micrograph of Ropinirole HCl Microspheres prepared with Eudragit RS100 and HPMC K15M

Table 12: The major peaks observed and corresponding functional groups solubility

Sr. No.	Groups	Peak assignments	Standard Peaks(cm-1)	Observed Peaks (cm-1)
1	-CH group of alkanes	-C-H- rocking vibration	600-1500	761.73
2	-CH group of alcohols,ethers,carboxylic acids,esters.	-C-O- stretching	1000-1300	1071.38
3	Carbonyl group	-C=O stretching	1680-1760	1729.19
4	-CH group of alkanes	-C-H stretching	2850-2960	2927.89
5	Amine group	-N-H stretching	3300-3500	3479.80

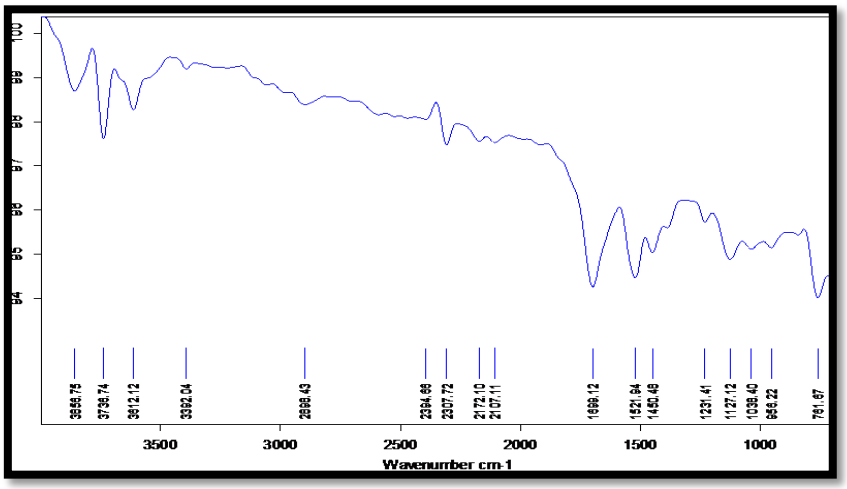


Fig.11: **The FT-IR spectrum of the formulation shows the charecteristic peaks of the drug and polymers.**

The peaks obtained at specific wavenumbers show that there is not significant interaction between the drug and the polymers.

KINETIC MODELING

Table13: Release kinetics study of RopiniroleHCl microspheres of F12 formulation.

Code	Zero Order	First Order	Higuchi	Korsmeyer Peppas	Hixson crowell	Release exponent
	R^2	R^2	R^2	R^2	R^2	n
F12	0.9977	0.578	0.869	0.9978	0.873	0.6003

Fig 12: Zero order release study of F12 batch.

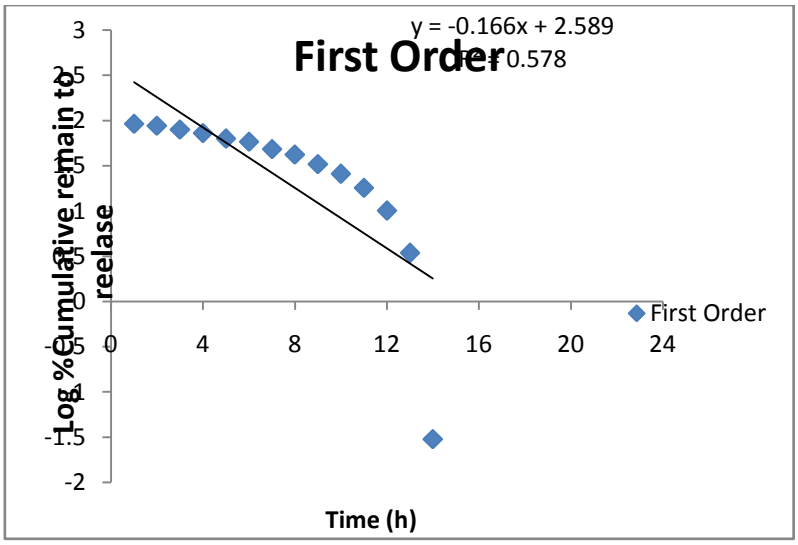


Fig 13: First order release study of F12 batch.

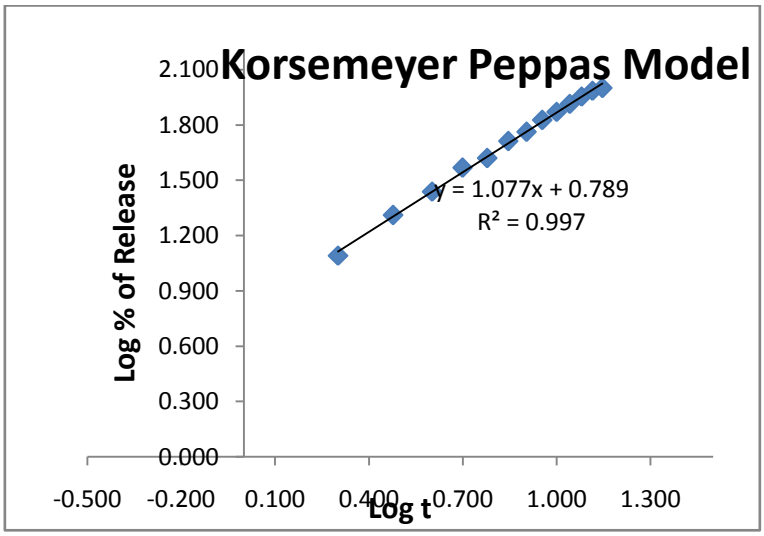


Fig 14: Korsemeyer Peppas model study of F12 batch.

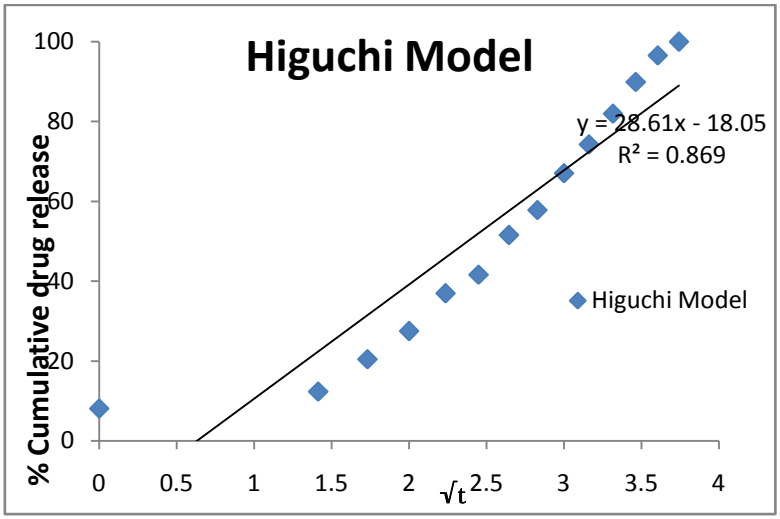


Fig 15: Higuchi model study of F12 batch

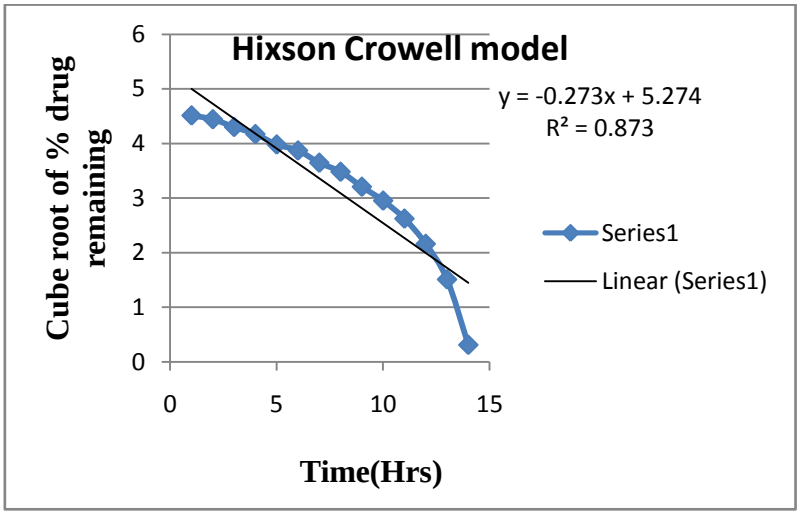


Fig.16: Hixson Crowell model study of F12 batch.

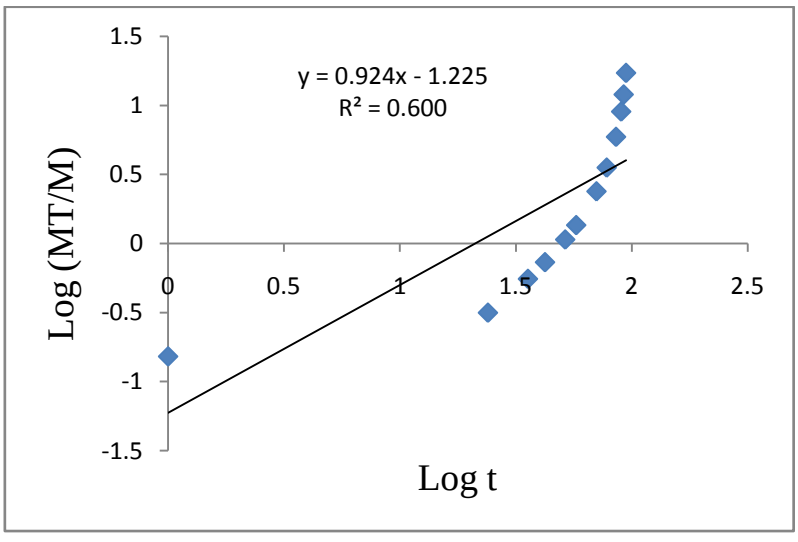


Fig 17: Graph of Release exponent.

The *in-Vitro* release data was applied to various kinetic models to predict the drug release kinetic mechanism. The release constant was calculated from the slope of appropriate plots and the regression coefficient (r^2) was determined. The correlation coefficient (r^2) of Ropinirole HCl was in the range of 0.578-0.9978 for SR-ODTs of microspheres of ERS100 & HPMC K15M various formulations. It was found that the *in-vitro* drug release of orodispersible tablet containing sustained release microspheres was best explained by Zero order kinetics and followed Korsemeyer Peppas model **Fig** . The value of n was 0.6003 i.e.n >0.5 for F12 formulation, indicated that drug release is by Non-Fickian mechanism as shown in **Fig** .

CONCLUSION

Different development aspects of orodispersible tablets containing sustained release microspheres were studied. Sustained released microspheres of Ropinirole HCl were successfully prepared using Eudragit RS100 and HPMC K15M by spray drying technology. Microspheres were prepared at different concentration of Eudragit RS100 and HPMC K15M which were formulated into Orodispersible tablets. It was found that as the concentration of Eudragit RS100 and HPMC K15M increases up to optimum ratio (9:1), microspheres showed good yield, particle size, entrapment efficiency and drug release. Change in concentration of Eudragit RS100 and HPMC K15M in formulation has enormous impact on drug loading and drug release The drug entrapment efficiency of different batches of microspheres of Eudragit RS100 and HPMC K15M was found in the range of 26.09-64.07 %. In case of F12 formulation of Ropinirole HCl SR-ODT, microspheres showed good entrapment efficiency than other formulations.

Percentage drug loading of all formulations were in the range of 2.61-6.41%. Higher percentage of drug loading was obtained in F12 formulation (6.41%). Optimum size of microspheres was obtained for F12 formulation. Tapped density of all formulations was found to be of 0.73-0.78 gm/cm^3 and Bulk densities were 0.64-0.68 gm/cm^3. *In-Vitro* drug release study of Eudragit RS100 and HPMC K15M ratio (9:1) for F12 showed 103.75 % drug release upto 14 hour. F12 formulation showed microspheres of Ropinirole HCl were spherical and smooth. Microspheres of Ropinirole HCl in formulation F12 showed drug release in slow and sustained manner over 14 hours. The *In-Vitro* release data was applied to various kinetic models. The correlation coefficient (r^2) for different kinetic studies was in the range of 0.852-0.990 for microspheres of F12 formulation. The value of n = 0.5 for F12

formulations, indicated that drug release is by Non-Fickinian mechanism. Present research work has successfully developed at different processing and formulation parameters for sustained release Ropinirole HCl microspheres to formulate them into Orodispersible tablets.

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