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RESEARCH ARTICLE

FORMULATION & DEVELOPMENT OF PELLETS OF TOLTERODINE TARTRATE: A QUALITATIVE STUDY ON WURSTER BASED FLUIDIZED BED COATING TECHNOLOGY

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ABSTRACT:

In recent pharmaceutical applications, multiparticulate dosage forms are gaining much importance over single-unit dosage forms. The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulation and yet devoid of the danger of alteration in drug release profile and formulation behavior due to unit to unit variation. The aim of present work is qualitative study on formulation of multiparticulate modified release pellets of Tolterodine Tartrate, by "*Wurster Based Fluidized Bed Coating Process*"(layering technique).The main purpose of the present study was to investigate the feasibility of the wurster process for preparing extended release pellets and subsequently comparing the release profile of the pellets so prepared with a marketed reference product in various media. Additionally, the effects of some independent process variables were evaluated. The effect of the various process parameters i.e. inlet air temperature, product temperature, exhaust temperature, atomization speed, spray pump speed, atomization air volume and air flow on the Wurster process was studied. The results suggested that the process parameters greatly vary with the physical properties of the drug, polymers and solvents used in process for layering of pellets.

Key Words: non-pariel-seeds (N.P.S), E.R coating (extended release coating), Wurster technology, process parameters

INTRODUCTION:

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm and are intended usually for oral administration [1]. Pellets offer a great flexibility in pharmaceutical solid dosage form design and development. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules and tablets [2]. Successful film coating can be applied onto pellets due to their ideal spherical shape and low surface area-to-volume ratio. Available techniques for manufacturing of pelletized multiparticulate systems are:

- Wurster process (solution or suspension layering).
- Extrusion spheronization
- Powder layering

In a study on chronotherapy of rheumatoid arthritis by Akhgari *etal* [3], the effect of varying the ratios of Eudragit L100 and Eudragit S100 on release of coated pellets of indomethacin was evaluated along with the effect of coat thickness using a statistical approach. The major mechanism by which the drug is released from pellets depends on the type of coating; insoluble coating, pH-dependent coating (whose solubility changes dramatically at some location in GI tract) and slowly erodible coating [4]. The method of application and processing conditions may influence the porosity of the coating and consequently the release mechanism.

Bottom-Spray Coating [5]**:** This processing option uses the energies and controls of the Wurster to create a pneumatic mass transport inside a special insert which consists of a perforated bottom screen with defined free areas. Most of the process air is channeled through the center via a tube as such producing a venture effect, which sucks the product from outside the partition past the spray nozzle. Leaving the cylindrical partition and entering the conical expansion chamber the particle velocity is dramatically reduced, excess moisture is rapidly evaporated with the dry product returning again and again through the coating zone to receive more coating material. This uniform statistical residence time of all particles in the coating zone results in a very homogenous coating. Due to the high kinetic energy provided by the pneumatic mass flow moist particles are separated as such allowing the individual coating of even very small particles. Due to the nozzle being positioned directly inside the product and concurrently spraying, a premature viscosity change of the coating droplet is avoided. A layer of coating does not occur during a single pass through the coating zone, but relies on many such passes to produce complete coverage of the surface. Droplet formation, contact, spreading, coalescence and evaporation are occurring almost simultaneously during the process. The nozzles typically used in the fluidized bed coating process are binary: liquid is supplied at a low pressure and is sheared into droplets by air. Droplet size and distribution are more controllable with this type of nozzle than with a hydraulic nozzle, especially at low liquid flow rates. However, the air used for atomization also contributes to evaporation of the coating solvent. This evaporation results in increasing the droplet's viscosity and it may inhibit spreading and coalescence upon contact with the core material. Another factor affecting droplet viscosity is the distance that the droplets travel through the primary evaporation media (the

fluidization air) before impinging on the core. This problem is amplified with the use of organic solvents which evaporate much more quickly than water. In all three process techniques, the nozzle is positioned to minimize droplet travel distance. The most significant process variable is the selection of technique to be used. The majority of the process & formulation variables effecting the film formation are listed below[6].

Process variables:
1. Evaporation
a) Fluidization air volume
b) Fluidization air temperature
c) Fluidization air humidity
2. Application Rate.
a) Solution concentration
b) Coating Zone
3. Droplet Size
Formulation variables:
Coating thickness
Particle size of final dosage form.
Desired Surface characteristics

The objective of the present study was to study the applicability of Wurster coating technology for making sustained-release pellets in a three-step process: (a) seal coating of N.P.S (b) loading of drug by suspension layering onto seal coated nonpareil seeds and (b) subsequent film coating of drug-loaded pellets with ethyl cellulose polymer dispersion in the same equipment.

MATERIALS AND METHODS:

Materials:

Sugar pellets (Nu-pareil, Hanns Werner, Tornesch, Germany) of size fractions 25-30# were used as the cores for coating. Seal coat solution included, ethylcellulose (was obtained from Dow Chemical Company, Midland, USA) and PVPK30 (was obtained from BASF Corporation, USA). Drug layering suspension consisted of Tolterodine Tartrate, (obtained from Ranbaxy Dewas) was of USP grade and hypromellose (Methocel-E5, Colorcon, NJ, USA). Finally extended release coating of polymer was done using aq. dispersion of ethylcellulose (Surelease@, Colorcon, West Point, PA).

Method:

Dummy batches of seal coated pellets, drug layered pellets & E.R coated pellets were prepared to optimize the formulation as well as process variables of Wurster processor. Nonpareil seeds were loaded and seal coating (ethylcelluose) was performed followed by drying and sifting. Further the seal coated pellets were divided into batches and binder concentration was optimized in the drug layer using methocel (HPMC E5) as binder. Finally the dried and sifted drug layered pellets were divided into groups to optimize the percent weight buildup of extended release polymer SURELEASE to obtain the desired dissolution profile.

RESULTS & DISCUSSION:

The drug was found to be compatible with excipients by D.S.C. During formulation and optimization of seal coating, drug layering and E.R coating, various formation and process variables were studied for Wurster based fluid bed coating technology. Finally the optimized batch of E.R coated pellets was evaluated for drug content, particle size distribution and surface morphology (SEM analysis) and *Invitro* dissolution study.

To evaluate the possible interaction between the drug and polymers, thermal analysis was performed by differential scanning calorimetry. The DSC curve of the pure drug showed a single endothermic peak at 210.5^{o}C (Fig.1), corresponding to the melting of the drug (205^{0}C-210^{0}C). In the physical mixture of drug and excipients, endothermic peak for drug was still observed at 206.84^{o}C (Fig.2). The analysis of thermo grams revealed no physical interaction between the polymer and the drug.

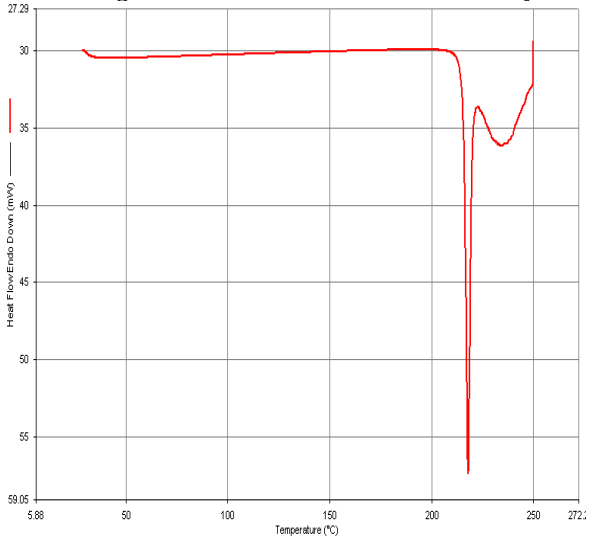

Figure 1: DSC thermogram of pure drug

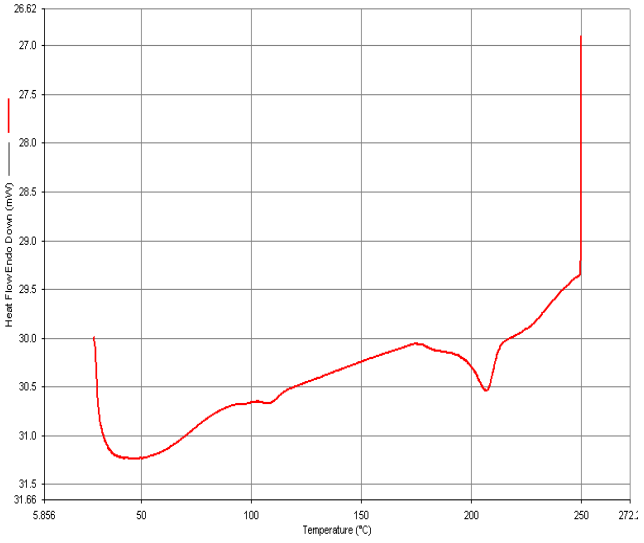

Figure 2: D.S.C Thermogram of Drug Excipients Mixture

SEAL COATING:

Due to high solubility, the sugar spheres immediately get dissolved in aqueous media without build up of sufficient osmotic pressure in the core. In order to retard the dissolution rate of non-pariel seeds, a film of water insoluble ethyl cellulose (8-12% wt/wt) is applied on non-pariel seeds. Before seal coating of nonpareil seeds, dummy batches were prepared to optimize the formulation variables as well as process variables for seal coat (Table.1). The formulation variable chosen was the strength of seal coat solution (organic).Upon increasing the strength of coating solution, it was found that nozzles of Wurster column get blocked due to higher viscosity (because of evaporation of organic solvent inside the column). Hence the conc. of seal coat solution was selected as 4% randomly. The seal coated pellets were evaluated for % weight build-up and % weight of fines generated. The results (Table.2) show that nonpareil seeds were coated to their desired weight build-up (9-10%) with fines within the range of their limits (2-5%). To avoid the generation of electrostatic charges over nonpareil seeds in Wurster column, small quantity of talc was added intermittently.

Table 1: Process parameters of seal coating (Dummy trial 1)

Time (hrs)	Pump speed (rpm)	Spray rate g/min	Blower speed (rpm)	Nozzle press. (pas)	Atom. press. (bar)	Diff. press. (mbar)	Bed temp (^oC)	R.H %	Inlet Temp (^oC)	Outlet Temp (^oC)
0-1	11	64	4.2	2	1.3	5	25	32.6	39	32
1-2	17	100	5.7	2	1.3	4.9	26	32.6	42	33
2-4	17	100	5.7	2	1.3	4.9	26	32.5	30	29
4-6	17	100	5.7	2	1.3	4.9	26	32.4	44	33
6-7	17	100	5.7	2	1.3	4.9	26	32.4	29	28
7-8	18	106	5.9	2	1.3	4.9	26	32.4	41	33

Table 2: Evaluation of seal coated pellets for % weight build-up and % fines

Batch No.	% Wt. Build-up(wt/wt)	% Fines
FB1	9.499%	2.73%
FB2	9.964%	1.79%
FB3	10.163%	2.96%

DRUG LAYERING:

Drug layering was performed by coating aqueous suspension of drug over seal coated pellets. Binder conc. was selected as formulation variable to be optimized in drug layer to achieve proper film formation and minimize the production of fines during coating.Seal coated pellets were further coated with drug layering suspension up to the desired weight buildup having the same conc. of drug but variable binder conc. (1.5%, 2.5% and 4 %) in drug layer.

At 1.5% binder concentration, the suspension might be so diluted that the solid particles deposited loosely on the substrate surface, resulting in low granule density, high porosity and large pore size. As the binder concentration was increased to 2.5% and 4% successively, the solid particles adhered tightly to the substrate surface. Thus the granule density was increased and the porosity and pore size were decreased. Owing to tight binding of the solid particles from the concentrated suspension to the surface of nonpareil seeds, the pellet surface appeared to be smoother than those prepared at lower binder concentrations. Process variables were optimized by dummy batches (Table.3) then finally selected parameters were set for drug layering.

Drug layered pellets were evaluated for assay, drug release profile and amount of fines generated, according to which binder concentration in drug layer was selected. Assay results of drug layered pellets indicate the desired drug content (99 to100%) and content uniformity in all batches besides different conc. of binder in each batch. The dissolution of every uncoated batch was found to be complete within 20 min. The results are depicted in Fig.3. However it was observed that lower binder concentration resulted in slightly faster initial dissolution.

Weight loss in form of fines was also recorded for final selection of binder conc. in drug layer which was found be minimum and within limits (2.1%) in FD3. Due to high drug content, uniform drug release profile, good appearance and less fine generation, formulation batch FD3 (4% HPMC) was chosen for further coating with extended release polymer.

Table 3: Process parameters of drug layering (Dummy trial):

Time (hrs)	Pump speed (rpm)	Spray rate (g/min)	Blower speed (rpm)	Nozzle press. (pas)	Atom. press. (bar)	Diff. Press. mbar	Bed temp. (^oC)	R.H (%)	Inlet temp (^oC)	Outlet temp (^oC)
0-1	6	35.2	4.8	2	2.5	4.8	38	32.7	54	37
1-2	7	41.1	4.5	2	2.5	4.8	38	32.8	52	37
2-3	6	35.2	4.5	2	2.5	4.8	38	32.7	57	42
3-4	8	47.05	4.7	2	2.5	4.9	38	32.5	55	39
4-5	10	58.8	5.3	2	2.5	4.9	38	32.5	56	40
5-6	10	58.8	5.4	2	2.5	4.9	38	32.5	52	39

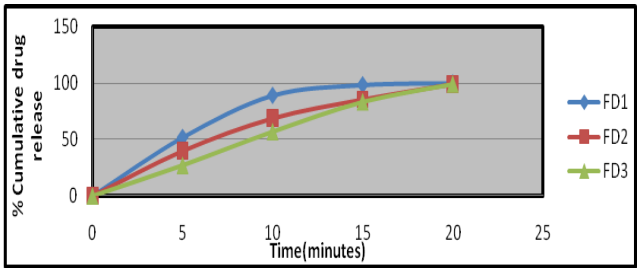

Figure 3: *In-vitro* release profile of drug layered beads (different conc. of binder in 3 batches)

SURELEASE COATING:

Aqueous dispersion of ethyl cellulose (SURELEASE 25%) was diluted to 15% to coat over drug layered beads along with hypromellose as binder in coating solution & formulation variable selected was % weight buildup (% coating) of extended release polymer. To optimize % coating of extended release polymer, three formulations, FS1, FS2 and FS3 with different levels of polymeric coating (6.5% w/w, 7.5% w/w and 8.5%w/w respectively) were manufactured and analyzed for desired drug release profile compared to innovator's product. Drug release from the coated pellets depends on the uniformity of the coating. The success of any coating process is based on the uniformity of coating on the pellets within a batch and reproducibility from batch to batch. When coating is based on weight gain, the thickness of the membrane is controlled by the surface area of the pellets on which the coating is applied.

Drug release through ethyl cellulose membrane is expected to occur by diffusion through the membrane and the micro-pores in the membrane. Therefore, drug release depends on the thickness and the porosity of the membrane. Increasing the level of ethyl cellulose coating, the mean pore diameter and the porosity decreased and the pore size distribution shifted toward smaller pores. In a comparative study of different coating levels of ethyl cellulose**,** drug release was presumed to be mediated via the tortuous matrix of the polymer layer at 2-10% coating while at levels from 12-20%, the release occurred by diffusion through the polymer film. At intermediate levels of 11-12%, both mechanisms are operative. Thus drug release occurs via the tortuosity of the drug-binder layer and concentration gradient across the polymer film.

Process variables such as spray rate, droplet size, bed temperature, spray mode and so forth can strongly influence the drug release. The coating temperature should be sufficiently high to achieve efficient water removal and subsequent particle coalescence. In general, it should be 10°C to 20°C higher than the manufacturing temperature of the polymer dispersion. Generally it has been seen that drug release with Surelease-coated pellets decreases on increasing the product temperature from 32°C to 48°C because of more complete film formation. However, an excessively high inlet temperature can potentially cause difficulties in processing such as electrostatic interactions and agglomeration of the beads because of excessive drying or softening and sticking of the coating. Process variables were optimized by dummy batches (table 4). E.R coated pellets were evaluated for dissolution profile, micromeritic properties (particle size distribution, angle of repose, % compressibility index), drug content and scanning electron microscopy (final optimized batch).

Table 4: Process parameters of ER coating (Dummy trial)

Time (hrs)	Pump speed (rpm)	Spray rate (g/min)	Blower speed (rpm)	Nozzle press. (pas)	Atom. press. (bar)	Diff. press. (mbar)	Bed temp (°C)	R.H (%)	Inlet Temp (°C)	Outlet Temp (°C)
0-0.30	9	52.98	5.8	2	2.5	4.8	38	32.7	47	37
0.30-1	9	52.98	7.9	2	2.5	4.8	3.8	32.8	50	35
1-1.30	9	52.98	8.2	2	2.5	4.8	3.8	32.7	28	29
1.30-2	9	52.9	8.9	2	2.5	4.8	3.8	32.9	29	29
2-2.30	10	58.8	9.3	2	2.5	4.9	3.8	32.9	50	38
2.30-3	10	58.8	6.8	2	2.5	4.7	3.8	32.8	29	29
3-3.30	13	76.4	6.8	2	2.5	4.6	3.8	Do	32	32
3.30-4	15	88.2	6.9	2	2.5	4.7	3.8	33	31	31

Table 5: Final optimized formula for seal -coating, drug -layering & E.R coating of N.P.S

OPTIMIZED FORMULA																	
SEAL COAT				DRUG LAYER							POLYMER LAYER						
S.No	Ingredients	Quantity (Kg)	Percent Solid /Volume (L)	Ingredients	Quantity (FD1) [for 4.1 % wt buildup		Quantity (FD2) [for 5.1% wt buildup		Quantity (FD3) [for 6.6 % wt buildup]		Ingredients	(FS1) [for 6.5 % wt build up]		(FS2) [for 7.5 % wt build up]		(FS3) [for 8.5 % wt build up]	
1.	Ethylcelluose	0.900	3.6%		Wt. (Kg)	Vol. (L)	Wt. (Kg)	Vol. (L)	Wt. (Kg)	Vol. (L)		Wt .(basis of solid content) (Kg)	Wt of aq. dispersn (Kg)	Wt. (basis of solid content) (Kg)	Wt of aq. Dispersn (Kg)	Wt. (basis of solid content) (Kg)	Wt. of aq. dispersion (Kg)
2.	PVP K30	0.100	0.4%	Drug	0.260 (2.6 %)	-	0.260 (2.6 %)	-	0.260 (2.6%)	-	Surelease	0.650	2.15	0.750	2.5	0.850	2.83
3.	Methylene chloride	2.5	1.8 L	Methocel	0.150 (1.5 %)	-	0.250 (2.5 %)	-	0.400 (4%)	-	Methocel	0.140	-	0.140	-	0.140	-
4.	Isopropyl alcohol	22.5	28.58 L	Water (for 4% suspension)	Q.S to 10.25 Kg	Q.S to 10.25 L	Q.S to 12.75 Kg	Q.S. to 12.75 L.	Q.S to 16.5 Kg	Q.S to 16.5 L.	Water (for 15% dispersion)	Q.S to 3.26 Kg	-	Q.S to 3.746 Kg	-	Q.S to 4.25 Kg	-

Table 6: Optimized process variables for different stages of coating

Process Variables	Coating stages of E.R coated pellets		
	Seal Coating	Drug Layering	ER Coating
Inlet air temperature (^{0}C)	38-42°C	53-57°C	37-43°C
Product bed temperature (^{0}C)	33-37°C	40-46°C	33-37°C
Atomization air pressure (bar)	1.2-3	1.2-3	1.2-3
Relative humidity (%)	32-33%	32-33%	32-33%
Blower speed (rpm)	3-7	4-7	5-10
Spray rate (g/min)	35-50	35-60	50-90

EVALUATION OF E.R COATED PELLETS:

Quantitative estimation of drug in E.R coated pellets and content uniformity:

Powdered pellets equivalent to 10 mg of drug was transferred to 100 ml volumetric flask and made-up the volume to the mark with methanol and ultrasonicated for 10 minutes. The solution was then filtered was further diluted with methanol to obtain 40 µg/ml of drug solution. The concentration of drug was determined by measuring the absorbance of the sample at 284.0 nm in zero order spectrum modes. The test was repeated to check the content uniformity. An assay result of ER coated pellets was found to be uniform among all batches and lies in pharmacopoeial limits (95 % to 105%) besides different thickness of polymeric layer in each batch (Table.7).

Table 7: Drug content (assay) of ER coated pellets

Batches ⇨ / Assay ⇩	FS1 (%)	FS2 (%)	FS3 (%)
1.	99.91	98.20	99.83
2.	99.79	99.29	97.87
3.	99.45	98.62	99.12
Average:	99.71	99.03	98.94
Std. Dev.	± 0.238607	± 0.549758	± 0.992321

Characterization for Micromeritic Properties:

Particle size distribution: Upon sieve analysis, ER coated pellets showed a random size distridution (Fig.4). 85-90% of particles were found to be greater than 22 mesh and are about 710-850 µm in size. Optimum particle size distribution was obtained in all the three batches, which resulted in good flow properties.

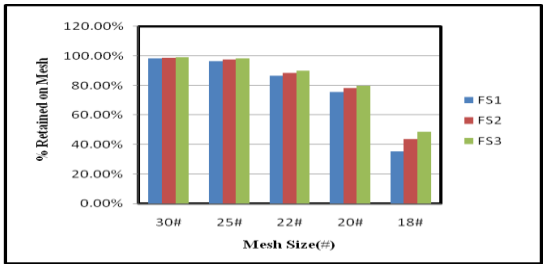

Figure 4: Particle size distribution of E.R coated pellets

Physical Characterization:

E.R coated pellets were evaluated for angle of repose, compressibility index and Hausner's ratio. The results (Table.8) indicated that values of angle of repose and compressibility index for all three batches (lies b/w 20-25^0 and 5-15% respectively) shows the good flow property of pellets.

Table 8: Characterization of pellets for their physical properties

Batch No. → / Parameters ↓	FS1	FS2	FS3
Angle of repose (°)	21	23.4	21.4
Bulk density (g/cm^3)	0.54	0.63	0.47
Tapped density (g/cm^3)	0.625	0.74	0.57
Compressibility Index (%)	13.6	14.8	17.5
Hausner's ratio	1.15	1.17	1.22

In-vitro Dissolution Study of E.R Coated Pellets.

In-vitro dissolution study was performed in both phosphate buffer (pH 6.8) as well as in simulated gastric fluid to estimate the release of drug at various sites of gastrointestinal tract and to determine the maximum absorption site. The different formulations prepared by changing the process variables were subjected to *invitro* drug release studies.

Weighed and placed E.R coated pellets equivalent to 4 mg of drug (based on theoretical claim) into each of three dissolution vessels (USP TYPE 1) and emptied contents of one capsule of marketed formulation (innovator's product) into fourth dissolution vessel and started the dissolution at 100 rpm. At specified time intervals samples were withdrawn. Filtered the solution and measured the absorbance of samples at λ_{max} 281.5 to determine the % cumulative drug release.

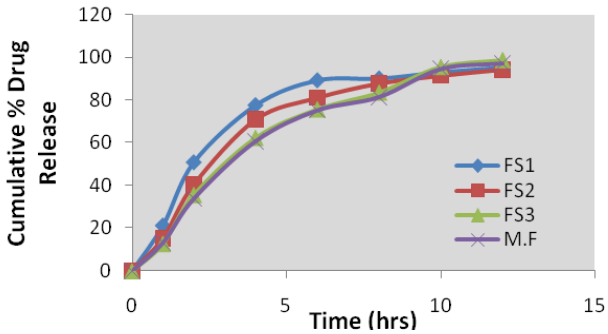

Figure 5: Comparative *invitro* release profile of ER coated pellets w.r.t marketed formulation (M.F) in phosphate buffer (pH 6.8)

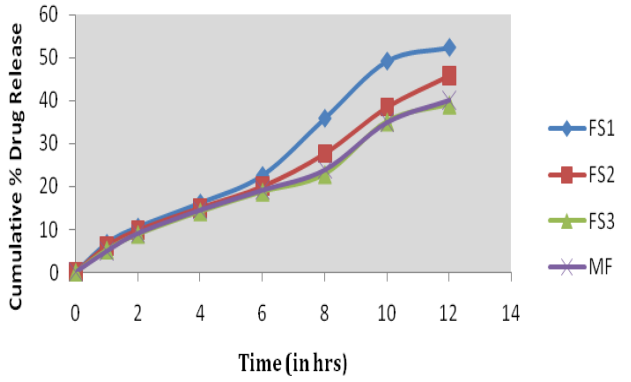

Figure 6: Comparative *invitro* release profile of ER coated pellets w.r.t marketed formulation (M.F) in simulated gastric fluid (pH 1.2)

Surface Morphology and Scanning Electron Microscopy:

The surface characteristics of the pellets were observed by SEM using a scanning electron microscope.

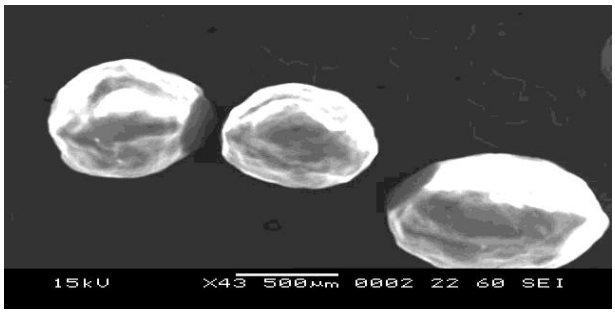

Figure 7: Photomicrograph of ER coated pellet

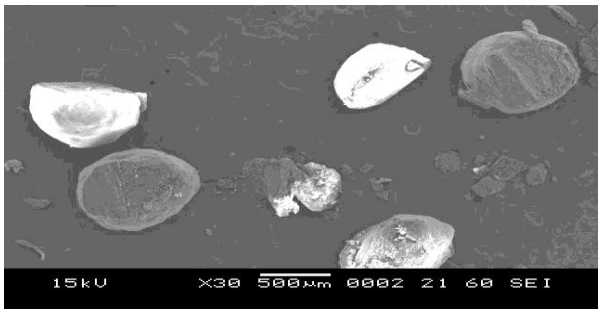

Figure 8: Cross-sectional SEM image of ER coated pellets

Scanning Electron Microscopy (SEM) was performed using (JEOLJSM–6380LA) Analytical Scanning Electron Microscope. Pellets were deposited on carbon conductive 2.5 mm double sided tape and dusted to remove the excess. The samples were imaged using 5-15 KV electron beam. Also the cross sectional images were captured to indentify the drug layer and polymer layer separately.

Data Interpretation by Kinetic Models [8-11]

In order to investigate the release mechanism, the data was fitted to models representing Zero-order, First-order, Higuchi's square root of time, Korsmeyer's Peppas model and Hixson Crowell model of drug release.

The data was processed for regression analysis and interpretation of data was based on the value of resulting correlation coefficients. Higher value of correlation coefficient was obtained in case of Hixson Crowell model. It can be concluded that ficikian diffusion was the predominant mechanism of drug release.

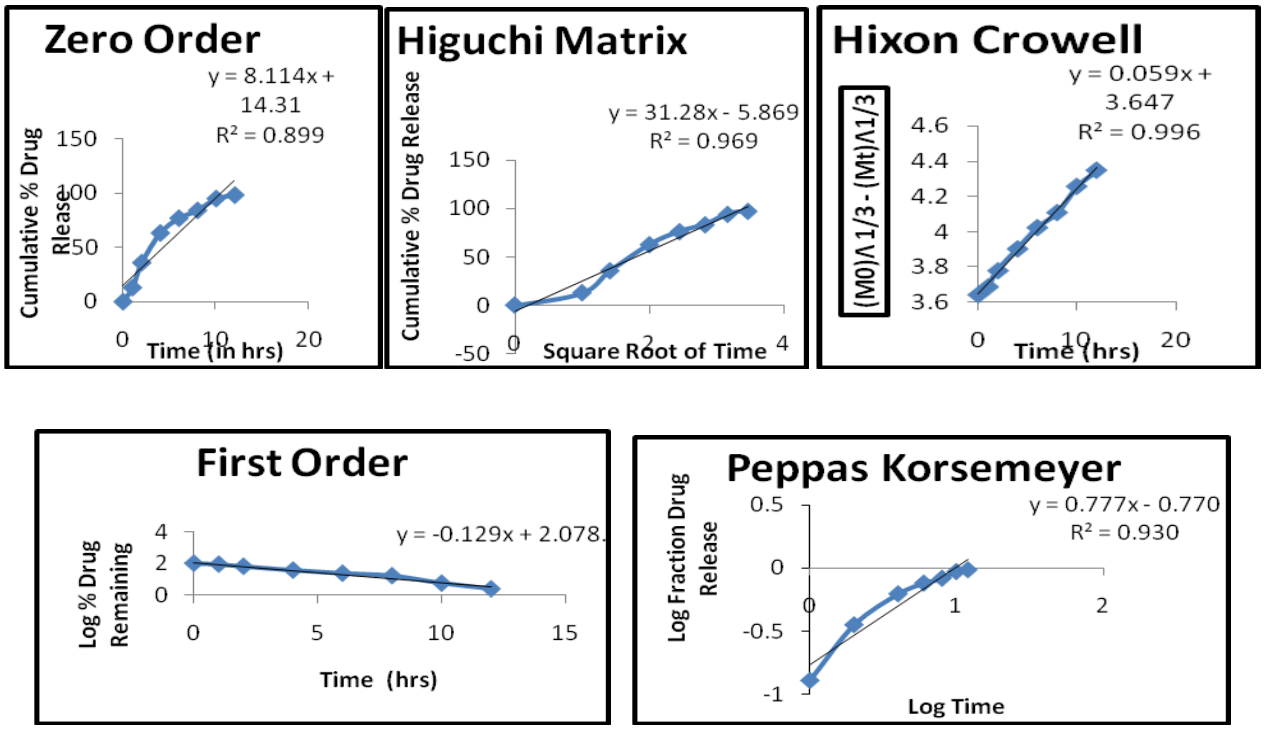

Figure 9: Graphs for Kinetic Models of Drug Release Mechanism

DISCUSSION:

The nozzles typically used in the fluidized bed coating process are binary: liquid is supplied at a low pressure and is sheared into droplets by air. Droplet size and distribution are more controllable with this type of nozzle than with a hydraulic nozzle especially at low liquid flow

rates. There are several process variables as well as formulation variables that affect the efficiency of nozzle. For instance, usage of organic solvent for coating may lead to nozzle blockade due to increased viscosity of solvent during processing because of evaporation of solvent. Hence aqueous solution is more preferred w.r.t to organic solution. Spray rate should not be too high because it may lead to deposition of residual solvent at nozzle tip as well as sticking of coating sol to filter bags leading to reduced m/c efficiency. Strength of coating sol/dispersion/suspension plays important role in nozzle blockade; hence it should not be highly conc. as well as not very much diluted. Particle size of coating material should also be optimum. To improve machine efficiency, a proper control over atomizing velocity, atomizing pressure, fluidization velocity, fluidization volume, inlet temperature, temperature of product bed, relative humidity as well as spray rate should be maintained. Filter bags should be shaken intermittently at regular intervals to remove dust and fines which may result to sticking of coating sol over them leading to weight loss from the system. Development of static electricity takes place due to high fluidization velocity, responsible for high shear b/w the particles and fines generation. Hence talc is added in b/w the process to avoid development of charges over particle surface and ultimately reduction of fines.

CONCLUSION:

Fluid bed processors offer unique opportunity to develop and produce coated controlled release products. However various process parameters easily can alter the performance of a product and hence should be examined thoroughly during the scale up phase. The inter play of various processing parameters presents a great challenge in optimizing the coating process, hence it is extremely necessary to investigate and understand these variables to ensure a reproducible performance of controlled release products.

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