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Wurster based pelletization technique; a qualitative approach

Namrata Gautam[1], Md.Akram Minhaj[2], Piyush Trivedi[3] and Md.Ikram[4]

[1,3]School of Pharmaceutical Sciences, Rajiv Gandhi Technical University, Airport Bypass Road, Gandhi Nagar, Bhopal (MP) – 462033 India.

[2]Faculty of Pharmacy, Jamia Hamdard, New Delhi.

[4]Department of Pharmaceutics, IEC College of Pharmacy, Gr.Noida.

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ABSTRACT

Now a days in pharmaceutical cadre, multiparticulate dosage forms have shown much importance over single-unit dosage forms. The main objective of designing multiparticulate dosage form is to develop a reliable formulation that has advantages over single unit formulation. It is devoid of the danger of alteration in drug release profile and formulation behavior due to unit to unit variation. The present research emphasizes mainly on qualitative study of "*Bottom-Spray Wurster Technology*", by formulation of multiparticulate modified release pellets of tolterodine- tartrate. The aim of the present study is to investigate the feasibility of the Wurster process for preparing modified release pellets and subsequently to evaluate the effects of some independent process variables i.e. inlet air temperature, product temperature, exhaust temperature, atomization speed, spray pump speed and atomization air volume.

Introduction

Coating of particles is an important unit operation in the pharmaceutical industry. There are numerous applications of coating like physical and chemical protection, aesthetic purposes, taste masking and enhanced identification of drugs [1]. 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. Pellets offer a great flexibility in designing and development of pharmaceutical solid dosage forms. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules and tablets [2-3]. Pellets can be manufactured by several technologies, like marumerization (extrusion-spheronisation) or powder layering on inert spheres (e.g. nonpareil seeds) exhibiting high drug loading capability. Successful film coating can be applied onto pellets due to their ideal spherical shape and low surface area-to-volume ratio.

In Wurster technology, the substrate is placed in the product container which is typically an unbaffled inverted truncated cone. A fine retention screen and an air or gas distribution plate comprise the base of the product container. Air is drawn through the distribution plate and the product bed. Inside, a cylinder half the diameter of the base of the chamber, referred to as a *partition* is located. Also there is a second smaller partition, referred as *nozzle surround*, which rests on the bottom of the product container and extends above the nozzle. It is responsible for keeping the substrate away from entering the region of highest droplet density in the spray zone. Product does not enter the spray zone until the pattern is fully developed. The bottom of the Wurster insert is comprised of a fine retention screen and an air distribution or orifice plate. In the center of the plate, a nozzle is positioned to spray upwardly. The porosity of the plate in the area beneath the partition is high, allowing a high volume and velocity to pneumatically transport particles vertically through the partition and spray zone. The coated particles exit the partition and begin to decelerate in the expansion chamber. When the air velocity is such that the particles can no longer be entrained, they drop into the area between the partition and the wall of the coating chamber known as the *down bed*. The air volume in the down bed depends on the size and number of holes in the orifice plate in the area outside of the partition. This air volume should be enough only to enhance downward motion, keeping the down bed as weightless suspension. A critical process variable, *partition height,* a gap between the base of the partition and the orifice plate, is selected such that down bed motion is smooth and as rapid as possible.

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:

a) Coating thickness

b) Particle size of final dosage form.

c) Desired Surface characteristics

Particles cycle through the spray zone in a matter of seconds. 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. 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 before impinging on the core. This problem is amplified

Tele:

E-mail addresses: akram.minhaj1234@gmail.com

with the use of organic solvents which evaporate much more quickly than water. The majority of the process & formulation variables effecting the film formation are listed below [4-5].

Present study focuses on feasibility of Wurster coating technology for making extended release pellets utilizing a three-step process, i.e. (a) seal coating of N.P.S (b) loading of drug by suspension layering onto seal coated nonpareil seeds and (c) subsequent film coating of drug-loaded pellets with ethyl cellulose polymer dispersion in the same equipment.

Materials & Method:

Materials

Sugar pellets (Nu-pareil, Hanns Werner, Tornesch, Germany) (25#) were used as the cores for coating. For seal coat, ethyl cellulose (Dow Chemical Company, Midland, USA) and PVPK30 (BASF Corporation, USA) were utilized. Drug layer; consisted of Tolterodine-tartrate, (Ranbaxy Dewas) was of USP grade and Hypromellose (Methocel-E5, Colorcon, NJ, USA). Finally extended release coating of polymer was prepared using aq. dispersion of ethyl cellulose (Surelease@, Colorcon, West Point, PA).

Method

Various trial batches were prepared at different stages of seal coating, drug layering & E.R coating to study & optimize the process parameters, having a key role in Wurster technology. The very first step performed after optimization with trial batches was seal coating of N.P.S with ethylcelluose. Subsequently, drying & sifting of beads was performed to remove excess moisture as well as any duplexes formed during coating process. Further the seal coated pellets were divided into batches to coat a drug layer over them. Also the binder (HPMC E5) concentration in drug layer was optimized during layering. Finally the dried and sifted drug layered pellets (optimized batch) were divided into groups to optimize the percent weight buildup of extended release polymer (SURELEASE) required for the desired dissolution profile.

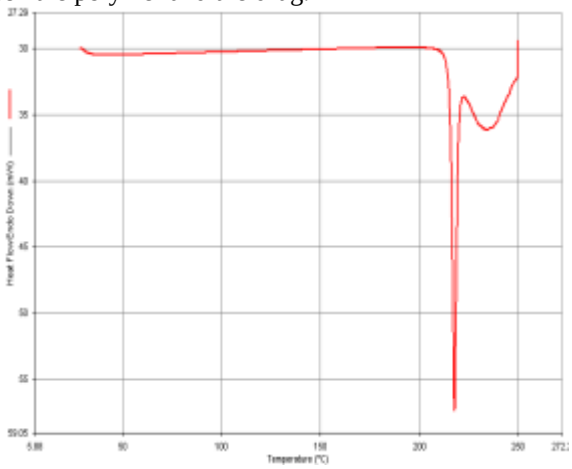
Brief description of steps involved:

1. Prepare seal coating sol of Ethylcellulose and PVP K30 acc. to respective formula.
2. Set the parameters (process and formulation) of Wurster processor for seal coating of NPS.
3. Load and Seal coat the weighed quantities of NPS up to desired wt buildup.
4. Dry and sift the beads through 30# BSS to remove fines.
5. Disperse weighed qty of drug and Hypromellose in water at 35-40^{0}C to prepare drug layering suspension (w/v).
6. Set the parameters (process and formulation) of Wurster processor for drug layering.
7. Reload and coat the seal coated beads with above suspension.
8. Dry and sift the beads firstly through 18# BSS followed by 30# BSS to remove duplexes and fines respectively.
9. Prepare a solution of Methocel in water & add desired quantity of aq. dispersion SURELEASE to prepare extended release coating layer.
10. Set the parameters (process and formulation) of Wurster processor for polymer coating.
11. Reload the drug layered beads and coat with polymer dispersion up to desired wt.
12. Dry and cure the pellets, sift through 16# BSS to remove duplex and 30# BSS to remove fines.

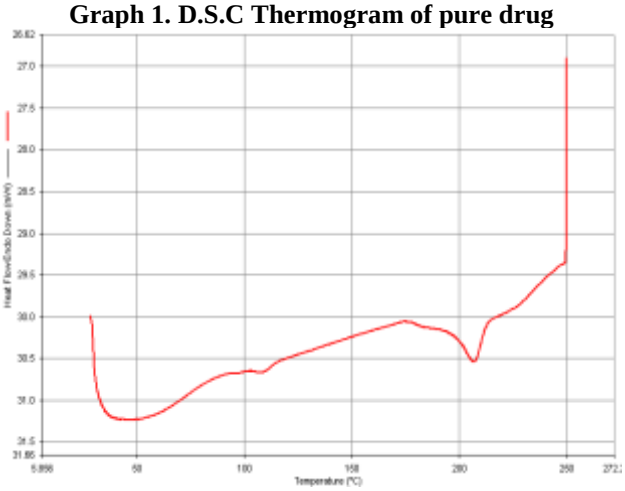
Results & Discussion:

A thermal analysis of drug and excipients was performed by DSC unit (Pyris DSC, Perkin-Elmer) to evaluate incompatibility present. Indium was used to calibrate the temperature change and enthalpy response. During different stages of formulation & development of trial batches (seal coating, drug layering and E.R coating), formulation & process variables were studied and optimized. 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.

No incompatibility was observed between drug and polymers by differential scanning calorimeter. The pure drug showed a single endothermic peak at 210.5^{o}C (Fig.1), corresponding to its melting point (205^{0}C-210^{0}C). Also the endothermic peak of the physical mixture of drug and excipients was obtained at 206.84^{o}C (Fig.2). Since no shifting of endothermic peak was seen in the thermogram (drug-polymer mixture), it reveals that there was no physical interaction between the polymer and the drug.



Graph 1. D.S.C Thermogram of pure drug



Graph 2. D.S.C Thermogram of drug excipients mixture

Seal coating:

The nonpareil seeds contain nearly 80% w/w sucrose and remaining starch. The high concentration of sucrose leads to rapid dissolution of sugar spheres in aqueous media. Due to requirement of modified release systems, the dissolution rate of non-pariel seeds should be retarded, therefore generally a film of water insoluble polymer (8-12% wt/wt) is applied on non-pariel seeds. Various trial batches were prepared to optimize the process parameters of Wurster coater. It was reported that upon increasing the strength of coating solution, the nozzles of Wurster column get blocked due to higher viscosity of coating solution, the reason might be increased evaporation of organic solvent inside the column. Therefore the conc. of seal coat solution was optimized & selected as 4% w/v. Further the seal coated pellets obtained were analysed for the % weight build-up of seat coat and % weight of fines generated. The various optimized formulation batches of seal coat, showed that the

nonpareil seeds were coated to their desired weight build-up (9-10%) & the fines generation was within the range of its limit (2-5%). To avoid the generation of electrostatic charges over nonpareil seeds in Wurster column, small quantity of talc was added intermittently.

Table 1. 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:

For coating of drug over seal coated pellets, aqueous suspension of drug was prepared and sprayed over them. Binder concentration in the drug layer plays an important role in drug release mechanism; therefore it was selected as a formulation variable to be optimized to achieve a proper film formation. Also it is an important parameter for minimum production of fines during coating. Trial batches were prepared to optimize & select process parameters for drug layering in Wurster coater.

Three batches of drug layered pellets were prepared by layering drug suspension over seal coated pellets. Drug layering was performed up to the desired weight buildup on seal coated pellets, having the same conc. of drug in each batch, but variable binder conc. (1.5%, 2.5% and 4 %).

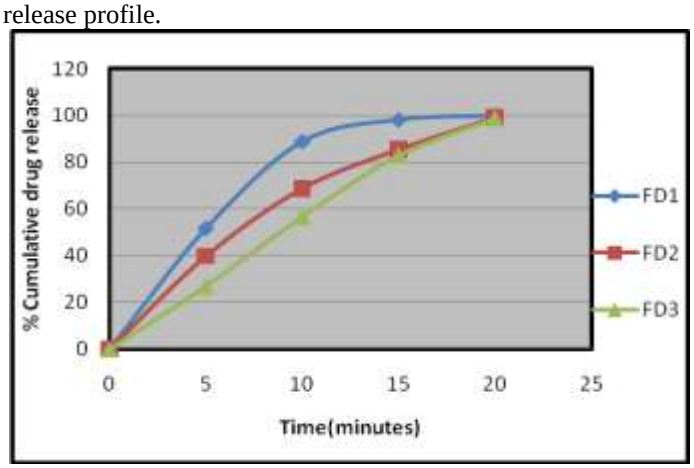
It was found that, when binder concentration is low (1.5%), the suspension might be so diluted, such that the solid particles deposit loosely on the substrate surface, resulting in low granule density, high porosity and large pore size. Whereas upon increasing the binder concentration up to 4%, results the strong adherence of solid particles to the substrate surface leading to increased granule density, less porosity and less pore size. Due to firm binding of the solid particles of drug from their concentrated suspension (2.5-4% binder) to the surface of nonpareil seeds, the drug layered pellet surface appeared to be smoother w.r.t drug layered pellets having lower binder concentration (1.5%).

Characterization of drug layered pellets was performed by evaluating the following parameters: assay of pellets, drug release profile and amount of fines generated. Upon assaying the drug layered pellets, it was found that the drug content is nearly 99 to100% in each batch besides different binder concentration in batches. Dissolution study revealed that, drug layered beads show complete dissolution within 20 min (Fig.3), on contrary it was found that, lower binder concentration resulted in faster initial dissolution.

"Percent-fines generation" is an important parameter for final selection of binder conc. in drug layer. According to the results obtained, an optimized binder concentration in drug layer was selected. Formulation batch FD3 (4% HPMC) showed highest drug content, uniform drug release profile & good appearance, therefore it was chosen for further coating with extended release polymer and 4% HPMC was considered as optimum binder conc. in drug layer.

Surelease coating:

Surelease is an aqueous dispersion of ethyl-cellulose (25%), supplied by Colorcon Ltd. The aqueous dispersion was diluted up to 15% for extended release coating over drug layered beads, having hypromellose as binder in it. Various process variables for E.R coating in Wurster processor were optimized by trial batches. Also percent weight buildup of extended release polymer was selected as a formulation variable for desired release profile. Three formulations, FS1, FS2 and FS3 with different levels of polymeric coating (6.5%, 7.5% and 8.5% respectively) were manufactured and evaluated for desired drug release profile.



Graph 3. *Invitro* dissolution profile of drug layered beads

Also a comparative release profile of formulations was developed with innovator's product to establish bioequivalence. 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.

It is expected that the mechanism of drug release through ethyl-cellulose membrane is diffusion by micro-pores in the membrane. Therefore, drug release depends on the thickness and the porosity of the membrane. Upon increasing the level of ethyl-cellulose coating, the mean pore diameter and the porosity decreases and the pore size distribution shifts towards smaller pores. According to comparative studies on 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.

Various process variables of Wurster technology, such as spray rate, droplet size, bed temperature and, spray mode strongly influence the drug release. Therefore the coating temperature should be sufficiently high to achieve efficient water removal as well as to avoid particle coalescence. In general, it should be 10°C to 20°C higher than the manufacturing temperature of the polymer dispersion. It has been reported that drug release with SURELEASE-coated pellets decreases on increasing the product temperature from 32°C to 48°C due to more complex film formation. It has been estimated that excessively high inlet temperature causes difficulties in processing, leading to electrostatic interactions and agglomeration of the beads because of excessive drying or softening along with sticking of the coating.

Finally, Surelease coated pellets were evaluated for their dissolution profile, micromeritic properties (particle size distribution, angle of repose, % compressibility index), drug content and scanning electron microscopy [6-7].

Evaluation of E.R coated pellets:

Assay & Content Uniformity:

Pellets equivalent to 10 mg of model drug were powdered & transferred to 100 ml volumetric flask. In order to make the volume up to 100 ml, methanol was added and ultrasonicated for 10 minutes.

Table 2. 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]	
					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)
1.	Ethylcelluose	0.900	3.6%														
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 3. 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

Table 4. 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

Table 5. Characterization of pellets for particle size distribution

Batch no.⇨	FS1	FS2	FS3
Sieve no. ⇩	% Retained		
30#	98.38%	98.79%	99.12%
25#	96.41%	97.45%	98.32%
22#	86.5%	88.32%	89.91%
20#	75.45%	78.17%	79.56%
18#	35.21%	43.69%	48.63%
16#	Nil	Nil	Nil

Table 6. Characterization of pellets for their physical properties:

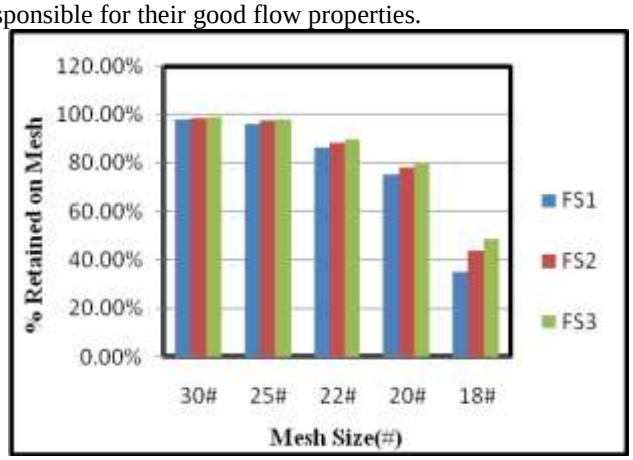
Batch No. → Parameters ↓	FS1	FS2	FS3
Angle of repose (°)	21	23.4	21.4
Bulk density (g/cm^3)	0.54	0.63	0.47
Tapped density (g/cm^3)	0.625	0.74	0.57
Compressibility Index (%)	13.6	14.8	17.5
Hausner's ratio	1.15	1.17	1.22

Filtered the above sol & diluted it with methanol to obtain 40 µg/ml of drug solution. The concentration of drug was obtained by U.V method. Above steps were repeated to check the content uniformity of drug in different samples of pellets. Results showed that the content of drug in E.R coated pellets was found to be uniform among all batches and lies in pharmacopoeia's limits (95 % to 105%) (Table.7)

Characterization for micromeritic Properties:

Particle size distribution:

A random size distridution of E.R coated pellets was obtained upon sieve analysis, (Fig.4). Maximum particles (about 85-90%) were found to be larger than 22 mesh, in the range of about 710-850 µm in size. Therefore in all the three batches, an optimum particle size distribution was observed which is responsible for their good flow properties.



Graph 4. Particle size distribution of E.R coated pellets.

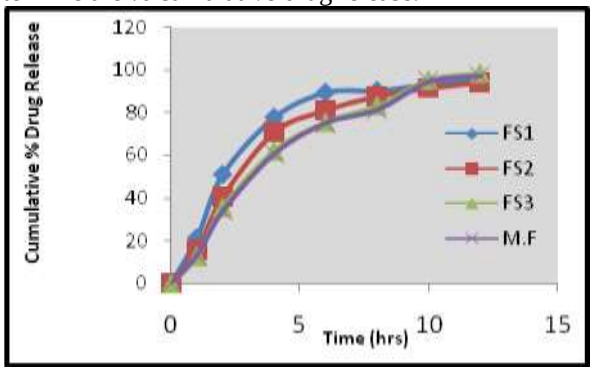
Physical Characterization:

For determination of flow properties of Surelease coated pellets, various physical characterization parameters like, angle of repose, compressibility index and Hausner's ratio were evaluated. The results obtained (Table.9), indicated that the angle of repose and compressibility index (all the three batches) lies b/w 20-25^0 and 5-15% respectively which is the confirmation of the good flow property of pellets.

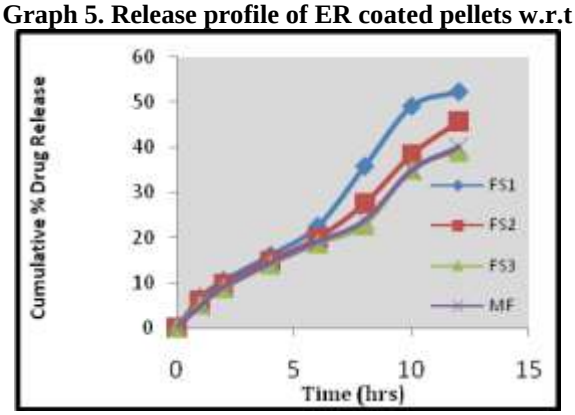
Invitro Dissolution Study (E.R Coated Pellets).

To estimate the maximum absorption site of drug in gastrointestinal tract, *Invitro* dissolution study was performed in phosphate buffer (pH 6.8) as well as in simulated gastric fluid. Therefore, various batches of extended release formulation were subjected to *Invitro* drug release study.

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 test 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.



Graph 5. Release profile of ER coated pellets w.r.t



Graph 6. Release profile of ER coated pellets w.r.t Marketed formulation (M.F) in S.G F

Marketed formulation (M.F) in PBS (pH 6.8)

Surface Morphology and Scanning Electron Microscopy:

Various morphological characteristics (coating smoothness, uniformity of coating, particle size & coating thickness) of the pellets were observed by SEM using a scanning electron microscope. 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.

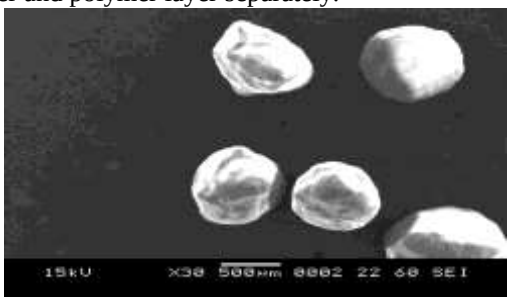


Fig 1. Photomicrograph of ER coated pellet

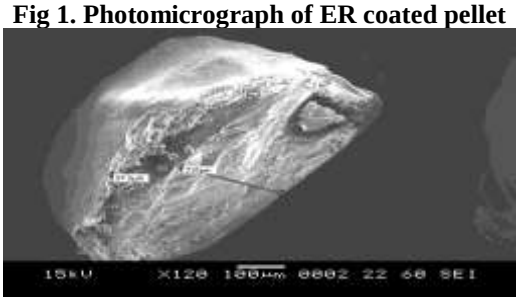
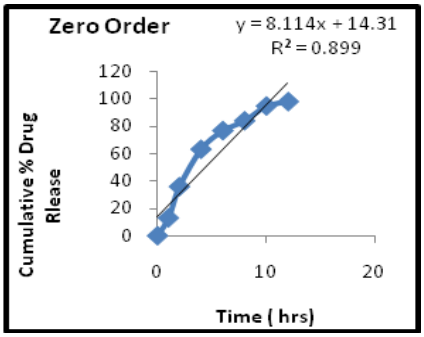
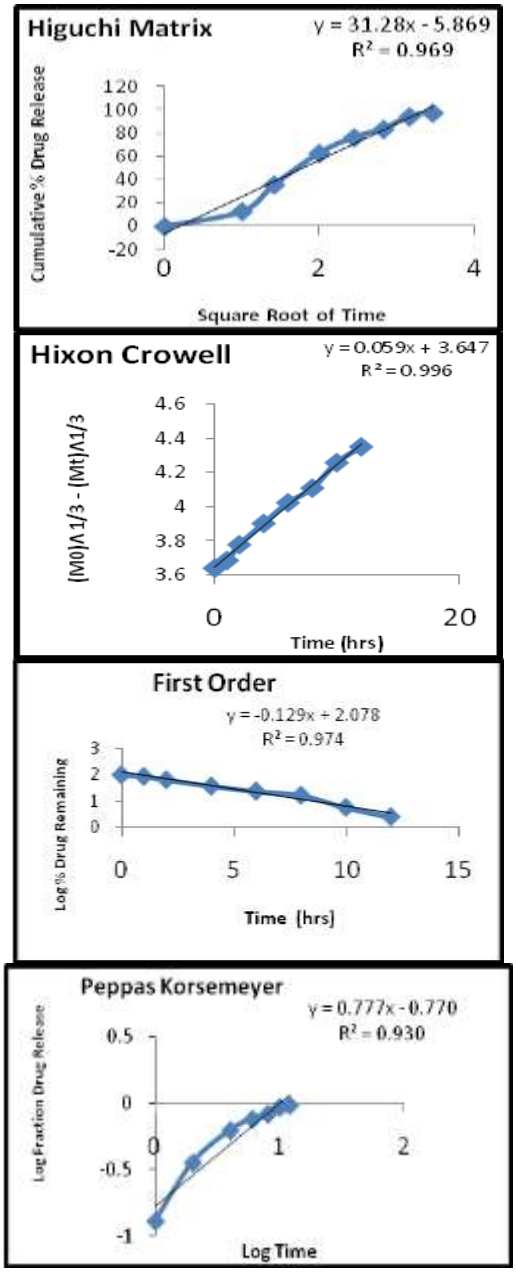


Fig 2.Cross-sectional SEM image of ER coated pellets

Data Interpretation by Kinetic Models [8-10]

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





Graph 7. Kinetic Models of Drug Release Mechanism

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.

Generally binary nozzles are used in the fluidized bed coating process in which, liquid is supplied at a low pressure and is sheared into droplets by air. Usage of such type of nozzles is beneficial, as the droplet size and distribution are more controllable with respect to hydraulic nozzles, having a low liquid flow rate. Several process parameters and formulation variables play a major role in the efficiency of nozzle, for example usage of organic solvent for coating leads to nozzle blockade due to increased viscosity of solvent during processing because of evaporation of solvent. Therefore, aqueous solvents are more preferable in comparison to organic solvents. Also spray rate should be kept optimum, as the higher spray rate leads to deposition of residual solvent at nozzle tip & sticking of coating sol to filter bags that ultimately leads to reduced machine efficiency. One of the important formulation parameter which is responsible for nozzle blockade is strength of coating sol/dispersion /suspension; hence it should not be highly conc. as well as not very much diluted. Also an optimum particle size of coating material should be chosen. 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 to achieve maximum machine efficiency. At regular intervals, filter bags should be shaken to remove dust and fines which may result to sticking of coating sol over them leading to weight loss from the system. Generally static electricity is developed due to high fluidization velocity which is responsible for high shear b/w the particles and ultimately fines generation, hence talc should be added intermittently to avoid development of charges over particle surface.

Conclusion:

Wurster processors are the highly sophisticated instruments responsible for coating and drying process simultaneously in large scale in industry and offer unique opportunity for formulation and development of coated controlled release products. However various parameters (process & formulation) play an important role in performance of a product, therefore they 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 these variables should be investigated and evaluated properly in order to ensure a reproducible performance of controlled release products.

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