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DIFFERENTIAL SCANNING CALORIMETRY AND SURFACE MORPHOLOGY STUDIES ON COATED PELLETS USING AQUEOUS DISPERSIONS

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The present study was conducted to examine the physicochemical changes during passage of drug through polymeric membranes and observe the surface morphology features of the coated pellets using scanning electron microscopy (SEM). Drug solution was first sprayed around inert pellets to form drug-layered pellets that were coated with two commercial aqueous dispersions namely, Eudragit NE30 and Kollicoat SR30 using bottom-spray fluidized bed technique. Differential scanning calorimetry (DSC) confirmed that no interactions existed between drug and polymers. Small peak of drug was observed in the DSC thermograms of Eudragit NE30 coated pellets indicating that small amount of drug was still present in the polymeric membrane after dissolution. Views of SEM revealed as the coating levels of two types of aqueous dispersions were increased the surface of the pellets become more uniform and compact. Therefore, the diffusion length for dissolution medium to enter the drug layer and dissolved drug to diffuse out would be increased at higher coating levels. The polymer surface of coated pellets after 12 hours dissolution testing seemed to be shrunk and size of the pellets were also reduced indicating the depletion of reservoir layer.

Keywords: Coated pellets, SEM, DSC

INTRODUCTION

The aqueous-based copolymer is characterized by short processing times, economical production and reproducible results (Ghebre-Sellassie et al 1986). Eudragit NE30 (NE30), a non-biodegradable copolymer of ethyl acrylate and methyl methacrylate containing 30% solid content in aqueous dispersion has molecular weight of about 800,000. Due to its very low minimum film forming temperature (5 ^{0}C), soft and flexible films can be prepared at room temperature without addition of any plasticizer (Lehmann, 1989; Eudragit Data Sheet, 1989). The films so formed are insoluble over the entire physiological pH but swell in the presence of water to produce permeable membranes.

Kollicoat SR30D (SR30) is a new aqueous dispersion of polyvinyl acetate and solely marketed by BASF, Germany. The product is stabilized with povidone and lauryl sulfate and has been used in preparation of matrix pellets and sustained release coatings (Batra et al, 1994; Zhang and McGinity, 2000). Both NE30 and SR30 were selected as polymer coatings. Drug-layered pellets and polymer coats were produced using bottom spray coater (Wurster technique). The drug-layered pellets and coated pellets were then evaluated using various techniques. The hardness of the coated pellets was measured using texture analyzer. The surface morphology of the coated pellets was judged with scanning electronmicrograghs while differential scanning calorimetry was conducted for pure drug and polymer films.

MATERIALS AND METHODS

Materials

Materials were received from the following sources: Diltiazem HCl (Reddy Pharma, Singapore), eudragit NE40D (Rohm Pharma, Germany), Kollicoat SR30 (BASF, Germany), lactose monohydrate BP (HMS, Holland), microcrystalline cellulose (Avicel PH 101, FMC corporation, USA), polyvinylpyrrollidone (K30, USA) and talc BP (Merck).

Pellets coating with NE40 and SR30

Drug-layered pellets were first prepared by spraying 20% w/v aqueous drug solution onto inert pellets. The drug was first dissolved in a 2% w/v binder solution poly-vinylpyrrollidone and 2% w/v talc was then added to the drug solution with continuous stirring before and during the application of drug layering onto 150 g inert pellets. All the coating processes were performed using fluidized bed coater under the conditions given below:

Inlet air temperature	55-60^{o}C
Atomizing air pressure	0.6 bar
Spray rate	2.5-3.0 ml/min
Spray nozzle diameter	0.8 mm

For aqueous polymer coating, 10 % w/v dispersion of NE30 and SR30 was prepared by adding 50 ml of each dispersion in about 150 ml distilled water separately while mixing with magnetic stirrer. The talc (3.0 g) was then added and

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Table 1
Hardness of inert pellets, drug-layered pellets and NE30-coated pellets

No	Inert pellets	Drug-layered pellets	Force on compression (Kg)				
			NE30-coated pellets				
			3%	4%	5%	6%	7%
1	0.76	1.04	1.36	1.70	1.88	2.06	2.10
2	0.72	0.99	1.66	1.70	1.71	1.81	1.72
3	0.71	1.01	1.54	1.72	1.56	1.99	1.75
4	0.74	0.98	1.44	1.65	1.99	2.01	1.86
5	0.73	1.05	1.67	1.57	1.89	2.34	1.88
6	0.70	1.08	1.43	1.71	2.00	1.79	2.14
7	0.75	1.01	1.60	1.50	1.86	1.71	1.92
8	0.79	1.04	1.37	1.61	1.65	1.82	2.08
9	0.80	0.99	1.39	1.77	1.94	1.86	2.14
10	0.67	1.06	1.54	1.72	1.77	1.64	1.75
Average	0.74	1.03	1.50	1.67	1.83	1.90	1.94
SD	0.04	0.03	0.12	0.08	0.15	0.20	0.17

agitated in the dispersion throughout the coating process. Five coating levels of NE30 dispersion (3-7%) and SR30 dispersion (7-11%) were examined and based on theoretical weight gains. Similar operating conditions were used as in drug layering except that the inlet temperature was set at 25-30^{0}C. Actual weight gain was not calculated due to losses of coated pellets during processing and handling.

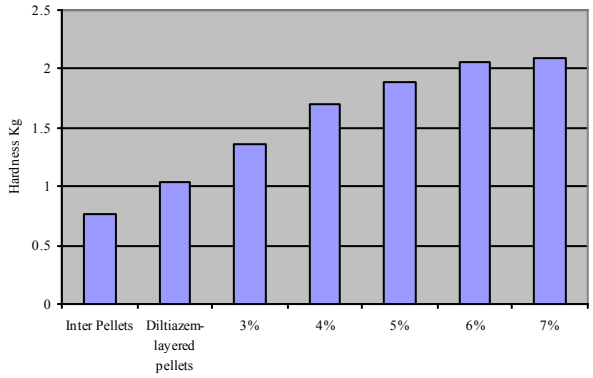


Fig. 1: Hardness of inert pellets, drug-layered pellets and 3-7% NE30-coated pellets.

The coated pellets were transferred to a paper-lined tray, cured overnight in an oven with an air-circulating fan at 37^{0}C and stored in a desiccator before evaluation.

Hardness of pellets

Coated and uncoated pellets were compressed by applying force to determine the hardness using TA-XT2 texture analyzer (stable micro systems, haslemere, surrey, UK). The plastic test probe in cylindrical shape was mounted vertically on the shaft of the tensile tester and was aligned with the center of a single pellet placed on the metallic surface. The probe was lowered at pre-test speed of 4 mm/sec and contacted at test speed of 2 mm/sec with the pellet and covered 0.2 mm distance under force to break the pellets. The unit of force such as Newton, Kg or g could be selected for determining the hardness of pellets or granules. The probe was then returned to start automatically at a post-test speed of 4 mm/sec. The force required to break/compress the pellets were considered as hardness of the pellets. Data collection and calculation were performed using XTRAD Dimension software package of the instrument. For each selected batch, a total of at least 10 replicates were recorded and averaged.

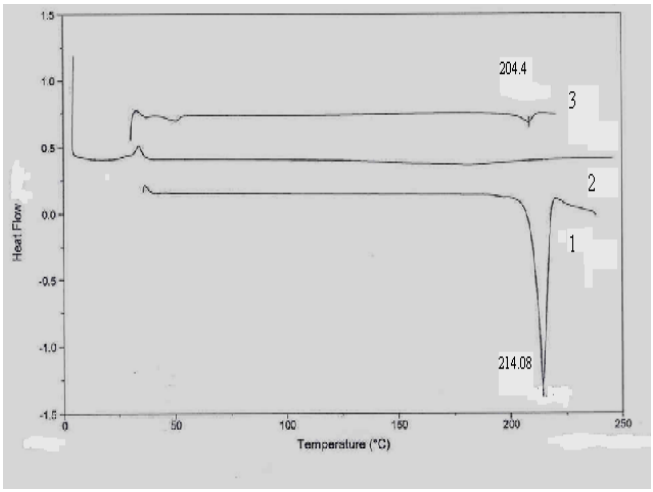
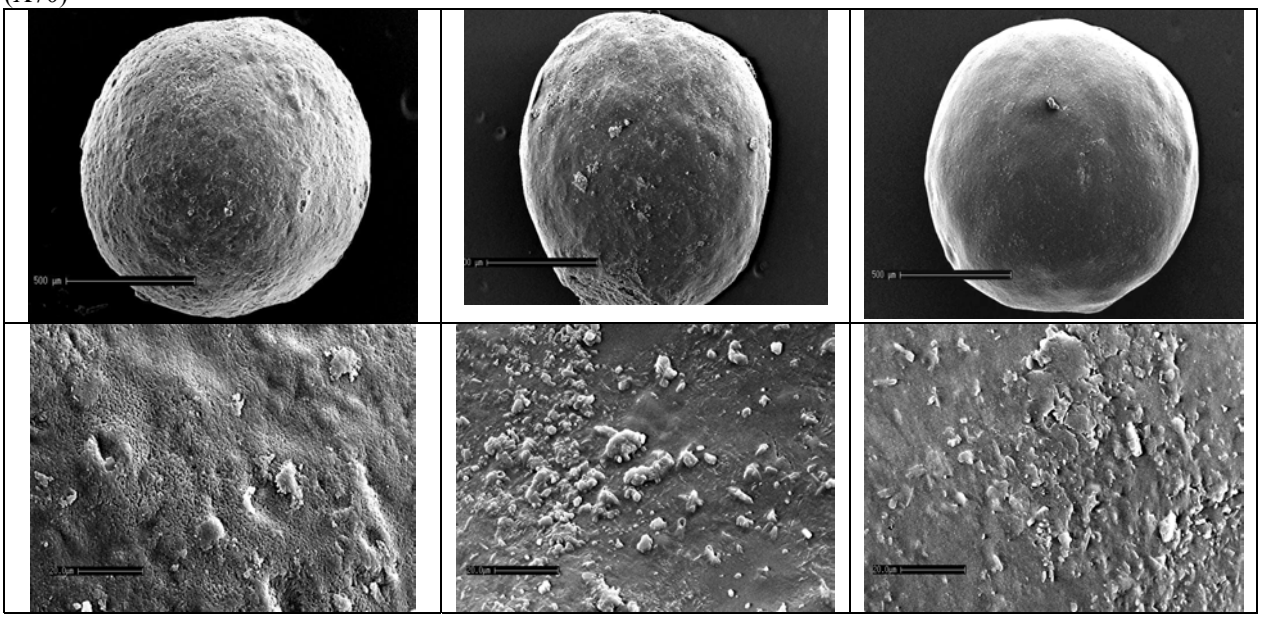


Fig. 2: DSC thermograms of (1) diltiazem-layered pellets, (2) SR30-coated pellets and (3) NE30-coated pellet after dissolution.

A. Diltiazem-layered pellet B. 3% NE30-coated pellet C. 7% NE30-coated pellet

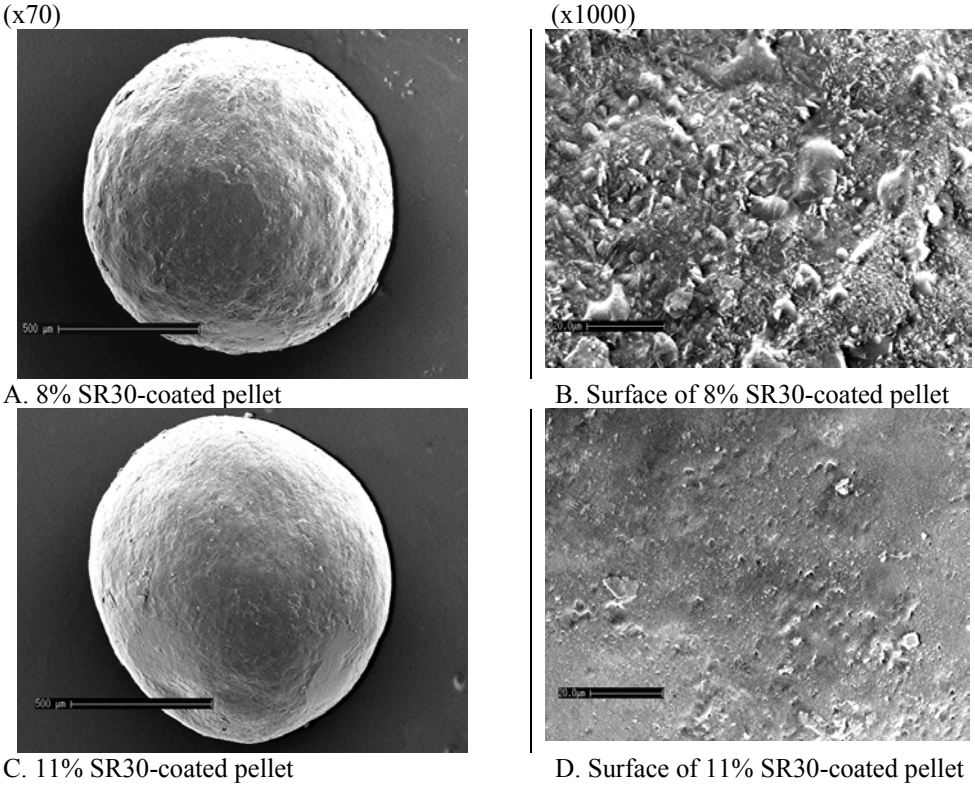
(X70)



(X1000)

Fig. 3. Scanning electron photomicrographs of drug-layered and NE30-coated pellets at low magnification (X70) and high magnification (X1000).

(x70) (x1000)



A. 8% SR30-coated pellet B. Surface of 8% SR30-coated pellet

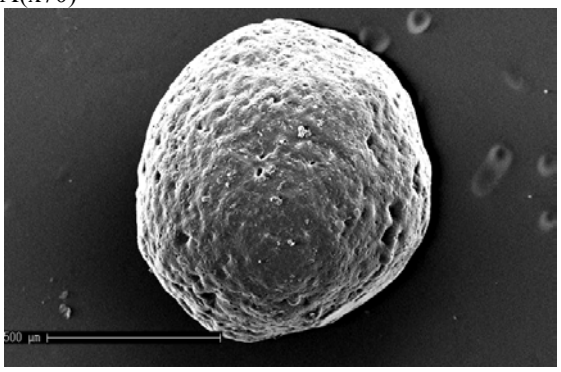
C. 11% SR30-coated pellet D. Surface of 11% SR30-coated pellet

Fig. 4: Scanning electron photomicrographs of SR30-coated pellets.

Differential scanning calorimetry (DSC)

The outer coating of both NE30 and SR30 coated pellets was collected after complete dissolution by applying pressure to remove the content. The ruptured outer film was then washed with water and dried at 37^{o}C in an air-circulated oven. Both these samples along with the

A(x70)



B (x3000)

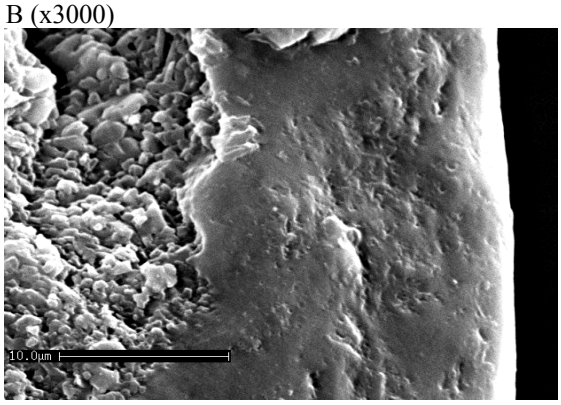


Fig. 5: Scanning electron photomicrographs of A) NE30- coated pellet after dissolution and B) Cross-section of NE30- coated pellet.

diltiazem-layered pellets in powder form were examined on differential scanning calorimeter (TA instruments model 2010, USA). The instrument was calibrated with Universal Analysis software (TA Instruments, 1997) using indium as the standard. Samples weighing 10-20 mg were heated in sealed aluminum pans from 25 to 250^0C at a scanning rate of 10^0C/min with an empty aluminum pan as a reference. As the melting point of diltiazem is above 200^0C therefore, wide scanning range was used to investigate any interaction between polymer and drug. Nitrogen was used as the purge gas with the flow rate of 50 ml/min.

Scanning electron microscopy (SEM)

The surface and cross-sectional view of the pellets were recorded under a scanning electron microscope (Leica Cambridge S-360, UK). The coated pellets were mounted onto stubs using double-sided adhesive tape. The mounted samples were sputter coated (Polron Sc 515,UK) under an argon atmosphere with gold palladium and examined at 15 KV accelerating voltage.

RESULTS AND DISCUSSION

Hardness test, differential-scanning calorimetry (DSC) and scanning electron microscopy (SEM) of uncoated and coated pellets were employed to evaluate the performance of the coating system and aqueous based coating formulations used in the present study. A number of methods for the measurements of hardness of pellets were reported in the literature (Wan and Jeyabalan, 1986; Gold *et al.,* 1971). Hardness of the single pellets was measured with texture analyzer and the results were plotted in fig. 1. As the coating level of NE30 increased, the hardness of the coated pellets was gradually increased compared to drug-layered pellets, which were considered to be zero percent coated pellets. The average hardness of inert pellets and zero percent pellets was 0.74 and 1.03 Kg. The average hardness range for 3-7% NE30 coated pellets was found to be 1.50-1.94 (table 1) whilst there were no differences in the values of 7-11% SR30 coated pellets. The average hardness range for 7-11% SR30 coated pellets was found to be 1.90 - 2.11 Kg. The coated pellets were compressed into a single de-shaped mass with few powder particles while the drug-layered pellets or inert pellets were found to break into small fragments.

DSC studies of diltiazem-layered pellets and the films of both NE30 and SR30 coatings confirmed that there were no drug-polymer interactions. As shown in fig. 2, the layered pellets exhibited a sharp melting peak of diltiazem at 214.08^oC while NE30 coating displayed a small peak at slightly lower temperature indicating the presence of diltiazem in the coating film after dissolution. SR30 coating films displayed no melting peak and indicated that no drug was remained inside the film and the whole drug diffused out from the drug reservoir layer. DSC studies of NE30 and SR30 coatings confirmed that there were no drug-polymer interactions.

SEM studies were carried out on drug-layered pellets and NE30 coated pellets at both lower (x70) and higher (x1000) magnifications. Views of SEM in fig. 3 (A, B and C), both drug-layered and coated pellets at low magnification were seemed to exist as spherical discrete units whilst the surface morphology of the layered pellets was appeared to be visibly different from that of coated pellets. The surface of the layered pellets was continuous but granular compared to smooth and homogenous polymer coating. The surface of pellets coated with 7% NE30 was more compact, continuous and uniform while in 3% coating, apparent uncoated patches were seen. Therefore, the diffusion length for dissolution medium to enter the drug layer and dissolved drug to diffuse out would be increased at higher coating levels that would result in slower release rate. Views of SEM in fig. 4 (A and C), 7% and 11% SR30 coated pellets at low magnification were also seemed to exist as spherical discrete units whilst the surface of 11% SR30 coated pellets compared to 8% coated pellets was more compact, continuous and uniform (B and D).

The polymer surface of NE30 coated pellets after 12 hours dissolution testing (fig. 5, A) seemed to be shrunk or acquired wrinkled appearance and size of the pellets were also reduced indicating the depletion of reservoir layer. The

surface of the film had also some visible pores and through which the drug was transported from the reservoir layer into the dissolution medium. In addition, the pellets after dissolution indicated that the main mechanism of drug transport is diffusion through the membrane that had converted to wrinkled surface in the absence of water. The cross section of one portion of NE30-coated pellet formed a fused continuous and distinct layer of both drug layering and polymer coating around the inert pellet (fig. 5, B). The inert pellet is visible as a porous and granular material beside the uniform coated layer.

CONCLUSION

Hardness of NE30-coated pellets was increased as the coating levels of NE30 dispersion were increased while no gradual increase in the SR30-coated pellets was observed. DSC studies revealed that no interactions were existed between NE30 or SR30 and diltiazem. Moreover, SEM studies indicated that as the coating levels of both NE30 and SR30 dispersions were increased the surface of the pellets become more uniform and compact.

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EFFECTS OF TRYPTOPHAN AND VALINE ADMINISTRATION ON BEHAVIORAL PHARMACOLOGY OF HALOPERIDOL

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Development of antipsychotics with slight/no extra-pyramidal symptoms (EPS) and/or other side effects is one of the exploring fields of drug research. Haloperidol is a high potency typical neuroleptic used in the treatment of schizophrenia but produces muscles related side effects commonly known as EPS. These effects are not produced following the administration of atypical neuroleptics such as clozapine. A severe side effect of clozapine treatment is however, agranulocytosis. This involves investigation on the mechanism by which a typical neuroleptic acting via serotonergic mechanism tends to produce less or no EPS. The present study was, therefore, designed to determine the effect of serotonin precursor tryptophan and a large neutral amino acid other than tryptophan (valine) on the modulation of haloperidol induced catalepsy and akinesia. Cataleptic effects of the drug and activity reducing effects were monitored on inclined surface and in an activity box or open field respectively. The results are discussed in the context of a role of tryptophan and valine induced changes of brain serotonin in modifying the extrapyramidal and monoaminergic effects of the typical neuroleptic haloperidol. In the present study administration of TRP and valine decreased activity in rats, haloperidol-induced catalepsy' was not modulated by prior administration of tryptophan or valine. Brain serotonin levels were elevated by haloperidol treatment and correlated very well with the behavioral response. These findings suggest a possible serotonergic involvement in neuroleptic induced tardive dyskinesia and an amelioration of the disorder through TRP supplementation.

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