

Compression and evaluation of extended release matrix pellets prepared by the extrusion/spheronization process into disintegrating tablets

Raveendra Pai^{1,*}, Kanchan Kohli², Birendra Shrivastava³

¹Formulation Development Services, Matrix Laboratories Ltd., Hyderabad, India, ²Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard University, New Delhi, India, ³Faculty of Pharmaceutical Sciences, Jaipur National University, Jaipur, India

In this study, a novel approach for compression of matrix pellets into disintegrating tablets has been studied in an attempt to overcome the issues pertaining to rupture of polymer coat during compression of reservoir-type pellets. Extended release matrix pellets were prepared by the extrusion/spheronization technique using commercially available aqueous dispersions of ethyl cellulose, acrylic polymers and sodium alginate at 10%, 20% and 30%w/w levels. Sertraline hydrochloride was used as the model drug and an *in vitro* release profile of 12 h was targeted. Tablets containing matrix pellets were prepared by the direct compression process. Acceptance Value, a pharmacopeial test, was applied to study the uniformity of drug distribution. Effect of compression force (2-6 kN), extrusion screen aperture size, diluent blend composition and pellet percentage on drug release and acceptance value were studied. As polymer is uniformly distributed within each pellet, the drug release pattern from uncompressed pellets was comparable to compressed tablets. Surface morphological changes due to calcium chloride treatment were observed using Scanning electron microscopy. The pellet segregated from the surface of the tablet was found to be flattened in the direction of applied compression force with minor deformities. In conclusion, matrix pellets can constitute an alternative approach to reservoir-type pellets in obtaining disintegrating tablets for extended delivery of drugs.

Uniterms: Pellets/extended release/evaluation. Pellets/obtenção. Pellets/compressão. Extrusion/spheronization technique.

Nesse trabalho, estudou-se nova abordagem para a compressão de matrizes de péletes em comprimidos desintegrantes, com o intuito de resolver os problemas relativos à ruptura do polímero de revestimento durante a compressão dos péletes do tipo reservatório. Matrizes de péletes de liberação estendida foram preparadas pela técnica de extrusão/esferonização, utilizando dispersões aquosas comercialmente disponíveis de etil celulose, polímeros acrílicos e alginato de sódio a 10%, 20% e 30% p/p. O cloridrato de sertralina foi utilizado como fármaco modelo e focalizou-se no perfil de liberação *in vitro* de 12 horas. Os comprimidos contendo matrizes de péletes foram preparados pelo processo de compressão direta. O valor de aceitação, teste farmacopéico, foi aplicado para estudar a uniformidade de distribuição do fármaco. O efeito da força de compressão (2-6 kN), o tamanho da abertura de extrusão, a composição da mistura diluente, a porcentagem de pélete na liberação de fármaco e o valor de aceitação foram estudados. Como o polímero é uniformemente distribuído dentro de cada pélete, o padrão de liberação do fármaco dos péletes não-comprimidos foi comparável àquele dos comprimidos. As mudanças morfológicas da superfície devidas ao tratamento com cloreto de cálcio foram observadas utilizando-se a microscopia eletrônica de varredura. O pélete segregado da superfície do comprimido mostrou-se plano em direção à força de compressão aplicada com menores deformidades. Em conclusão, os péletes matriz podem se constituir em abordagem alternativa para péletes do tipo reservatório na obtenção de comprimidos desintegrantes para fármacos de liberação estendida.

Unitermos: Pellets/liberação prolongada/avaliação. Pellets/obtenção. Pellets/compressão. Técnica de extrusão/esferonização.

*Correspondence: R. Pai. Formulation Development Services, Matrix Laboratories Ltd. Plot No 34A, Bollaram Industrial Area, Jinnaram Mandal, Medak District, Hyderabad - 502325, India. E-mail: raveendrapai@yahoo.co.in

INTRODUCTION

Multiple unit extended release dosage forms are preferred over single unit dosage forms as they spread uniformly throughout the gastrointestinal tract producing less variability and lower risk of local irritation due to the minute amount of drug carried (Bodmeier, 1997; Bechgaard, Nielsen, 1978). A multi-unit particulate system (MUPS) comprises a tablet dosage form wherein pellets are compressed into tablets along with appropriate excipients or cushioning agents. Conventional design of oral modified release systems involves coating of spherical pellets with polymer that regulates the rate and extent of drug release. However, there are some disadvantages with capsules, such as feasibility of tampering, difficulties in esophageal transport, and higher production costs (capsule shells), hence, such pellets are compressed into disintegrating tablets. Tablets can be prepared at a lower cost because of the higher production rate of tablet presses (Murthy, Vijaya, Ratna, 2008). In addition, tablets containing multiparticulates can be scored without losing their controlled release properties, which allows a more flexible dosing regimen (Bodmeier, 1997). The formulation challenge producing tablets from pellets is obtaining uniformity of drug content in the tablet and maintaining the desired drug release after compression. The application of compression pressure can lead to structural changes in the film coating consequently altering drug release. Most of the studies on the compression of pellets coated with ethyl cellulose and acrylic polymers have revealed damage to the coating with loss of the extended release properties (Bansal, Vasireddy, Parikh, 1993). Compression of pellets at higher force is reported to reduce the release from the tablets due to fusion of pellets (Lopez-Rodriguez *et al.*, 1993) whereas the release of drug was found to be faster from tablets due to the brittle nature of pellets (Branka *et al.*, 2009). Smaller pellets were reported to be less affected by the compression process than larger pellets. Use of microcrystalline cellulose and polyethylene glycol 3350 produced rapidly disintegrating tablets containing pellets, with lowest change in the drug release pattern after tableting (Torrado, Paronen, 1994). Various techniques have previously been explored in a bid to reduce the damage to rate-controlling polymer film. However, a recent study involved the use of polyethylene glycol as a cushioning agent and tablet compression at elevated temperature as an alternative to using reservoir-type pellets (Wieslaw, Jaroslaw, Ilona, 2010).

Extrusion/spheronization is an established technique for producing spherical pellets in a typical size range of between 0.5 and 2 mm. Various polymers have

been employed for preparing pellets using the extrusion spheronization technique (Pornsak *et al.*, 2007; Helton *et al.*, 2005). In the present study, Sertraline Hydrochloride (SRT), commonly prescribed for depressive illness, was used as the model drug. There are various reports in the literature on the side effects associated with sertraline treatment at prescribed doses, such as severe nausea, headache, diarrhea, sexual dysfunction, tremor, dizziness and fatigue (Grimsley, Jann, 1992; Dogan, 1991). A granted patent publication US 6,899,896B1 (Curatolo *et al.*, 2005) claimed to produce better patient compliance when sertraline was released at a specified rate from a hydrogel-based dosage form. The *in vitro* release profile of up to 12 h was found to increase patient compliance and the therapeutic efficacy of sertraline. Hence in the present study, commonly used extended release polymers such as sodium alginate, aqueous dispersion of ethyl cellulose and acrylic polymers were evaluated to prepare matrix pellets (Hodsdon *et al.*, 1995; Bhagat *et al.*, 1990).

The objective of this study was to investigate the possibility of producing extended release matrix pellets by the extrusion/spheronization technique using Aquacoat[®] ECD 30, Eudragit[®] L 30D 55 and Eudragit[®] NM 30D, Sodium alginate (Keltone[®] LV CR) as polymers to achieve *in vitro* drug release of up to 12 h. These matrix pellets were compressed into tablets which should disintegrate rapidly in the dissolution medium. The study also investigated the effect of formulation variables on the uniformity of the tablet content and *in vitro* drug release profile.

MATERIALS AND METHODS

Materials

Sertraline hydrochloride was obtained from Matrix Laboratories Ltd, India. Sodium alginate (Keltone[®] LVCR) was procured from ISP Corporation India. Eudragit[®] L 30D 55 and Eudragit[®] NM 30 D grades were obtained from Evonik India Ltd, Mumbai. Aquacoat[®] ECD, (30 %w/w dispersion) was obtained from FMC Biopolymer. Other excipients used in the pellet preparation and tablet compression were obtained from Matrix Laboratories Ltd, Hyderabad, India.

Methods

Preparation of Matrix pellets by extrusion/spheronization

Matrix pellets were prepared using the various compositions shown in Table I. All the batches were of 2000 units and 100 mg in strength. First, dry powder mixture

was prepared by mixing sertraline, microcrystalline cellulose and hydroxypropyl cellulose (wherever required) in a laboratory scale Rapid mixer granulator [Allen Bradley 5L, USA] at slow impeller speed for around 10 min. To granulate this blend, an aqueous dispersion of ethyl cellulose and eudragit polymers were used. Additional water, if required, was added during granulation to obtain a wet mass suitable for extrusion. While using the sodium alginate polymer, water was used as the binding liquid. The wet mass was extruded through a screen extruder [Multi-gran MG 55, Fugii Paudal Co Ltd Japan] equipped with a standard screen having an 0.8 mm diameter aperture, and rollers rotating at 30 rpm. The extrudates were transferred to the spheronizer [QJ 230T-1, Fugii Paudal Co Ltd Japan.] equipped with a crosshatch plate [1mm] and processed at 850 rpm rotation speed for the desired time (415 min). The spheronization time was varied according to the polymer used in the pellet preparations where the longest spheronization time was required for the composition containing 30% w/w sodium alginate. The resultant pellets were dried in a fluid bed dryer [Rapid dryer, Retsch, Germany] with an inlet air flow at 50 °C for about 20-30 min. The dried pellets were sifted and retained on an ASTM # 20 mesh (841 μ) and the fines below # 40 mesh (420 μ) were discarded. The process yield was calculated from the quantity of fraction of dried pellets obtained after sifting (Pai, Kohli, 2011).

Calcium ion complexation

Wet pellets (about 320 g) obtained from (#F 11) composition were poured into 500 mL of calcium chloride solution of different concentrations (10% w/w, 20% w/w and saturated solution of calcium chloride). The pellets were allowed to form gelatinous precipitate by chemical

reaction between sodium alginate and calcium chloride on the surface of the pellets. The pellets were left under slow stirring for 10 min and then filtered, washed with distilled water and vacuum dried.

Preparation of MUPS tablets

MUPS tablets were prepared by the direct compression approach using the compositions shown in Table II. For this, 320g of calcium chloride-treated pellets were mixed with microcrystalline cellulose, polyethylene glycol and crospovidone in a laboratory scale blender [Conta Blender, Bowman & Archer] for 10 min. Finally, magnesium stearate passed through a 250 μ m sieve was added to the mixture and blended for 5 min. The degree of filling of the blending vessel was 50% by volume to ensure proper mixing. The tablets of 1066 \pm 50 mg were compressed using one set of 19.5 X 9.5 mm capsule shaped, biconvex tooling on a 12-station automated single rotary compression machine [Smart Press, SRC 10i, Pacific Industries, India]. The compression machine is equipped to measure the compression forces applied to the blend. Considering the criticality of the compression process, the machine speed was set to 10 rpm. Minimum gap was maintained between the turret and the feed frame to minimize the physical stress on the blend during rotation. Tablets were compressed at different compression forces in a 2-6 kN range in order to obtain tablets with a crushing strength ranging from 80 to 240 N.

Characterization of pellets and compressed tablets

• Density and friability

The bulk density was determined by pouring pellets into a previously weighed 10 ml graduated glass cylinder

TABLE I - Composition of extended release matrix pellets using various polymers

Composition (mg)	#F1	#F2	#F3	#F4	#F5	#F6	#F7	#F8	#F9	#F10	#F11	#F12
Sertraline ^a	112	112	112	112	112	112	112	112	112	112	112	112
Microcrystalline Cellulose Avicel PH102)	166	134	102	166	134	102	166	134	102	176	144	112
Hydroxypropyl cellulose	10	10	10	10	10	10	10	10	10	x	x	x
Aquacoat ECD 30	32	64	96	x	x	X	x	x	X	x	x	x
Eudragit L 30D 55	x	x	x	32	64	96	x	x	x	x	x	x
Eudragit NM 30D	x	x	x	x	x	X	32	64	96	x	x	x
Sodium Alginate	x	x	x	x	x	X	x	x	x	32	64	96
Water	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Total Weight (mg)	320	320	320	320	320	320	320	320	320	320	320	320

^a Weight of hydrochloride salt equivalent to 100 mg sertraline base. qs-Quantity sufficient

TABLE II - Composition of MUPS tablets prepared using calcium chloride-treated pellets

Composition (mg)	TAB #1	TAB #2	TAB #3	TAB #4	TAB #5
Sertraline Pellets ^b	320	320	320	320	320
Microcrystalline Cellulose Avicel 102	646	446	446	263	78
Microcrystalline Cellulose Avicel PH101	-	200	-	117	35
Milled Avicel PH 102	-	-	200	-	-
Polyethylene glycol, 6000	64	64	64	64	64
Crospovidone	31	31	31	31	31
Magnesium Stearate	5	5	5	5	5
Total weight (mg)	1066	1066	1066	800	533
Percent of pellets (%w/w)	30	30	30	40	60
Acceptance Value	18.7	12.2	14	NP	NP

^bComposition #F11, NP; Not performed

where the weight of the pellets needed to occupy a 10ml volume was noted. The bulk density was calculated by the ratio of weight to occupied volume.

Friability was measured using Electrolab Friability testing apparatus [Electrolab Ltd, Mumbai, India] by tumbling 10g of the pellets for 4 min at 25rpm. The tested pellets were gently tapped on an ASTM # 40mesh to remove the fines generated and weight loss was measured. For testing the friability of the tablets, ten tablets were initially weighed on an analytical balance, transferred to the friabilator and run for 4 min. The tablets were weighed after removing the powdered dust, and weight lost during testing was calculated.

- Sphericity

The sphericity of the pellets was measured using the simplest approach described by Lovgren and Lundberg (Lovgren, Lundberg, 1989), by measuring the length and width of the two dimensional image of the pellets on an optical microscope [Olympus BX55TF, Japan]. The shape factor was expressed as % Sphericity, where 100 % corresponds to a perfect circle. The longest length and breadth of the pellets were measured accurately when the pellets were rested in their most stable position. A frequency distribution of the percent ratio of length to breadth of 100 pellets was calculated and the Sphericity (S) was expressed (Eriksson, Nystrom, Aldeborn, 1993).

- Hardness testing

The force required to fracture a tablet was measured using a tablet hardness tester [Dr Schleuniger, Pharmatron 8M]. Hardness of at least 10 tablets from each formulation was measured and reported as a range.

- Disintegration testing

The disintegration time of the tablet was tested using USP disintegration apparatus on 6 tablets from each composition. [Electrolab Disintegration Apparatus, India]. Distilled water was used as the medium at a temperature

of 37 °C. The time taken until no material from any of the tablets was left on the mesh was recorded.

- *In vitro* dissolution testing

In vitro release study of the pellets and compressed tablets was performed using acetate buffer pH 4.5 in a dissolution test apparatus [Electrolab, Mumbai, India]. The test employed 900 mL of the specified buffer at 37 °C and a USP Type II apparatus (paddle) rotating at 50 rpm. Samples were collected at 1, 2, 4, 6, 8, 10 and 12 h intervals and analyzed by a UV-Visible spectrophotometer [UV 2450, Shimadzu Corporation, Japan] at 273nm. Dissolution of pellets and MUPS tablets was conducted for 6 representative samples.

- Drug content analysis

To determine drug content, an amount of crushed pellets equivalent to 100 mg of sertraline was weighed into a flask (1000 mL) and extracted with a minimum quantity of methanol and made up to volume with acetate buffer pH 4.5 then sonicated for around 30 min. UV absorbance of the solution filtered through 0.43µ filters was measured using a UV-Visible spectrophotometer [UV 2450, Shimadzu Corporation, Japan] at 273nm (λ_{max}). To avoid the influence of excipients, the placebo blend was also treated similarly and kept as a blank. Standard solution was prepared by accurately weighing [Mettler Toledo, India] 100 mg of sertraline and following a similar dilution procedure. From the absorbance of the test solution, the amount of drug in the solution was calculated.

- Acceptance Value

Acceptance Value is a test recommended by the USP 30 [2007] for evaluating content uniformity in dosage forms. As MUPS tableting involves the compression of two varying density components together, achieving content uniformity within the pharmacopoeial limits is a challenging task (Flament *et al.*, 1994). Hence, the Acceptance Value was considered as a tool for evaluating

uniformity and content of 10 individual tablets, measured with the method described above. Acceptance value was calculated as per the equation below.

$$AV = |M - X| + kS \quad (1)$$

Where k is acceptability constant ($k = 2.4$ while testing 10 tablets), S is standard deviation of assay values of 10 units, X is mean of the assay value. $M = X$ when X value is between 98.5 - 101.5%. $M = 98.5$ if X value is below 98.5 and $M = 101.5$ if X value is above 101.5. Absolute value for $M - X$ is to be considered for calculation of Acceptance value.

- Scanning electron microscopy

Scanning electron microscope [Jeol, JSM 6380LV, Japan] was used to observe the physical properties and surface modification due to calcium ion complexation in sodium alginate-containing pellets. The untreated pellets were compared with the calcium chloride-treated pellets. Scanning electron microscopy was also used to observe the pellet distribution in the tablet and to evaluate the possible physical deformities due to the compression force applied. The pellets from the surface of compressed tablets which comes into direct contact with the tooling surface were separated carefully and observed under scanning electron microscope to observe any mechanical damage incurred during compression of the pellets.

Stability evaluation of compressed tablets

Accelerated stability studies were carried out on the MUPS tablets prepared using calcium chloride-treated pellets as per ICH recommendation. The tablets were packed in HDPE bottles and charged in a stability chamber for a 3M period at 40 °C/75% RH. After completing the stability period, the tablets were evaluated for their physical and chemical attributes including drug content and drug release profile.

RESULTS AND DISCUSSION

Preparation of matrix pellets and effect of polymers

The concept of compression of matrix pellets into disintegrating tablet dosage form was derived as a response to issues pertaining to compression of reservoir-type pellets coated with polymers for extended release of drug. In reservoir-type pellets, the nature, type and amount of polymer coating has a significant impact on compression-induced changes in the coating structure. Most of the studies on compression of pellets coated with polymers have

shown damage to the coating with loss of the extended release properties due to rupture of the coat (Dashevsky, Kotler, Bodmeier, 2004) resulting in faster drug release (Sarisuta, Punpreuk, 1994). Polymers typically used in the coating of pellets are either cellulosic polymers or acrylic polymers. Hence, in the present study three commercially available aqueous dispersions of ethyl cellulose (Aquacoat® ECD 30) and acrylic polymers (Eudragit® L 30D; Eudragit® NM 30D) were evaluated in an attempt to develop matrix pellets with an extended drug release profile. For this purpose an SRT, hydroxypropyl cellulose and microcrystalline cellulose blend was granulated with aqueous dispersions of polymers [Table 1] in a rapid mixer granulator. Considering the aqueous granulation process, a higher level of microcrystalline cellulose was used in the composition to facilitate the extrusion spherization process due to its unique water absorbing and retaining characteristics (Baert, Remnon, 1993).

During initial trials of granulation, operational variables such as kneading time and spherization time were found to have a significant impact on the length of the extrudates and shape /size of the pellets, respectively. The nature of the granules suitable for extrusion was decided based on the preliminary experiments. The process parameters were varied accordingly to obtain pellets with the desired properties. In order to involve minimum process variables while using the different polymers blending time, binder addition time, screw feeder rate and drying temperature were kept constant. Based on the property of the polymer and its quantity in the composition, the spherization time was varied accordingly to obtain pellets with suitable properties observed visually. The properties of the pellets prepared using 10%, 20% and 30% w/w polymer are given in Table III.

While preparing pellets using a lower level of polymer, an additional quantity of water was added in order to attain the desired granule mass for extrusion. Extrusion of the blend containing a higher level of polymer (30% w/w) through the 0.8 mm screen aperture proved difficult leading to an increase in spherization time (12-15 min). Polymer levels beyond 30%w/w were not evaluated as these were generating lengthy extrudates and leaving tackiness during extrusion. The drug release pattern from the pellets containing ethyl cellulose and acrylic polymer was not satisfactory (Figure 1A to 1C).

More than 85 % drug release was observed within 4h from the pellets containing Aquacoat ECD and Eudragit NM 30D. However, use of Eudragit L 30D 55 at a 30% w/w level was able to extend the drug release to 6 h. This drug release phenomenon can be ascribed to the erosion of polymer from the surface of the pellets and release

TABLE III - Physical characterization data of matrix pellets prepared using extrusion/spheronization process

Polymers	Trial	% w/w	Nature of pellets	Process yield (% w/w)	Drug content (%w/w)	Friability (%w/w)	Bulk Density (g/mL)	Sphericity (%)
Aquacoat ECD	F1	10	Spherical + fines	78.6	93.3	0.380	1.125	76 ± 8%
	F2	20	Spherical	86.4	92.1	0.240	1.095	84 ± 5%
	F3	30	Spherical	82.0	90.6	0.236	1.115	80 ± 5%
Eudragit L 30D 55	F4	10	Spherical + fines	72.2	89.4	0.380	1.186	76 ± 7%
	F5	20	Spherical+ fines	84.5	90.6	0.240	1.182	81 ± 5%
	F6	30	Spherical	86.8	93.4	0.288	1.195	65 ± 8%
Eudragit NM 30D	F7	10	Almost Spherical	80.2	90.0	0.400	1.213	78 ± 9%
	F8	20	Spherical	82.1	92.3	0.380	1.236	82 ± 6%
	F9	30	Dumbbell-Shaped	72.8	91.1	0.385	1.328	65 ± 7%
Sodium Alginate	F10	10	Spherical	78.4	93.2	0.245	0.876	78 ± 4%
	F11	20	Spherical	88.9	92.8	0.210	0.888	86 ± 5%
	F12	30	Dumbbell-Shaped	76.3	91.2	0.220	0.877	72 ± 6%
Calcium Chloride-Treated	F10	20	Spherical	-	91.9	0.180	0.886	88 ± 5%

of drug from the new surface becoming dissolved in dissolution media. Moreover, these polymers are not soluble in the dissolution media employed (pH 4.5 acetate buffer) for *in vitro* drug release testing. As the desired profile was not obtained in the pellet stage, compression of these pellets into MUPS tablet was not considered further.

Pellet preparation was done using sodium alginate, a widely used polymer for matrix tablets and film coatings, wherein spheronization took slightly longer time (8-10 min). A small quantity of water (1-3 mL) was sprinkled from the top of the spheronizer to avoid rapid drying of the pellets in the spheronization chamber. The dried pellets were subjected to *in vitro* dissolution testing at the specified testing conditions. Complete drug release was observed within 4 h (Figure 1D). The rapid dissolution from the pellets could be ascribed to the formation of soluble hydrogel where drug release could occur due to both diffusion and erosion mechanisms (Pai, Kohli, 2011).

Effect of calcium chloride

Development of pellet dosage forms containing sodium alginate in the presence of calcium ions has been reported previously (Sriamornsak, Kennedy, 2006). De-

layed extended release profiles of drug release have been achieved using sodium alginate in the form of beads by complexing it with calcium chloride (Patel, Nagle, Murthy, 2008). In this approach, #F11 composition blend was granulated with water and wet spheroids were poured into a beaker containing calcium chloride solution. *In vitro* drug release from calcium chloride-treated pellets extended the release of sertraline to around 12h. Although there was no considerable difference in the *in vitro* drug release profile for the pellets treated with different concentrations of calcium chloride solution, slowest release was observed from the pellets treated with saturated calcium chloride solution (Figure 2). Cross-linking of the calcium ions generates an insoluble calcium alginate layer on the surface of the beads, reducing the entry of the dissolution media into the pellets. When treating with saturated calcium chloride solution, more calcium ions per unit area are available to react with the alginic acid moiety to form a rigid, insoluble gelatinous mass compared to the other two concentrations studied. As complexation is an instant surface phenomenon, the drug release from the saturated calcium chloride solution-treated pellet was much closer to the desired drug release profile as illustrated in Figure 2.

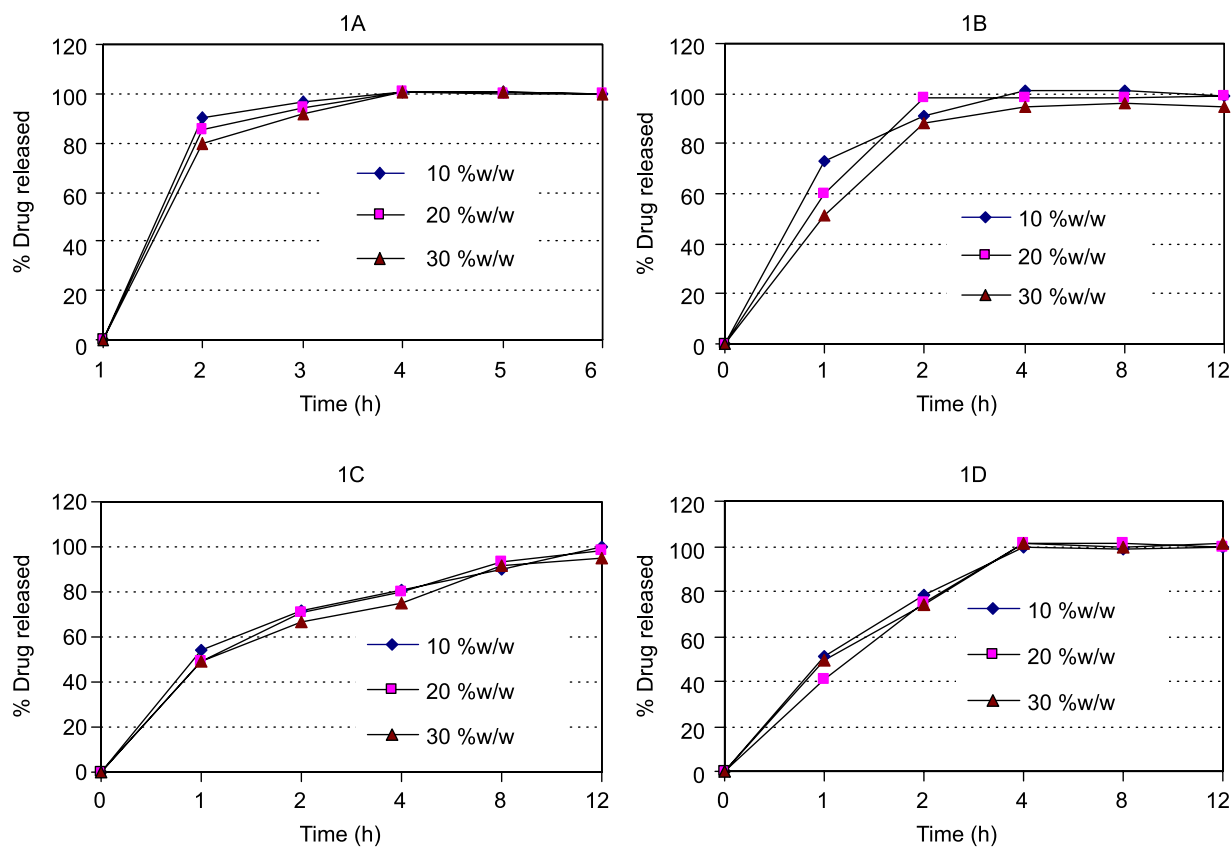


FIGURE 1 - *In vitro* dissolution profiles of sertraline from pellets containing 10 %w/w, 20 %w/w and 30 %w/w **1A**: Aquacoat® ECD, **1B**: Eudragit® NM30D, **1C**: Eudragit® L30D 55, **1D**: Keltone® LV CR.

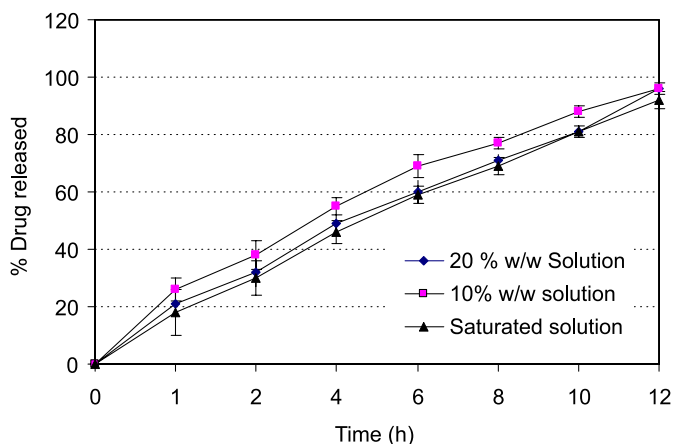


FIGURE 2 - *In vitro* dissolution profiles of sertraline from calcium alginate pellets treated with (-■-) 10%w/w Calcium chloride solution, (-◆-) 20 %w/w Calcium chloride solution and (-▲-) Saturated calcium chloride solution.

Pellet characterization

Pellets obtained with all polymers tested showed comparable density, sphericity and friability as compiled in Table III. However, the density of the pellets prepared

with sodium alginate was lower compared to pellets obtained from the other polymers. This observation can be attributed to the swelling nature of the alginate in the presence of water during granulation and subsequent increase in porosity upon drying. The process yield of the desired fraction pellet was found to vary with the nature and level of the polymer used. The lowest process yield of 72.2% was observed while using 10%w/w Eudragit L 30D 55 due to generation of the fines fraction below the ASTM 40 mesh. However, when using 30%w/w Eudragit NM 30D, the process yield was only 72.8% with rejection being due to retention of pellets on the upper mesh size (ASTM 20 mesh) given the formation of large (dumb bell shaped) pellets. The process yield from the rest of the polymer levels was comparable. Drug content of the pellets was found to vary from 89 to 93 %w/w considering the process loss at various stages during manufacture. The general observation is that the process yield was low due to fines generation when a low level of polymer was used whereas at higher levels of polymer, the process yield was also found to be low as a result of the larger or irregular-shaped pellets generated because of difficulties in spheronization. The shape of the pellets obtained varied

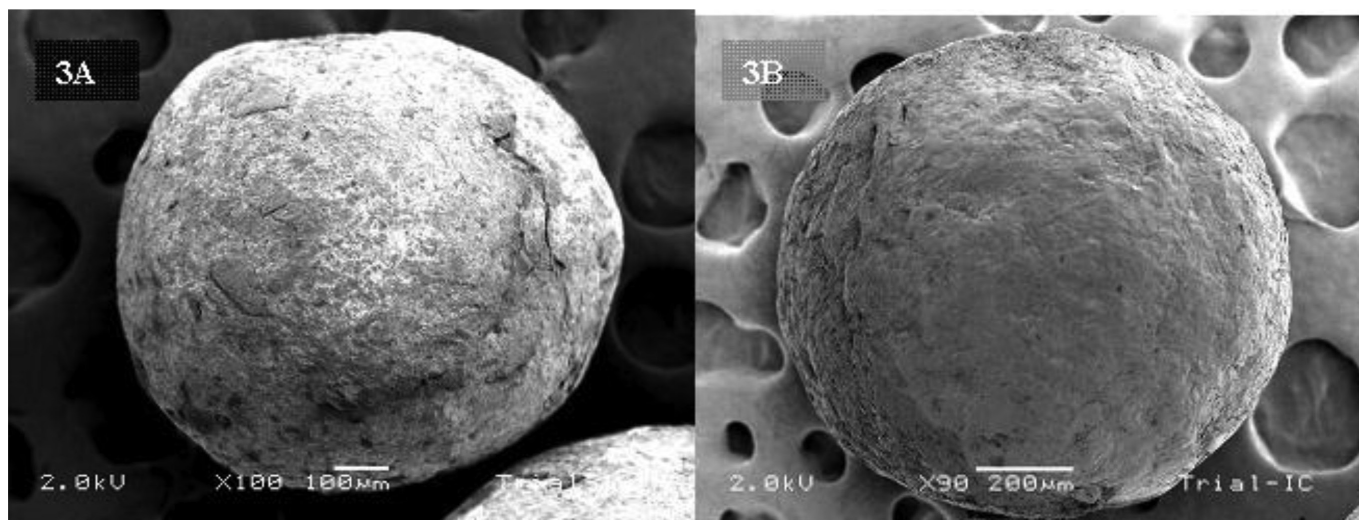


FIGURE 3 - A. Scanning electron micrographs of pellets prepared using sodium alginate as polymer. **B.** Calcium chloride-treated pellets.

from spherical to elongated spherical or dumbbell shape in some cases. The lowest sphericity of 65% was observed in the pellets prepared using higher levels of polymer and the most spherical pellets obtained showed a sphericity value of 88%. The scanning electron micrographs of sodium alginate-containing pellets and calcium chloride-treated matrix pellets are shown in Figure 3.

The surface of the matrix pellets treated with calcium chloride was smoother and uniformly covered with gelatinous mass of calcium alginate. The pellets were almost spherical and no significant morphological differences were observed.

Compression of core pellets into MUPS tablets

Based on the release profile of the pellets, only calcium chloride-treated pellets were considered for compression into MUPS tablets. For compressing these pellets, microcrystalline cellulose was used as a filler in diluent blend (TAB #1) because of its cushioning property leading to minimum damage to the pellets during compression. Due to differences in the size and density of both pellets and excipients, weight variation and content uniformity problems are regularly observed during compression of pellets where these could be controlled by carefully selecting pellets with narrow size distribution together with excipients of similar size and shape. The composition of the extra granular blend was prepared using different grades of microcrystalline cellulose and evaluated for content uniformity. In one of the approaches, part of the microcrystalline cellulose was milled and replaced the original composition (Table II). Based on this, to obtain uniformity in drug content within

the compressed tablets by maintaining a minimum size difference, pellet fractions passed through ASTM # 20 mesh and retained over #40 mesh were used. The direct compression approach was used to obtain disintegrating tablets where the pellets were mixed with microcrystalline cellulose, croscopovidone (PPXL) to achieve fast disintegration with polyethylene glycol used as the cushioning agent at the ratio (Table I) shown in Table II. Percentage of pellets in the composition was maintained at a 30% w/w level based on previous studies involving compression of blends containing pellets from 30%w/w to 40%w/w of the composition (Lundqvist, Podczeck, Newton, 1998) that yielded satisfactory results. Tablets were compressed on a single rotary compression machine using one set of tooling and carefully adjusting the gap between the turret and the feed frame to avoid pellet entrapment and subsequent physical damage. The tablets with the optimized composition were compressed at different compression forces (2-6 kN) to obtain an average crushing strength of 80 N to 240 N and evaluated for physical and release characteristics as depicted. Increasing the compression force increased hardness and extended disintegration time but led to lower friability as depicted in Table IV. This phenomenon might be attributed to the formation of more condensed compact with increased compression force. However, hardness showed no impact on the drug release pattern as the tablets were disintegrating into individual pellets in the dissolution vessels. As the overall composition contained a large fraction of microcrystalline cellulose, the effect of croscopovidone and polyethylene glycol level was found to have minimal impact on the disintegration time of the tablets hence the dissolution profile.

TABLE IV - Physical characterization data of compressed tablets using optimized composition

Composition	Compression Force (kN)	Hardness (N)	Thickness (mm)	Friability (%w/w)	Disintegration Time (s)
TAB #2	2-3	80-120	6.4 ± 0.1	0.86	45
	3-5	120-180	6.6 ± 0.1	0.32	75
	5-6	180-240	6.8 ± 0.1	0.11	150

Comparison of release from uncompressed pellets and MUPS tablets

Sodium alginate pellets (Figure 3) treated with calcium chloride solution were compressed into disintegrating tablets using the compositions listed in Table II, at an optimum crushing strength of 160 N, and were evaluated by *in vitro* drug release studies. A dissolution study of six tablets was conducted as per the specified method and the release profile compared with uncompressed pellets (Figure 4).

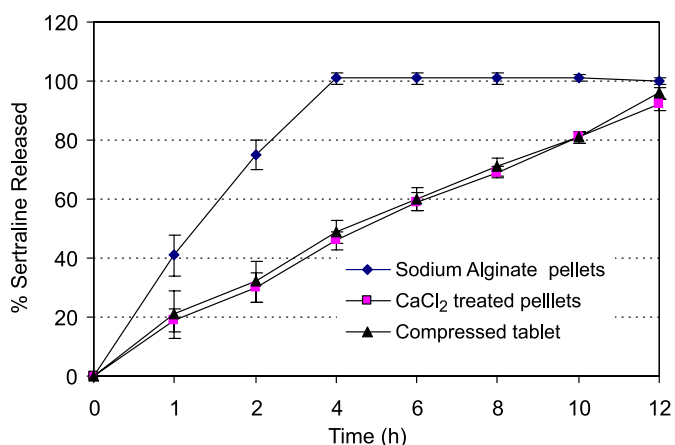


FIGURE 4 - *In vitro* dissolution profiles of sertraline from pellets containing (-♦-) 20%w/w plain sodium alginate, (-■-) Calcium chloride-treated pellets and (-▲-) compressed tablets.

The release profile of the MUPS tablets was identical to the release from the uncompressed pellets. The similarity in the release profiles could be attributed to the absence of a thin film of rate-controlling polymer as in the case of reservoir type pellets which are prone to damage during applied compression forces. In the present study, each pellet was presumed to behave like a monolithic matrix mini tablet distributed within the cushioning diluent blend where the drug release was not dependent on the status and nature of the extended release film. The pellets positioned on the surface of the tablet were visually inspected using a magnifying glass for any physical deformities on the pellet surface. Individual pellets subjected to compression force

through direct contact with the tooling surface were slowly segregated manually and observed under scanning electron microscope. From the scanning electron micrographs, segregated pellets were found to be physically modified with loss of spherical shape due to flattening of the part of the surface being pressed in the direction of the applied force (Figure 5).

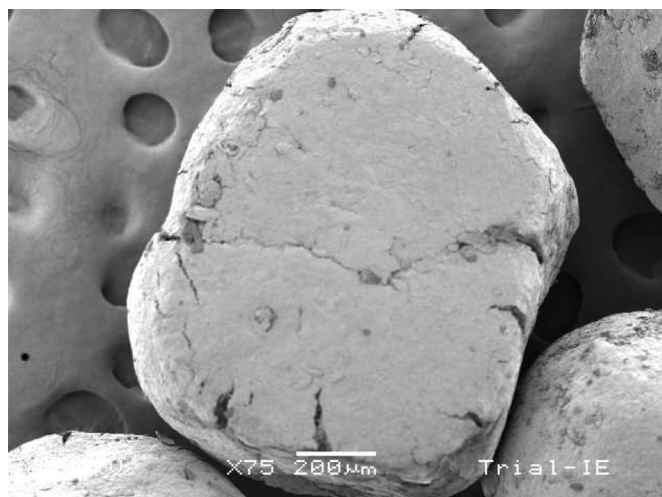


FIGURE 5 - Scanning electron micrograph of segregated individual pellet from the tablet surface directly exposed to the tooling surface during compression.

However, minor physical deformities or changes in shape are not expected to have significant impact on the release profile of the matrix pellets. This can be attributed to the presence polymer uniformly distributed within each pellet and whenever pellets encounter minor damage during compression, polymer within the pellet would still control drug release. Hence, only negligible alterations in drug release from both uncompressed pellets and the tablets were observed. Scanning electron micrographs (Figure 6) of the tablets showed well-distributed pellets in the diluent blend where pellets remained separate from each other preventing fusion and formation of non-disintegrating matrix mass. Pellets were intact and no pellets were found to be fragmented by the applied compression force within the diluent blend. This was possible by keeping the pellet

percent at 30%w/w where individual pellets remained well separated and protected from the compression deformities.

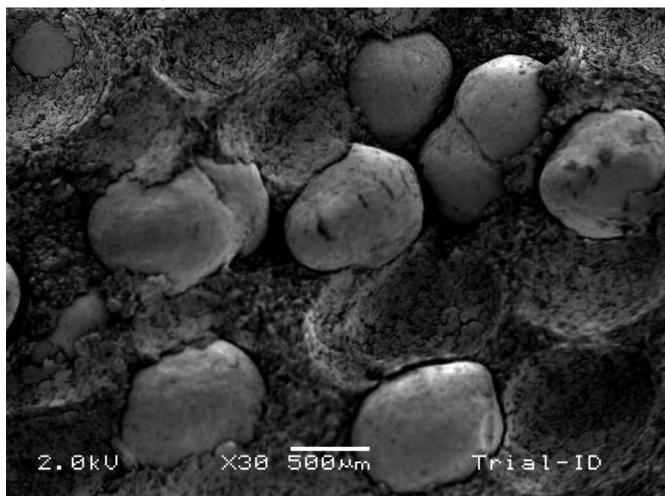


FIGURE 6 - Scanning electron micrograph of compressed tablet indicating distribution of matrix pellets within the diluent blend.

Content uniformity and Acceptance Value (AV)

In the present study, content uniformity of the ten compressed tablet was evaluated by measuring the sertraline content in individual tablets. The acceptance value of the compressed tablet was found to be 18.7 for TAB #1 composition containing Avicel PH 102 only as the filler. The higher AV indicates the poor ability of Avicel PH102 in preventing segregating tendency as previously reported (Beckert, Lehmann, Schmidt, 1998). The variation in the content can be due to the differences between density and size of the pellets compared to the diluent blend (0.4g/cc) which may cause segregation of the pellets. Moreover, when compressing the tablets using a single punch on a 12-station compression machine, the residence time of the blend in the feed frame is longer hence the possibility of preferential movement of the pellets into the die cavity increases, leading to variation in pellet uniformity within the tablets.

Influence of Filler on AV

To evaluate the effect of filler, three different compositions (TAB # 1-3) were tried as shown in Table 2. In the composition TAB #2, around 30 % w/w of Avicel PH 102 was replaced with Avicel PH 101 and the blend compressed into tablets reducing the AV value to 12.2. In another approach, 30 % of Avicel PH 102 was milled (18R, Quadro comill, at high speed) and Avicel PH 101 was replaced with the milled microcrystalline cellulose wherein the AV value was 14. This phenomenon of ob-

taining lower acceptance values could be attributed to the combination of free flowing (PH 102) and poorly flowing (PH 101 or milled) excipient in the diluent blend which might restrict the preferential movement of the pellets from the blend into the die cavities. Generally, obtaining content uniformity is difficult during compression of pellets into tablets due to various factors other than blend characteristics such as, blend residence time, operational equipment vibrations, number of toolings installed during compression etc. However, we predict a better uniformity with the TAB #2 compositions by running the compression machine with a complete set of tooling.

Influence of extrusion screen aperture size

To evaluate the influence of screen aperture size, wet mass of the composition #F11 was extruded using 1.0 mm, 1.2 mm and 1.5 mm screens. These pellets were dried and mixed with extra-granular excipients (TAB #2) and compressed into MUPS tablets. The tablets showed satisfactory physical characteristics. No significant difference in the dissolution profile of these tablets was observed (Figure 7).

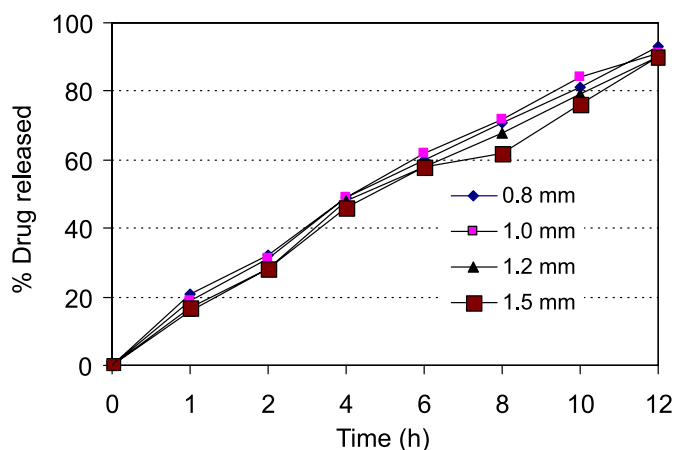


FIGURE 7 - Effect of extruder screen aperture size, (—◆—) 0.8mm, (—■—) 1.0 mm, (—▲—) 1.2mm and (—■—) 1.5mm, on *in vitro* sertraline release.

However, as the pellet size increased, the AV value was found to rise due to increased segregation tendency of the pellets (Figure 8). Based on this study, a screen aperture size of 0.8 mm was considered most suitable for extrusion of pellets to be compressed into tablets.

Influence of Pellet Percentage (%w/w) in the composition

Pellet proportion in the composition was increased from 30 % to 40 % and 60 % w/w by replacing the filler

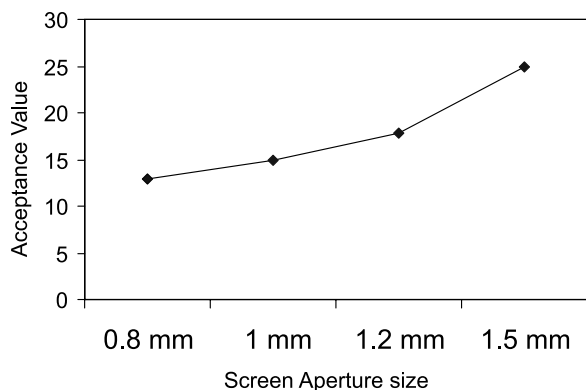


FIGURE 8 - Effect of extrusion screen aperture size (0.8 mm, 1.0 mm, 1.2 mm & 1.5 mm) on Acceptance Value of tablets.

composition. Accordingly, tablet weight was reduced (Table II) and compressed using suitable tooling. Tablets showed satisfactory physical characteristics. However, there was significant impact on the *in vitro* dissolution profile in the tablets (Figure 9).

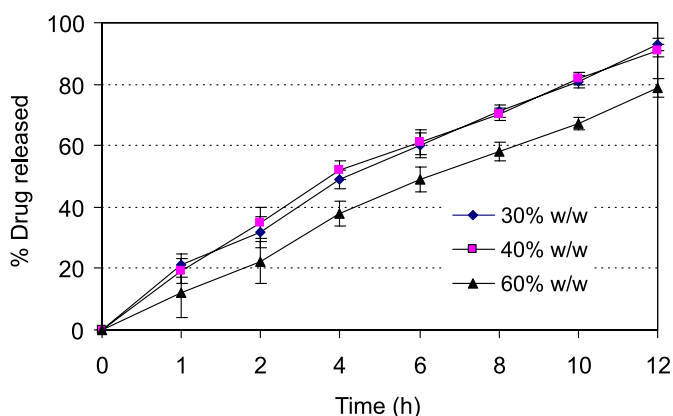


FIGURE 9 – Effect of pellet percentage (-♦-) 30% w/w, (-■-) 40% w/w and (-▲-) 60% w/w in tablet composition on *in vitro* sertraline release.

There was no significant difference in the drug release profile of the tablets containing 30–40%w/w pellets. At these levels, the tablets showed comparable physical characteristics and disintegration times. However, the tablets containing 60%w/w pellet failed to behave like rapidly disintegrating tablets in the dissolution vessels. As the percentage of pellets was increased, pellets were distributed closer in the diluent blend and underwent deformation leading to fusion of pellets into a non-disintegrating pellet mass consequently reducing drug release. This is in accordance with previous studies, confirming that tablets containing pellets below 60% w/w showed satisfactory results (Debunne *et al.*, 2004).

Stability study evaluation of compressed tablets

MUPS tablets prepared using sodium alginate (calcium chloride treated) pellets were subjected to stability study and evaluated for drug content and *in vitro* release profile. No significant change in the drug content was observed (99.2% w/w) compared to its initial assay content (98.9% w/w), respectively for the tablets prepared using sodium alginate-containing pellets. *In vitro* release profile of the tablets after completing the 3M accelerated stability study was studied and results are given in Figure 10.

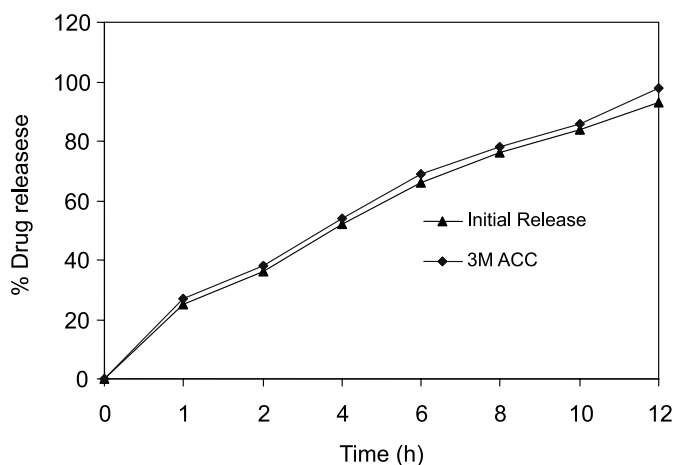


FIGURE 10 - *In vitro* drug release profile of tablets prepared using Sodium alginate-containing pellets during stability evaluation.

CONCLUSION

Using various polymers, *matrix* pellets were successfully prepared. The desired drug release was achieved from the alginate-containing pellets treated with saturated solution of calcium chloride. The drug release from matrix pellets and compressed tablets using these pellet was found to be similar. Acceptance value was easily achieved using a combination of Avicel PH 102 and Avicel PH 101 as fillers in the diluent blend. Further, the extrusion/spheronization technique can be explored to prepare extended release matrix type pellets which can substitute reservoir-type pellets in preparing the MUPS tablets. Future research could be dedicated to exploring other techniques to obtain greater uniformity of drug content in MUPS tablets.

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