International Journal of Drug Delivery 3 (2011) 329-339

http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Extended release matrix pellets: preparation and compression into disintegrating tablet

Raveendra Pai[1*], Kanchan Kohli[1]

***Corresponding author:**

Raveendra pai

[1] Formulation Development Services, Matrix Laboratories Ltd, A subsidiary of Mylan Inc USA.. Plot No 34A, Bollaram Industrial Area, Jinnaram Mandal, Medak District, Hyderabad -502325, India.

P.no. +918008001538,

Fax: +918458 279024

Email:

raveendrapai@yahoo.co.in

Abstract

The study involves a newer approach of compression of matrix pellets into disintegrating tablet to overcome the rupture of polymer coat during compression of reservoir type pellets.

Matrix pellets containing Sodium alginate (Kelton LV CR) at a level of 10, 20 and 30 %w/w was prepared by extrusion/spheronization technique. Sertraline hydrochloride was used as model drug and in vitro release profile of 12 h was targeted. Calcium chloride was used either by granulating the sodium alginate containing blend with 10% w/w solution or by pouring the wet pellets into saturated solution of calcium chloride. Tablets containing pellets were prepared by direct compression process. Acceptance value was used employed to evaluate the uniformity of drug content.

In vitro drug release from alginate containing pellets was complete within 4 h and the desired release profile could be achieved only from pellets treated with calcium chloride. The drug release from the uncompressed pellet and compressed tablet was identical, as each pellet was behaving like a monolithic mini matrix system. Scanning electron micrographs of the tablet indicated the uniform distribution of the pellets within the diluent blend. Scanning electron micrographs of the pellets obtained after completion the dissolution test were found to be left with empty sac like structure releasing the drug indicating anomalous type drug release.

Matrix pellets containing sodium alginate could be prepared by extrusion spheronization technique which can be an alternative approach in preparing disintegrating tablets from pellets.

Keywords: Extrusion/spheronization, Matrix pellets, Acceptance value, MUPS Tablets.

Introduction

Multiple unit extended release dosage forms are becoming very popular dosage forms over single unit dosage forms because of their ability to spread uniformly in the gastrointestinal tract minimizing the plasma level variability and reduced risk of local irritation [1-2]. Conventional design of extended release systems involves coating of spherical pellets with polymer that regulates their drug release rate and extent. However, considering the high cost of the capsule shells and encapsulation difficulties, more emphasis has been given to compress these pellets into disintegrating tablets. Multi unit particulate system (MUPS) is a tablet dosage form wherein pellets are compressed into tablets along with appropriate

excipients or cushioning agents in order to prevent the damage to the coating layer which regulates the drug release from the pellets. Polymers usually used to regulate the drug release from the pellets involves either cellulosic polymers or acrylic polymers [3].However, studies involving compression of pellets coated have reported the mechanical damage to the coating and loss of extended release properties [4] which could be due to the brittle nature of the film [5]. In contrary, drug release from the tablet was also slower from the pellets compressed at higher compression force due to fusion of pellets [6]. Various techniques were reported in minimizing the damage to the coat by suitably selecting the cushioning agents and maintaining the pellet size [7]. However recent studies involved use of polyethylene glycol as cushioning agent and compression the tablet at elevated temperature [8].

In the present study extrusion/spheronization an established technique for making spherical pellets was employed to prepare matrix pellets. Various polymers have been explored in preparing the pellets using extrusion spheronization technique [9]. Sodium alginate, a natural polymer has been used in the drug delivery systems like monolithic matrix tablets and extended release coated dosage forms [10-11]. As per the literature support from the granted patent publication US 6,899,896, sertraline hydrochloride (SRT) was used as model drug which is most commonly prescribed for depressive illness. As per the patent, increasing the sertraline dose beyond 50 mg, slow and prolonged release for about 12h would increase the patient compliance by reducing the side effects associated with the sertraline treatment at higher dose [12].

The objective of this study was to investigate the possibility of producing the extended release matrix pellets by extrusion/spheronization technique using and Sodium alginate (Keltone® LV CR) and to evaluate the effect of calcium chloride treatment on in vitro release profile. To compress the matrix pellets into MUPS tablets and evaluate the effect on the in vitro drug release and uniformity of drug content. As per our literature review, though there were various techniques being adopted to protect the extended release coat rupture during compression of pellets, no studies involving preparation MUPS tablets from the matrix pellets using sodium alginate has been extensively evaluated.

Materials and Methods

Materials

Sertraline was obtained from the Matrix Laboratories Ltd, India. Sodium alginate (Keltone® LVCR) was procured from ISP Corporation India. Calcium chloride and other excipients used in the pellet preparation and tablet compression were obtained from Matrix Laboratories Ltd, Hyderabad, India.

Methods

Preparation of Matrix type pellets by extrusion/spheronization

Different formulations of matrix type pellets were prepared with a composition shown in Table 1. All the batches were of 2000 units of 100 mg strength. During the pellet preparation, dry powder mixture was prepared by mixing sertraline, microcrystalline cellulose in a laboratory scale Rapid mixer granulator [Allen Bradley 5L, USA] at slow impeller speed for about 10 min. The blend containing sodium alginate was granulated using water as granulating fluid. Additional water, if required was incorporated during granulation to obtain wet mass suitable for extrusion and obtaining the quality pellets in terms of roundness (visually observed).

Appropriate quantity of the binding liquid and kneading time, which gave suitable wet mass for extrusion, was determined by trial and error process. The wet mass was extruded through a screen extruder [Multigran MG 55, Fugi Paudal

Co Ltd Japan.] equipped with a standard screen 0.8 mm diameter aperture, and the rolls rotating at 30rpm. The extrudes were transferred to the spheronizer [QJ 230T-1, Fugi Paudal Co Ltd Japan.] equipped with a crosshatch plate [1mm] and processed at 850 rpm rotating speed for desired time (4-15 min). The resultant pellets were dried in a fluid bed dryer [Rapid dryer, Retsch, Germany] with an inlet air flow at 50^0C for about 20-30 min. The dried pellets were sifted through ASTM 20 mesh (841 μ) and retentions were discarded. The fines below ASTM Mesh # 40 (420 μ) were also not included.

Table 1: Composition of extended release matrix pellets containing sodium alginate.

COMPOSITION (MG)	**#F1**	**#F2**	**#F3**
Sertraline[a]	112	112	112
Microcrystalline Cellulose) Avicel PH102)	176	144	112
Sodium Alginate	32	64	96
Water	qs	Qs	Qs
Total Weight (mg)	**320**	**320**	**320**

[a] Weight of Hydrochloride salt equivalent to 100 mg sertraline base. qs-Quantity sufficient.

Calcium chloride treatement of sodium alginate pellets

Calcium ion complexation was carried out on sodium alginate containing composition using the two approaches. In one of the approaches, Sertraline, microcrystalline cellulose and sodium alginate containing blend (# F2) was granulated with 10% w/w solution of calcium chloride ($CaCl_2$). In another approach, about 320 g of the wet spheroids containing 20 %w/w sodium alginate was poured in to 500 ml saturated solution of Calcium chloride and allowed to form the 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 about 10 min and then removed by filtration and washed with distilled water and vacuum dried.

Preparation of MUPS Tablets

MUPS tablets were prepared by direct compression approach where 320g of calcium chloride treated pellets were mixed with microcrystalline cellulose (Avicel PH 102, 446 mg, Avicel PH 101 200mg), polyethylene glycol (31g) and crospovidone (64g) in a laboratory scale blender [Conta Blender, Bowman & Archer] for 10 min. Finally, magnesium stearate (5g) passed through 250 μm sieve was added on to the mixture and blended for 5 min. The degree of filling of the blending vessel used was 50% by volume to ensure proper mixing. The tablets of 1066± 50 mg were compressed using one set of 19.5mmX 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 on the blend. Considering the criticality of the compression, the machine speed was set to 10 rpm. Tablets were compressed at different compression forces ranging 2-6kN in order to obtain the tablets with crushing strength ranging between 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 and the weight of the pellets to occupy 10 ml volume was noted. The bulk density was calculated by the ratio of weight to the occupied volume.

Friability was measured using Electrolab Friability testing apparatus [Electrolab Ltd, Mumbai, India] by tumbling 10 g of the pellets for 4 min at 25 rpm. The tested pellets were gently tapped on ASTM # 40mesh to remove the fines generated and the weight loss was measured. For testing the friability of the tablets, ten tablets were 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 by the simplest approach described by Lovgren and Lundberg [13], by measuring the length and width of the two dimensional image of the pellets using optical microscope [Olympus BX55TF, Japan]. The shape factor was expressed as a % 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 stabile position. A frequency distribution of the percent ratio of length to breadth of 100 pellets was calculated and the Sphericity (S) was expressed [14].

Hardness Testing

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

Disintegration testing

The disintegration time of the tablet was tested on 6 tablets using USP disintegration apparatus [Electrolab Disintegration Apparatus, India]. Distilled water was used as disintegration medium at 37 ^{0}C temperature. 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 on 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 specified buffer at 37 ^{0}C, paddles rotating at 50 rpm. Sink conditions was kept through out the test. Samples were collected at 1, 2, 4, 6, 8, 10 and 12 h intervals and analyzed by UV-Visible spectrophotometer [UV 2450, Shimadzu Corporation, Japan] at 273nm. Dissolution of pellets and MUPS tablets was conducted on 6 representative samples.

Drug content analysis

To determine the drug content, weight of the crushed pellets equivalent to 100mg of sertraline was weighed into a flask (1000ml) and extracted with minimum quantity of methanol and made up the volume with acetate buffer pH 4.5 and sonicated for about 30 min. UV absorbance of the solution filtered through 0.43µ filters was measured using UV-Visible spectrophotometer [UV 2450, Shimadzu Corporation, Japan] at 273 nm (λmax). To avoid the interference of the excipients, placebo blend was also treated similarly and kept as blank. Standard solution was prepared by weighing [Mettler Toledo, India] accurately 100 mg of sertraline and following the 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 pharmacopoeia for evaluating the content uniformity in the dosage forms [15]. As MUPS tablet involves compression of two varying density components together, achieving the content uniformity within the pharmacopoeial limits is a challenging task [16]. Hence Acceptance value was considered as a tool for evaluation of uniformity of the drug content was considered. The drug content of 10 individual tablets was measured with the method as 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 for 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 to be considered for calculation of Acceptance value.

Scanning electron microscopy

In order to observe the distribution of pellets within diluent blend, scanning electron microscopy was used [Jeol, JSM 6380LV, Japan]. For this purpose, tablets were subjected to hardness testing and the broken tablet surface was focused. To understand the drug release mechanism, pellets obtained after completing the in vitro dissolution test (for 12 h) were collected separately by slowly decanting the dissolution media, dried and observed using scanning electron microscope.

Results and Discussion

Preparation of Matrix type pellets and effect of polymers

In maintaining the drug release from the pellets after compression type, nature and amount of polymer plays major role. In most of the studies of compression of the coated pellets, showed damage to the coating with a loss of the extended release properties [17] and usually faster drug release was observed [18]. Hence, compression of matrix pellets into disintegrating tablet dosage form concept was arrived to address the issues pertaining to compression of reservoir type pellets coated with polymers for extended release of drug. In the present study commercially available sodium alginate was evaluated to develop matrix type pellets with extended drug release profile. The nature of the granules suitable for the extrusion was decided based on the preliminary experiments. The properties of the pellets prepared using 10%, 20% and 30% w/w polymer are represented in the Table 2.

Extrusion of blend containing higher level of polymer (30% w/w) through 0.8mm screen aperture was difficult and increase in spheronization time (12-15 min) was observed. Level of polymer beyond 30% w/w was not evaluated as it was generating lengthy extrudes leaving tackiness during extrusion. The spheronization process was continued until spherical pellets were observed. The drug release pattern from the pellets containing different level of sodium alginate was faster (Figure 1) with more than 85% of the drug release within 4h. The rapid dissolution from the pellets could be ascribed to surface erosion and formation of soluble hydrogel and wherein the drug release could happen due to both diffusion and erosion mechanism.

Table 2: Physical characterization data of extended release core pellets prepared by extrusion/spheronization process.

POLYMER	TRAIL	% W/W	NATURE OF PELLETS	FRIABILITY (%W/W)	DENSITY (G/CC)	SPHERICITY (%)
Sodium Alginate	# F1	10	Spherical	0.245	0.876	78 ± 4%
	# F2	20	Spherical	0.210	0.888	86 ± 5%
	# F3	30	Dumbbell-Shaped	0.220	0.877	72 ± 6%
Calcium Chloride Granulation	# F4	20	Spherical	0.195	0.869	85 ± 6%
Calcium Chloride Treated	# F5	20	Spherical	0.180	0.886	88 ± 5%

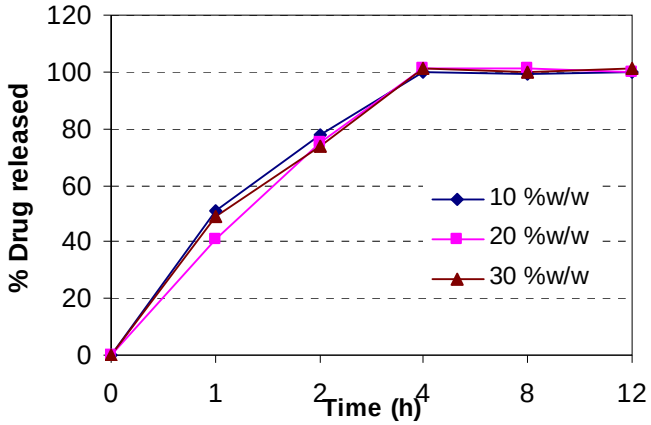

Figure 1: In vitro dissolution profiles of sertraline from pellets containing (-♦-) 10%w/w, (-■-) 20%w/w and (-▲-) 30%w/w Keltone® LV CR.

Effect of calcium chloride

Treating the sodium alginate containing pellets with calcium chloride for obtaining the extended drug release has been studied [19]. Similarly in our study, calcium chloride treated pellets could extend the release of sertraline for about 12h compared to sodium alginate containing pellets. Cross-linking of the calcium ions generates insoluble calcium alginate layer on the surface of the beads reducing the entry of the dissolution media into the pellets. Hence the drug release from these beads was extended to the desired profile as illustrated in Figure 2. Though in vitro release from the pellets obtained by granulation with the 10% solution of calcium chloride was slower compared to plain sodium alginate containing pellets, the release was significantly faster compared to the pellets treated with saturated calcium chloride solution. The difference in the release profile can be attributed lower level of the calcium chloride which may produce incomplete and discontinuous complexation during granulation using the calcium chloride solution. Treating with the saturated calcium chloride produces uniform gelatinous insoluble mass on the surface of the each pellet which would be helpful in extending the drug release for a prolonged period

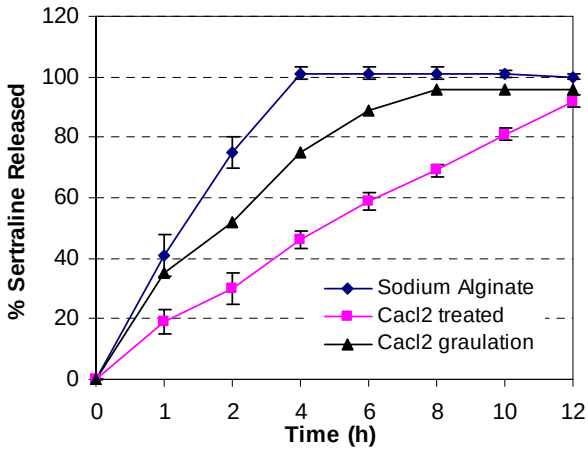

Figure 2: In vitro dissolution profiles of sertraline from pellets containing (-♦-) 20%w/w plain sodium alginate, (-▲-) granulated with calcium chloride granulated pellets and (-■-) Calcium chloride treated pellets.

Pellet Characterization

Pellets obtained with all these polymers showed comparable density, sphericity and friability as compiled in Table 2. The shape of the pellets obtained was varied from spherical to elongate spherical or dumbbell shape in some cases. Pellets were almost spherical in nature where in the sphericity value was ranging from of 72 % to 88%.

Compression of core pellets into MUPS tablets.

Based on the release profile of the pellets observed, only pellets treated with saturated solution of calcium chloride was considered for compression into MUPS tablets. These tablets are intended to disintegrate into discrete pellets in the gastrointestinal tract to release the drug from individual pellets. Due to differences in the size and density of pellets and the excipients, weight variation and content uniformity problems are regularly observed during compression of pellets. However, by selecting a narrow size distribution pellets together with excipients of similar size, shape would produce tables with uniform content [16]. Hence in our study, pellets fraction between ASTM # 20 mesh passed and #30 mesh retained pellets were

used. Direct compression approach was used to obtain disintegrating tablets using microcrystalline cellulose for reducing the damage, crospovidone to achieve fast disintegration [20] and polyethylene glycol a cushioning agent [7] along with magnesium stearate as lubricant. Pellet percentage was maintained at 30%w/w level based on the reported previous studies [21-22].

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 tablet compressed at an optimum crushing strength of 160N was considered and evaluated by in vitro drug release studies. Dissolution study of six tablets was conducted as per the specified method and the release profile was compared with the uncompressed pellets. The release profile of the MUPS tablets was identical to the release from the uncompressed pellets.

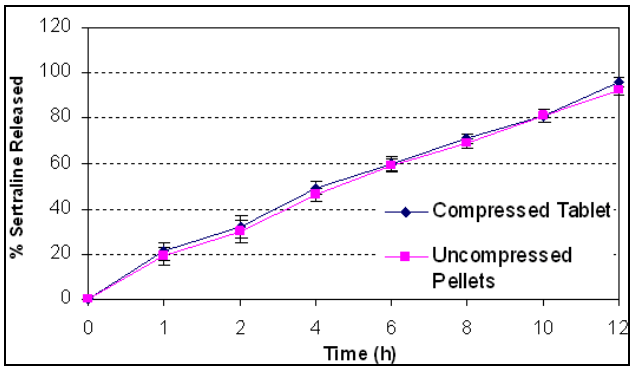

Figure 3: Comparison of in vitro drug release profile from (-■-) uncompressed pellets and (-♦-) compressed tablets prepared using sodium alginate 20%w/w and treated with calcium chloride solution.

The similarity in the release profile can be due to absence of thin film of rate controlling polymer as in the case of reservoir type pellets which are prone to damage during applied compression forces. In our study, each pellet was presumed to behave like a monolithic matrix mini tablet distributed within the cushioning diluent blend. Scanning electron micrographs of the segregated pellets from the surface of the tablets which are directly exposed to the tooling surface were found to be pressed in the direction of the applied force (Figure 4A).

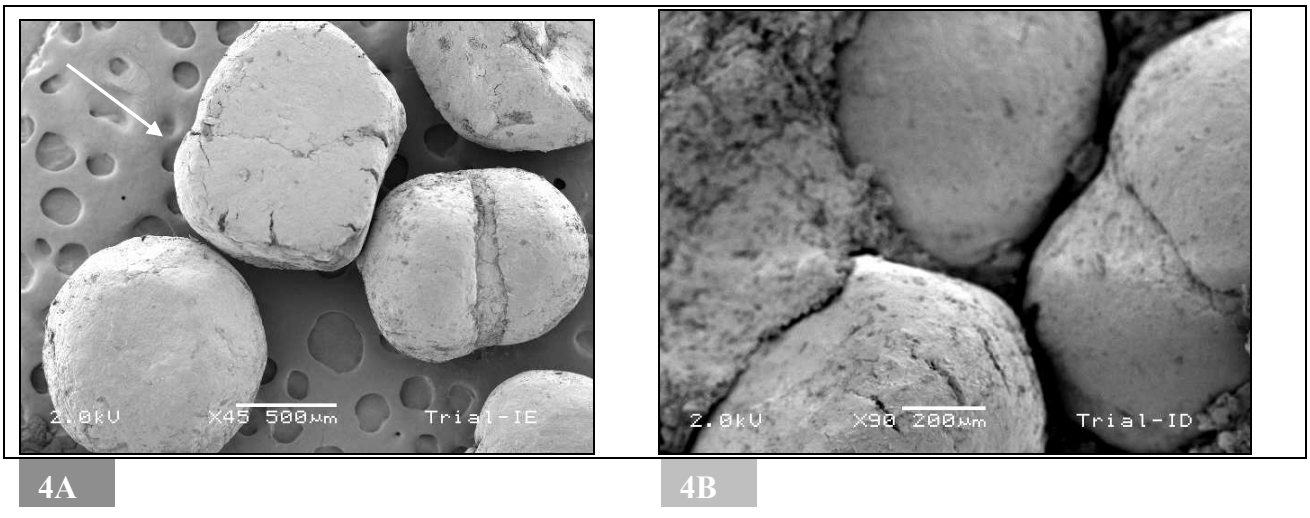

Figure 4: Scanning electron micrographs 4A: Segregated pellets from the tablet surface which are directly exposed to the tooling surface during compression and 4B: MUPS tablets containing matrix pellets distributed within the diluent blend.

However, minor physical deformities or change in shape is not expected to have significant impact on the release profile. This can be attributed to the presence polymer distributed

uniformly within each pellet cores and whenever pellets encounter minor damage during compression, polymer within the pellet would control the drug release. Hence minimum alteration in the drug release from the tablet was observed. Achieving such a property is difficult in reservoir type pellets where release rate is determined directly by the nature and status of the polymer film around each pellets.

Scanning electron micrographs (Figure 4B) of the tablet showed uniform distribution of the pellets as discrete units within the diluent blend and remaining separate from each other by preventing the fusion and formation of non-disintegrating matrix mass. Pellets were intact and no pellets were found to be fragmented with the applied compression force. This was possible by keeping the pellet percent at 30%w/w where individual pellets were well separated and protected from the compression deformities.

The tablets were compressed at different compression forces (2 -6kN) to obtain an average crushing strength of 80N to 240N with satisfactory physical characteristics. Increasing the compression force, increased the hardness and disintegration time however, friability was decreased (Figure 5). We attribute this phenomenon to the formation of more condensed compact with increased compression force. However, hardness showed no impact on the drug release pattern as the tables were disintegrating into individual pellets in the dissolution vessels. Once the pellets were separated, the drug release pattern obtained would be due to the collective contribution from the individual pellets.

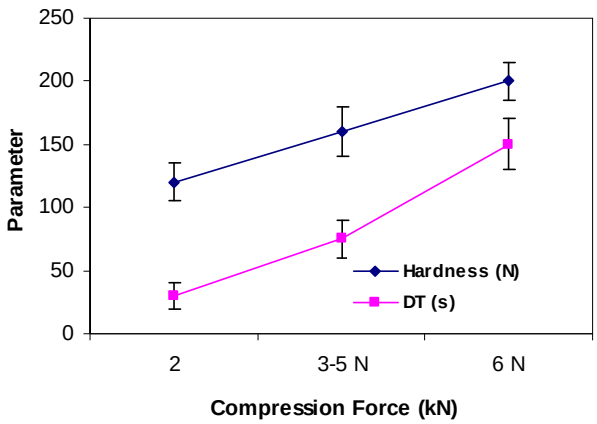

Figure 5: Effect of compression force on tablet characteristics, (-♦-) Hardness and (-■-) Disintegration time

Content uniformity and Acceptance value (AV)

Content uniformity of the ten compressed tablet was evaluated by measuring the sertraline content in the individual tablet and Acceptance value was calculated. Initial trials were tried only using the microcrystalline cellulose (Avicel PH 102, 646 mg) and acceptance value was found to be 18.7 indicating the poor ability of the filler to restrict the selective movement of the pellets as reported earlier [23]. However, acceptable AV value of 12.2 could be achieved by combination of free flowing (PH 102) and poorly flowing (PH 101) 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 tooling installed during compression etc. Moreover, when compressing the tablets using single punch on a 12 station compression machine, the residence time of the blend in the feed frame is more and possibility for preferential movement of the pellets into the die cavity increases leading to variation in the pellet uniformity in tablets.

Release Mechanism of drug release

Higuchi and Korsmeyer-Peppas models were commonly applied for understanding the dissolution mechanism [24-25] form pellets involving diffusion and erosion mechanisms. The drug release pattern from the MUPS tablets prepared from calcium chloride treated pellets containing 20% w/w sodium alginate (#F5) was analyzed for drug release kinetics theory by plotting the square root of time vs. percent drug release and release pattern was linear as per Higuchi's equation (r^2= 0.9812). To elucidate the possible mechanism, analysis of drug release data derived from the dissolution test was fitted to the exponential equation.

$$M_t/M_\infty = k_1 . t^n \quad \ldots\ldots \quad (2)$$

Where M_t/M_∞ represents the drug dissolved fraction at time t; k_1 is a constant incorporating the structural and geometric characteristics of the matrix pellets, n is the release exponent indicative of the drug release mechanism. The release exponent n value can range between 0.43 and 1, according to the geometry and the prevalence of the Fickian or case II (Relaxation transport) mechanism. Though the tablets were employed in the dissolution studies, these are expected to disintegrate into individual spherical pellets in the dissolution media. The lag period that pellets remains within the tablet until it disintegrates is negligible considering the total duration of the release profile. Hence exponent n in the Korsmeyer Peppas model for spherical particles was considered. For spherical particle, n vale between 0.43 and 0.85 indicates anomalous type of release involving the combination of both diffusion and erosion mechanism, when the n value is 0.85, Case II type and above 0.85 super case II type release mechanism are expected [26]. The release component of the calcium chloride treated composition showed fair linearity (r^2 =0.9824) with a slope (n = 0.5161) values, appears to indicate the sertraline transport anomalous type. The cross-linking property of calcium ions with negative charges of alginic acid molecules creates an insoluble barrier on the surface wherein sertraline initially could diffuse out of the pellets through Fickian diffusion followed by predominant erosion of polymer for the further release of drug during rest of dissolution time.

To evaluate and understand the mechanism of drug release, the pellets after completing the dissolution testing time were observed under scanning electron microscope. The pellets were carefully collected from the dissolution vessels by decanting the media. These pellets were partially dried using laboratory filter papers followed by drying at 40 ^{0}C in a vacuum oven for about a 2 hour. The dried pellets were observed under the scanning electron microscope Figure 6.

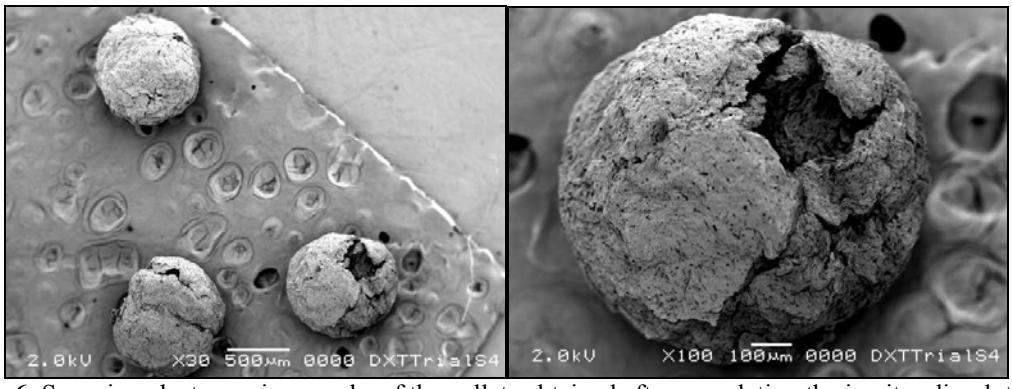

Figure 6: Scanning electron micrographs of the pellets obtained after completing the in vitro dissolution testing.

The pellets were found to form sac like structure made of insoluble membrane releasing the entire content. We presume the drug release from the pellets begins with the diffusion followed by erosion wherein the weaker part of the insoluble gelatinous matrix must have ruptured creating the channel and releasing the entire content slowly from the matrix core containg sodium alginate. This observation justifies the theoretically estimated mechanism of drug release from the pellets.

Conclusion

Using various sodium alginate polymer, matrix pellets could be successfully prepared. Pellets treated with saturated solution of calcium chloride extended the drug release up to 12h. There was no significant difference in the release pattern of MUPS tablet and the uncompressed pellets. Acceptance value could be well achieved using combination of Avicel PH 102 and Avicel PH 101 as fillers in the diluent blend. Further, extrusion/spheronization technique can be explored to prepare extended release matrix type pellets which can be an alternative technique to the reservoir type pellets in preparing the MUPS tablets. More emphasis could be diverted in exploring the other techniques to obtain better uniformity of drug content in MUPS tablets.

Conflict of Interest: None

Author's Contribution: RP Conceived the idea of obtaining the matrix type pellets and conducted the laboratory work and analysis. **KK** has provided the complete guidance in developing the pellet dosage form and performing the analysis.

References

1. Bodmeier R. Tableting of coated pellets. Eur J Pharm Biopharm. 1997;43:1-8.
2. Bechgaard H, Nielsen GH. Controlled release multiple units and single unit doses. Drug Dev Ind Pharm. 1978;4:53-57.
3. Harris MR, Sellassie IG. Aqueous polymeric coating for modified release pellets. In: McGinity JW, Editor. Aqueous polymeric coatings for Pharmaceutical dosage forms. New York: Marcel Dekker. 1989;p 63-79.
4. Bansal P, Vasireddy S, Parikh D. Effect of compression on the release properties of polymer coated niacin granules. J Control Rel. 1993;27:157-63.
5. Branka I, Svetlana I, Gabriele B, Zorica D. Evaluation of Diclofenac sodium release from Matrix pellets compressed into MUPS tablets. Yaugaku Zasshi. 2009;129(11):1375-1384.
6. Lopez-Rodriguez FJ, Torrado S, Escamilla C, Cadorniga R, Augsburger LL. Compression behavior of acetylsalicylic acid pellets. Drug Dev Ind Pharm. 1993;19:1369-1377.
7. Torrado JJ, Paronen P.Effect of different excipients on the tableting of coated particles. Int J Pharm. 1994;10:149-155.
8. Wieslaw S, Jaroslaw M, Ilona J. Hot tabletting of slow release tramadol hydrochloride microcapsules with cores obtained via compaction. Drug Dev Ind Pharm. 2010;32(6):209-217.
9. Pornsak S, Jurairat N, Manee L, Satit P. Alginate-based pellets prepared by extrusion /spheronization: A preliminary study on the effect of additive in granulating liquid. Eur J Pharm Biopharm. 2007;67:227-235.
10. Hodsdon AC, Mitchell JR, Davies MC, Melia CD. Structure and behavior in hydrophilic matrix sustained release dosage forms: 3. The influence of pH on the sustained-release performance and internal gel structure of the sodium alginate matrices. J Control Rel. 1995;33:143-152.
11. Bhagat HR, Mendes RW, Mathiowitz E, Bhargava HN. Novel self-correcting membrane coating technique. Pharm Res. 1990;8:576-583.

12. Curatolo et al., Hydrogel-Driven Layered dosage form. Patent No. US 2005;6:899:896B2.
13. Lovgren K, Lundberg P. Determination of Sphericity of pellets prepared by extrusion/spheronization and the impact of some process parameters. Drug Dev Ind Pharm. 1989;15:2375-2392.
14. Eriksson M. Nystrom C, Aldeborn G. The use of air permeability for assessment of external surface area and sphericity of pelletized granules. Int J Pharm. 1993;99(197):197-207.
15. European Pharmacopiea, **2005;**5.3:Chapter 2.9.4:3370-3372.
16. Flament MP, Leterme P, Gayot A, Gendrot E, Bruna E. Development and industrial scale-up of tablets containing modified release pellets. Pharm Tech Eur. 1994;6:9-25.
17. Dashevsky A, Kotler K, Bodmeier R. Compression of pellets coated with various aqueous polymer dispersions. Int J Pharm. 2004;279:19-26.
18. Sarisuta N, Punpreuk K. In vitro properties of film-coated diltiazem hydrochloride pellets compressed into tablets. J Control Rel. 1994;31:215-222.
19. Sriamornsak P, Kennedy RA. Development of polysaccharide gel coated pellets for oral administration. 2. Calcium alginate. Eur J Pharm Sci. 2006;29:139-147.
20. Rowe RC, Sheskey PJ, Weller PJ. Handbook of Pharmaceutical Excipients, fourth ed., Pharmaceutical Press, London. 2003.
21. Lundqvist AEK, Podczeck F, Newton JM. Compaction of and drug release from, coated drug pellets mixed with other pellets. Eur J Pharm Biopharm. 1998;46:369-79.
22. Beckert TE, Lehmann K, Schmidt PC. Compression of enteric coated pellets to disintegrating tablets. Int J Pharm. 1996;143:13-23.
23. Beckert TE, Lehmann K, Schmidt PC. Compression of enteric coated pellets to disintegrating tablets: uniformity of dosage units. Powder Technol. 1998;96:248-254.
24. Higuchi T. Mechanism of sustained-action medication: Theoretical analysis of rate of release of sold drugs dispersed in solid matrices. J Pharm Sci. 1963;52:1145-1149.
25. Korsmeyer RW, Gunny R, Docler E, Buri P, Peppas NA. Mechanism of solute from porous hydrophilic polymers. Int J Pharm. 1983;15:25-35.
26. Ritger PL, Peppas NA., A simple equation for description of solute release 1: Fickian and non-Fickian release from non-sweallable devices in the form of slabs, spheres, cylinders or discs. J Control Release. 1987;5:23-36.
27. International Journal of Pharmaceutics 2002;237:107–118.