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Original Article

EVALUATION OF DIFFERENT SYNTHETIC AND NATURAL POLYMERS AS PROTECTIVE LAYER ON HIGHLY SOLUBLE AND HIGH DOSE DRUG METOPROLOL SUCCINATEFOR MANUFACTURING OF CONTROL RELEASE MULTI UNIT PELLETS TABLETS

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ABSTRACT

Objective: Evaluation of different natural and synthetic polymers as protective layer (PL) in the manufacturing of control release (CR) multi-unit pellets (MUPS) tablets, highly soluble and high dose drug metoprolol succinate (MS) was selected as model drug. The function of PL is to protect CR functional coating layer of pellets from damage during compression of MUPS tablets.

Methods: MS is highly soluble biopharmaceutics classification system(BCS) Class–I molecule, hence selected aqueous solution layering method for drug loading in fluid bed processor (FBP), optimized formulation was manufactured by using seal coating on microcrystalline cellulose (MCC) pellets followed by drug loading (DL) and CR coating, applied by using the solution layering method in FBP. Given coating on these functional coated pellets with different natural and synthetic polymers like hydroxypropyl cellulose (Klucel LF), polyethylene glycol 6000 (PEG 6000), hypromellose 5 cps (HPMC 5cps), guar gum (GG) and xanthan gum (XM). Evaluated these pellet's for physical characterization and chemical characterization.

Results: Drug release profiles of CR MUPS tablets containing PL coating were compared to those CR pellets and *f2* values observed was 81.83, 49.92, 89.35, 66.44, and 85.25 with Klucel LF, PEG 6000, HPMC 5 cps, GG and XM coated MUPS tablets respectively. The dissolution data indicated that, there was no significant change were observed with MUPS containing Klucel LF, HPMC 5 cps, GG and XG PLs whereas faster release profiles were observed with PEG 6000PL MUPS tablets.

Conclusion: Based on these dissolution profiles it was concluded that by applying low viscous natural or synthetic binders like Klucel LF, HPMC 5 cps, GG and XG on functional coating pellets given good protection to functional coating pellets from damage during compression. It is a very effective and potent strategy for manufacturing of MUPS tablets. Whereas PEG 6000 polymer not able to give protection to functional coating pellets from damage during compression, it may be due to its very low viscosity of PEG 6000.

Keywords: MUPS, CR, Compression of pellets, Drug release, Natural and synthetic Polymers

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INTRODUCTION

Pharmaceutical solid dosage forms are using a functional coating to modify the release. Due to the disadvantages of coated single-unit dosage forms, such as dose dumping, less predictable gastrointestinal (GI) transit times and may potentially lodge in restrictions within the GI tract, which could lead to variable drug absorption and cause damage to the gastric mucosa if the drug is irritant, and hence coated MUPS are preferred. Coated MUPS can eventually be filled into capsules or compressed into tablets. Tablet dosage form is more desirable as unit production costs of considerably lower and machinery is more easily available. However, some challenges is there in the manufacturing of MUPS tablets, compression forces can result in damage of functional coating, segregation pellets during compression. Hence, it is important to understand the factors affecting coat damage during compression [1-3] and segregation of pellets during manufacturing of tablets.

There are many relevant articles and literature available on the preparation of pellets and coating technology. However, only few research articles discuss the issue of compaction of pellets into tablets [4]. A different techniques were used to prevent the damage of functional layers in past work, but remains an unmet need in drug delivery, some of techniques are use of cushioning excipients and/or compressible excipients, novel granulation techniques to protect the coating layer against fracture during compaction [5-10], improved by thermal exposure [11], Layering the top surface of beads with compressible excipients, such as MCC, to modify the mechanical properties of the beads was successful in addressing this issue. This approach, however, requires a huge amount of the layering excipients, but still with mixed results [12].

Natural (GG and XG) and synthetic polymers (Klucel LF, PEG 6000, HPMC 5 cps) were evaluated for different activities like binders, CR polymers, plasticizers[13-16] but its activity as a PL agent has not been evaluated in MUPS tablets. The objective of the present study was to evaluate these polymers as PL agents to protect pellets from compression force during compression, for this study high dose and high soluble drug MS was selected as a model drug, MS is a beta1-selective (cardioselective) adrenoceptor blocking agent, It is freely soluble in water, Its chemical name is (±)1-(isopropylamine)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt). This strategy helps in the easy development of MUPS tablets in the overcome big challenge of breaking pellets during compression.

MATERIALS AND METHODS

Materials

MS, gifted by CTX Lifesciences (P) Ltd, Gujarat, India, MCC spheres(Celphere CP 203) gifted by Asahi Kasei Chemicals, ethocel standard 10 premium gifted by Dow Chemicals, acetyltributyl citrate gifted by Vertellus Performance Materials Inc. 2110 High Point Road, Greensboro, N. C, HPMC 5cps gifted by Dow Chemicals, Klucel LF gifted by Aqualon Hercules, PEG6000, gifted by Clariant Chemicals (India) Ltd, isopropyl alcohol gifted by Deepak Fertilizers and Petrochemicals Corporation Ltd, methylene chloride gifted by Gujarat Fluro Chemicals Ltd, silicified MCC (Prosolv HD90) gifted by JRS Pharma, kollidon CL gifted by BASF, Ludwigshafen, Germany, sodium stearyl fumarate gifted by Rank Organics Chemical Pvt Ltd.

Methods

Preparation of MS CR pellets with PL coatings

MS CR pellets were composed of four parts, namely Celphere CP 203, seal coating, DL, CR-coating layer and protective coating layer successively. All the layers were prepared in a FBD (table 1) by solution layering methods. The formulation includes preparation of seal coated solution and coated this solution on Celphere CP 203 after completion of seal coating, DL solution and CR coated solution was prepared and coated on seal coated pellets, finally protective coating was given on the CR pellets to prevent cracking of functional layers during compression, after preparation of protective coated pellets prelubrication and lubrication was done followed by compression. Seal-coated pellets, DL pellets, CR coated pellets and protectively coated pellets were dried for 30 min at 45 °C and then weighed to calculate the weight gain when their temperature reached room temperature.

Preparation of seal coated pellets

Isopropyl alcohol and methylene chloride solvents were taken on a vessel, added ethocel standard 10 premium slowly to the solvent system with continuous stirring for 30 min, got a clear solution and acetyl tributyl citrate was added slowly to the above solution and mixed for 30 min got a clear solution. Selected core pellets were loaded in FBP (Glatt 1.1) and coated these core pellets with a seal coating solution by using 1.5 mm nozzle, and parameters were compiled below table (1). After completion of coating, seal coated pellets were dried at 45^0C for 30 min.

Preparation of DL pellets

Purified water was taken in a vessel equipped with propeller stirrer and added HPMC 5 cps slowly to the purified water with continued stirring for 30 min, it formed a clear solution and then added MS slowly to the above solution, mixed for 30 min, it formed a clear solution, and loaded this DL solution on seal coated pellets, the parameters were compiled in table (1).

Preparation of CR pellets

Isopropyl alcohol was taken on a vessel with stirrer and added ethocel standard 10 premium slowly to the solvent with continued stirring for 10 min and added methylene chloride solvent while stirring and continued stirring for 30 min and added Klucel LF slowly to the above solution to continue stirring for 30 min and formed a clear solution finally added purified water to the solution with continued stirring for 30 min. This clear solution was coated on DL pellets to get CR pellets, the parameters were compiled in the table (1).

Preparation of PL pellets

PL coating was done by dissolving the Klucel LF, PEG 6000, HPMC 5 cps, GG and XG in purified water and coated on CR pellets by a solution layering method in FBP method, the parameters were compiled in table (1).

Characterization of PL coated pellets and precompression blend

Apparent bulk density

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume, including the contribution of the interparticulate void volume. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. The bulk density is expressed in grams per ml (g/ml).

The bulk density was determined by transferring the accurately weighted amount of sample to the graduated measuring cylinder and noted initial volume. The bulk density of the sample was then calculated by using the below formula [17].

$$\text{Bulk density} = \frac{\text{Mass (M)}}{\text{Bulk volume } (V_0)}$$

Table 1: Seal coating, DL, CR coating and PL coating process parameters

Process parameter	Seal coating	DL	CR coating	PL coating
Coating type	Non-aqueous coating	Aqueous coating	Non-aqueous coating	Aqueous coating
Product temperature (^{0}C)	30±5	45±5	30±5	45±5
Atomization (Bar)	0.5-1.0	1-2.5	0.5-1.0	1-2.5
Spray rate(g/min)	5-20	5-15	5-15	5-20
Fluidization (CFM)	5-10	5-10	5-10	5-10
Wurster (mm)	18	18	18	18

The protective coated pellets were mixed with extragranular excipients, lubricants and prepared final blend, the final lubricated blend was compressed into tablets. The composition of pellets and tablets were compiled in the table (2) and table (3).

Table 2: MS 200 mg CR pellet formula

S. No.	Ingredients	Quantity/unit mg)
1.	Celphere CP 203, (150-300µ)	68.00
Seal coating		
2.	Ethocel standard 10 premium	11.90
3.	Acetyltributyl citrate	1.70
4.	Isopropyl alcohol	140.00
5.	Methylene chloride	70.00
	Weight of seal coated pellets	81.60
DL		
6.	MS	190.00
7.	HPMC 2910 5cps	9.50
8.	Purified water	950.30
	Weight of DL pellets	281.10
CR Coating		
9.	Ethocel standard 10 premium	75.83
10.	Klucel LF	19.17
11.	Isopropyl alcohol	1340.08
12.	Methylene chloride	670.04
13.	Purified water	349.52
	Weight of CR coated pellets	376.10

Table 3: MS 200 mg CR MUPS tablet formula

S. No.	Ingredients [mg/tablet]	Formulations				
		MTP1[a]	MTP2[b]	MTP3[c]	MTP4[d]	MTP5[e]
CR pellets		376.10	376.10	376.10	376.10	376.10
1	Klucel LF	37.61	---	---	---	---
2	PEG 6000	--	37.61	---	---	---
3	HPMC 5 cps	--	---	37.61	---	---
4	GG	--	---	---	37.61	---
5	XG	--	---	---	---	37.61
Weight of PL pellets		413.71	413.71	413.71	413.71	413.71
Extragranular						
6	Prosolv HD 90	378.79	378.79	378.79	378.79	378.79
7	PEG 6000	50.00	50.00	50.00	50.00	50.00
8	Kollidon CL	150.00	150.00	150.00	150.00	150.00
9	Sodium stearyl fumarate	7.50	7.50	7.50	7.50	7.50
Weight of Tablet		1000	1000	1000	1000	1000

MTP1[a]is MS 200 mg CR MUPS tablets with Klucel LF PL coating, MTP2[b]is MS 200 mg CR MUPS tablets with PEG 6000 PL coating, MTP1[c]is MS 200 mg CR MUPS tablets with HPMC 5 cps PL coating, MTP1[d]is MS 200 mg CR MUPS tablets with GG PL coating, MTP1[e]is MS 200 mg CR MUPS tablets with XG PL coating.

Tapped density (g/ml)

The tapped density was determined by using tapped density apparatus make. Electro lab, Model ETD-1020, the procedure involves the weighed quantity of sample was taken in 250 ml a measuring cylinder and the cylinder was kept on cylinder holder and allowed to tap for 10, 500, and 1250 taps on the same powder sample and read the corresponding volumes V10, V500, and V1250 to the nearest graduated unit. If the difference between V500 and V1250 is less than or equal to 2 % V1250 is the tapped volume If the difference between V500 and V1250 exceeds 2 % repeated in increments such as 1250 taps, until the difference between succeeding measurements is less than or equal to 2 %. Fewer taps may be appropriate for some samples when validated. The tapped density was determined by using the following formula [17].

$$\text{Tapped density} = \frac{\text{Mass (M)}}{\text{Tapped volume (Vt)}}$$

Compressibility index or Carr's index

The percentage compressibility of the drug was determined by using the following formula. It is measured in percentage (%) and limits were presented in table (4) [17].

$$\text{Compressibility index (\%)} = \frac{\text{Tapped density-Bulk Density}}{\text{Tapped density}} \times 100$$

Table 4: Limits for Carr's index

Carr's index (%)	Flow character
≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very, very poor

Table 5: Limits for Hausner's ratio

Hausner's ratio	Flow character
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-.59	Very poor
>1.60	Very, very poor

Hausner's ratio

It related to the flow properties of powder samples and is measured by the ratio of tapped density to bulk density or ratio of bulk volume to tapped volume, it is related to interparticle friction. Limits of hausners ratio were presented in table (5) [17].

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} = \frac{\text{Bulk volume}}{\text{Tapped volume}}$$

Angle of repose

The angle of repose is a characteristic related to interparticulte friction or resistance to movement between particles. It is the constant, three-dimensional angle (relative to horizontal base) assumed by a cone-like a pile of material formed by any of several different methods. The limits of the angle of repose were presented in table (6) [18-20].

$$\text{Tan } \emptyset = (h/r)$$

Where' h' is the height of the cone

'R' is the radius of the cone.

Evaluation of compressed tablets

Thickness (mm)

The thickness of the tablets was determined by using vernier calipers. Three tablets were picked up randomly and thickness was measured individually using the formula [21].

Thickness=MSR+[VSR×0.01]

Where,

MSR= Main scale reading

VSR= Vernier scale reading

Table 6: Limits for angle of repose (degrees)

Flow character	Angle of repose (degrees)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

Hardness (KP)

The hardness of the tablets was determined using hardness tester make: Pharmatest, Type: PTB–311E. It was expressed in KP. Three tablets were randomly picked and the average value of hardness was determined [22].

Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance, average weights were calculated, individual tablet weights were compared with the average weight. Not more than two individual weights deviate from the average weight by more than percentage shown in the following table and the results were shown in table 7[23].

$$PD= \frac{(W\ avg)-(W\ initial)}{(W\ avg)} \times 100$$

Where, PD = Percentage deviation

W avg = Average weight of tablets

W initial = Individual weight of tablet.

Standard weight variation (IP)

Table 7: Limits for weight variation

Average tablet weight (mg)	Percentage deviation (%)
Up to 80 mg	5
>80 mg,<250 mg	7.5
250 mg or more	10

Friability test (%)

Friability is the measure of tablet strength. It is expressed in percentage (%), the friability of the tablet was determined by using roche friabilator. 10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated for 100 revolutions (25 rpm/min), then tablets were taken out and dedusted. The percentage weight loss was calculated by reweighing the tablets. The percentage friability was then calculated by [24].

$$\%\ Friability= \frac{W1-W2}{W1} \times 100$$

Where,

W1 = Initial weight of the tablets

W2 = Final weight of the tablets

Friability limits: less than 1% is acceptable

***In vitro* disintegration test**

The test was carried out on 6 tablets using digital tablet disintegration tester make Electrolab in purified water at 37 ^{0}C±2 ^{0}C [25].

Drug release measurements and comparisons

Prepared MUPS pellets and tablets were subjected to *in-vitro* dissolution profiles in pH 6.8 phosphate buffer using apparatus II (paddle apparatus) [26], 500 ml, maintained at 37±0.5 °C.500 ml of in pH 6.8 phosphate buffer was transferred into each dissolution container. MS MUPS pellets and tablets were placed in each of the containers, and operated dissolution apparatus at 50 rpm for 20 h. At each specified interval of time, 5.0 ml of the sample was withdrawn from each container and replaced with equal volume of fresh pH 6.8 medium maintained at 37±0.5 °C. The collected sample was filtered through 0.45 µm membrane filter and analyzed the drug content by using ultraviolet-visible spectroscopy.

In this study, we evaluated the similarity between MUPS pellets and final compressed tablets in the pH 6.8 phosphate buffer and tested any breakage of coating layer during compression. As a parameter of similarity evaluation, the similarity factor (*f2*) plays a significant role in comparing the dissolution profiles. *f2* (shown in the following formula) is a logarithmic transformation of the sum-squared error of differences between MUPS pellets and the compressed tablets over all time points [27].

$$f_2 = 50 \times \log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{1/2} \times 100\right\}$$

Log stands for logarithm based on 10. It is recommended that two dissolution profiles can be determined to be similar when *f2* value exceeds 50.

RESULTS AND DISCUSSION

Micromeritic properties of PL pellets

The PL pellets of all the batches (MPT1-MPT4) were evaluated for bulk density, tapped density, compressibility index, hausners ratio and angle of repose and presented in the table (8). Bulk density ranged from 0.698 to 0.711 g/ml, tapped density ranged from 0.735 to 0.758 g/ml, Carr's index ranged from 4.898 to 6.201 %, and hausners ratio ranged from 1.052 to 1.066%.

Based on above results it indicated that the PL pellets possess satisfactory flow and compressibility index.

Table 8: Evaluation of PL pellets

Formulation	Description	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hauser's ratio
MPT1	Off white pellets	0.705	0.750	6.000	1.064
MPT2	Off white pellets	0.698	0.740	5.676	1.060
MPT3	Off white pellets	0.711	0.758	6.201	1.066
MPT4	Off white pellets	0.702	0.745	5.772	1.061
MPT5	Off white pellets	0.699	0.735	4.898	1.052

Micromeritic properties of the lubricated blend

The lubricated blend of all the batches (MPT1-MPT4) was evaluated for bulk density, tapped density, compressibility index, hausners ratio and angle of repose and presented in table (9). Bulk density ranged from 0.598 to 0.621 g/ml, tapped density ranged from 0.728 to 0.735 g/ml, carr's index ranged from 14.973 to 17.517%, and hausners ratio ranged from 1.176 to 1.212%.

Based on above results it indicated that the lubricated blends possess satisfactory flow and compressibility index.

Table 9: Evaluation of lubricated blend

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hauser's ratio	Angle of repose (degrees)
MPT1	0.619	0.728	14.973	1.176	36
MPT2	0.598	0.725	17.517	1.212	36
MPT3	0.621	0.735	15.510	1.184	37
MPT4	0.615	0.730	15.753	1.187	38
MPT5	0.610	0.728	16.209	1.193	35

Process parameters for tablet compression

Thickness of the MUPS tablets was found to be in the range of 7.5±0.021 to 7.6±0.040 mm. The hardness of the tablets was found to 15.7±0.458 to 16.2±0.306. Friability of all the tablets varied from 0.50±0.02 to 0.85±0.007 % which was less than 1% as per official requirement of I. P.

Weight variation of developed tablets indicated that no significant difference in weight of individual tablet from the average value.

The drug content in all the batches of MS MUPS tablets was in the range of 100.1±0.351 to 101.3±1.058 i.e., within the official limits. These parameters presented in table (10).

Table 10: Evaluation parameters of formulated tablets

Formulation	Thickness (mm)	Hardness (KP)	Friability (%)	Weight variation (mg)	Percentage drug content (%)	Disintegration (Sec)
MPT1	7.6±0.026	15.7±0.458	0.070±0.020	1000.7±2.517	100.1±0.351	145.33±4.51
MPT2	7.6±0.040	15.9±0.513	0.030±0.021	1000.3±1.528	100.4±1.026	138.00±2.00
MPT3	7.5±0.032	15.8±0.702	0.047±0.015	998.7±1.528	101.3±1.058	142.67±4.04
MPT4	7.5±0.038	16.2±0.306	0.033±0.021	998.0±1.000	101.0±0.458	127.67±0.58
MPT5	7.5±0.021	16.2±0.300	0.040±0.015	1000.3±1.041	100.8±0.808	134.33±4.04

The data presented are as mean values±SD, n=3

Drug release measurements and comparisons

The prepared CR pellets divided into six parts, one part was used for dissolution studies and other five parts were used for protective coating of five polymers Klucel LF, PEG 6000, HPMC 5 cps, GG and XG. The prepared PL coated pellets of synthetic polymers Klucel LF, PEG 6000, HPMC 5 cps and natural polymers GG, XG were free-flowing, free from agglomerates. We had taken CR common pellets, PL pellets of five different polymers and compressed into tablets and compared the dissolution profiles of CR pellets, PL pellets, MUPS tablets compressed with CR pellets and MUPS tablets compressed with PL pellets. The hardness was selected 15-18 KP where MUPS tablets made with the CR pellets are breaking and release the drug faster than CR pellets.

Effect of Klucel LF PL coating on drug release before and after compression of pellets

Drug release of Klucel LF PL pellets, MUPS tablets made with Klucel LF PL pellets were observed that there was no significant change, whereas MUPS tablets made with CR pellets showing significant increasing in release profile it might be indicating that breakage of CR pellets in MUPS tablets contain CR pellets and intact of Klucel LF PL pellets in MUPS tablets made with Klucel LF PL pellets. The release profiles were compiled in table (11).

Table 11: *In vitro* dissolution profiles of CR, Klucel LF PL coated pellets and tablets manufactured with that pellets

Time in h	% Drug dissolved			
	CR pellets	PL coated pellets	Tablets manufactured with CR pellets	Tablets manufactured with PL coated pellets
1	11(1.67)	12(1.63)	18(2.14)	9(1.22)
2	18(1.83)	18(1.26)	23(2.07)	17(1.03)
3	23(1.21)	24(1.75)	35(2.37)	24(1.21)
4	28(1.64)	29(2.07)	43(2.64)	27(1.75)
6	38(1.83)	39(1.79)	53(2.34)	40(1.38)
8	47(2.34)	49(1.94)	62(2.37)	50(2.59)
10	56(1.64)	58(1.94)	71(1.51)	56(2.14)
12	65(1.47)	66(1.94)	82(1.72)	68(1.05)
16	81(1.47)	81(2.17)	90(1.75)	82(1.38)
20	90(1.79)	90(1.72)	97(0.82)	93(1.37)
f2		88.6	45.26	81.83

The data presented are as mean values±SD, n=6

Effect of PEG 6000 PL coating on drug release before and after compression of pellets

Drug release of PEG 6000 PL pellets, MUPS tablets made with PEG 6000, MUPS tablets made with CR pellets were observed that there was a significant change in release profile it might be indicates that breakage of CR pellets, PEG 6000 PL pellets in MUPS tablets. It indicated that PL coating with PEG 6000 may not suitable to protect pellets from compression breakage**.** The release profiles were compiled in table (12).

Table 12: *In vitro* dissolution profiles of CR, PEG 6000 PL coated pellets and tablets manufactured with that pellets

Time in h	% Drug dissolved			
	CR pellets	PL coated pellets	Tablets manufactured with CR pellets	Tablets manufactured with PL coated pellets
1	11(1.67)	10(1.79)	18(2.14)	15(2.25)
2	18(1.83)	17(2.32)	23(2.07)	21(2.88)
3	23(1.21)	22(2.50)	35(2.37)	34(2.25)
4	28(1.64)	27(1.60)	43(2.64)	41(2.73)
6	38(1.83)	36(2.07)	53(2.34)	49(2.48)
8	47(2.34)	45(2.07)	62(2.37)	60(2.58)
10	56(1.64)	55(1.83)	71(1.51)	68(2.32)
12	65(1.47)	63(1.83)	82(1.72)	75(2.58)
16	81(1.47)	79(2.07)	90(1.75)	81(1.21)
20	90(1.79)	91(1.41)	97(0.82)	97(1.05)
f2		87.37		49.92

The data presented are as mean values±SD, n=6

Effect of HPMC 5 cps PL coating on drug release before and after compression of pellets

Drug release of HPMC 5 cps PL pellets, MUPS tablets made with HPMC 5 cps PL pellets were observed that there was no significant change whereas MUPS tablets made with CR pellets showing significant increasing in release it might be indicates that breakage of CR pellets in MUPS tablets contain CR pellets and intact of HPMC 5 cps PL pellets in MUPS tablets made with HPMC 5 cps PL pellets. The release profiles were compiled in table 13.

Table 13: *In vitro* dissolution profiles of CR, HPMC 5 cps PL coated pellets and tablets manufactured with that pellets

Time in h	% Drug dissolved			
	CR pellets	PL coated pellets	Tablets manufactured with CR pellets	Tablets manufactured with PL coated pellets
1	11(1.67)	10(1.51)	18(2.14)	10(0.75)
2	18(1.83)	18(1.26)	23(2.07)	20(1.21)
3	23(1.21)	22(1.51)	35(2.37)	24(0.82)
4	28(1.64)	26(1.05)	43(2.64)	29(1.64)
6	38(1.83)	37(1.75)	53(2.34)	40(0.52)
8	47(2.34)	45(1.97)	62(2.37)	48(1.10)
10	56(1.64)	54(1.86)	71(1.51)	57(1.55)
12	65(1.47)	64(2.56)	82(1.72)	65(1.86)
16	81(1.47)	80(1.10)	90(1.75)	82(1.38)
20	90(1.79)	88(2.32)	97(0.82)	91(0.75)
f2		86.93	45.26	89.35

The data presented are as mean values±SD, n=6

Effect of GG PL coating on drug release before and after compression of pellets

Drug release of GG PL pellets, MUPS tablets made with GG PL pellets were observed that there was no significant change whereas MUPS tablets made with CR pellets showing significant increasing in release, it might be indicates that breakage of CR pellets in MUPS tablets contain CR pellets and intact of GG PL pellets in MUPS tablets made with GG PL pellets. The release profiles were compiled in table (14).

Table 14: *In vitro* dissolution profiles of CR, GG PL coated pellets and tablets manufactured with that pellets

Time in h	% Drug dissolved			
	CR pellets	PL coated pellets	Tablets manufactured with CR pellets	Tablets manufactured with PL coated pellets
1	11(1.67)	9(1.37)	18(2.14)	10(0.52)
2	18(1.83)	15(1.03)	23(2.07)	15(0.75)
3	23(1.21)	20(1.22)	35(2.37)	21(0.98)
4	28(1.64)	24(1.22)	43(2.64)	25(0.55)
6	38(1.83)	32(1.97)	53(2.34)	33(0.84)
8	47(2.34)	42(1.51)	62(2.37)	41(1.05)
10	56(1.64)	51(1.86)	71(1.51)	49(1.03)
12	65(1.47)	60(1.55)	82(1.72)	59(0.84)
16	81(1.47)	79(0.89)	90(1.75)	77(1.21)
20	90(1.79)	87(1.10)	97(0.82)	85(1.17)
f2		69.11	45.26	66.44

The data presented are as mean values±SD, n=6

Effect of XM PL coating on drug release before and after compression of pellets

Drug release of XM PL pellets, MUPS tablets made with XM PL pellets were observed that there was no significant change whereas MUPS tablets made with CR pellets showing significant increasing in release it might be indicates that breakage of CR pellets in MUPS tablets contain CR pellets and intact of XM PL pellets in MUPS tablets made with XM PL pellets. The release profiles were compiled in the table (15).

Table 15: *In vitro* dissolution profiles of CR, XM PL coated pellets and tablets manufactured with that pellets

Time in h	% Drug dissolved			
	CR pellets	PL coated pellets	Tablets manufactured with CR pellets	Tablets manufactured with PL coated pellets
1	11(1.67)	11(1.86)	18(2.14)	9(1.03)
2	18(1.83)	17(1.63)	23(2.07)	16(1.05)
3	23(1.21)	22(1.63)	35(2.37)	21(1.05)
4	28(1.64)	28(0.89)	43(2.64)	27(1.05)
6	38(1.83)	37(1.47)	53(2.34)	35(0.84)
8	47(2.34)	48(1.05)	62(2.37)	46(1.22)
10	56(1.64)	55(1.38)	71(1.51)	55(1.76)
12	65(1.47)	65(1.26)	82(1.72)	66(1.76)
16	81(1.47)	80(1.47)	90(1.75)	82(1.21)
20	90(1.79)	91(1.05)	97(0.82)	90(1.17)
f2		92.47	45.26	85.25

The data presented are as mean values±SD, n=6

The results obtained from the flow evaluation of The PL pellets, lubricated blend, it was found that the flow rate, carr's index, hauser's ratio and angle of repose had values that comply with the official standard for good powder flowability [17-20]. The results of compression parameters of all batches (MTP1-MTP5) were well within the limits of the official standards. Tablet thickness is an important quality control parameter for packaging of tablets in container blisters, the void space in container pack, blister toolings selection depends on thickness of the tablets. Tablets thickness can be varied with particle size distribution, density of the granules, punches, dies and hardness. From the results, the tablets exhibited good uniformity of thickness and conform to the official standard limits.

The weight variation of tablets contributes to the dose uniformity of a drug [23], if the drug is higher dose more than 25 mg and formulation contain 25% of active, content uniformity of tablets can be checked by using weight variation method. The variation in tablet weight may be due to poor flow of granules, lack of uniformity in granule size, compression process variables such as feed frame paddle speed and press speed. The data obtained for weight uniformity test indicate that the tablets possess significant dose uniformity.

All formulated tablets had a hardness within the range of 15-18 KP, hardness play an important role on dissolution profiles depends on whether dosage form is matrix tablets or MUPS tablets. In case of matrix tablets if increase hardness, the rate of dissolution will decrease, whereas in case of MUPS tablets if increase hardness rate of dissolution increases and hence hardness play a very important role during compression. The hardness data indicated that all formulations having a good uniform and narrow range [22]. The results of friability indicated that all formulations had friability within the official limits ≤ 1% [24]. Friability is a routine test per compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimize customer complaints.

The CR pellets, PL coated pellets, Tablets manufactured with CR pellets, Tablets manufactured with PL coated pellets dissolutions were studied and comparatively compiled in tables. The drug release profile is important for bioavailability (BA); therefore, it is critical. Since in vitro drug release is a surrogate for in vivo performance, rate drug release depends on different factors like type of dissolution apparatus, dissolution media, pH of media, a method of dissolution, the composition of the polymer, a percentage weight gain of CR coating, size of core pellets, extragranular excipients. Hence above all formulations were used same factors except PL coating. The results of dissolution profiles indicated that drug was released in a controlled manner and released above 90% in 20 h in all formulations. The dissolution profiles of tablets manufactured with CR pellets had fasted release compared to pellets alone, it indicates that break the pellets during compression without any protective layer coating.

The dissolution profiles of tablets manufactured with GG, XG, Klucel LF, HPMC 5 cps PL coated pellets similar to pellets alone, there was no significant difference in dissolution profiles, it indicated that PL coatings were protecting pellets during compression. Binding nature, plastic nature, mechanical properties of these polymers may protect pellets from compression forces without retarding dissolution profiles. The dissolution profiles of tablets manufactured with PEG 6000 PL coated pellets were faster than pellets alone, it indicates PEG 6000 PL coating was not sufficient to protect pellets from compression force. It may be due to low binding nature, less mechanical properties of PEG 6000. The results of dissolution profiles indicate that GG, XG, Klucel LF, HPMC 5 cps PL coated pellets were good candidates for manufacturing of MUPS tablets.

CONCLUSION

MS CR tablets were prepared successfully by using ethyl cellulose and HPMC 5cps used as release-modifying excipients and low viscous natural or synthetic binders like Klucel LF, PEG 6000, HPMC 5 cps, GG and XM as PL coating agents. The flow properties of pellets and the lubricated blend were evaluated and found to be satisfactory. The process parameters of MS MUPS tablets were found to be well within limits.

Based on comparative dissolution profiles of MUPS tablets, CR pellets and PL coating pellets it was found that by applying low viscous natural or synthetic binders like Klucel LF, HPMC 5 cps, GG and XM on functional coating given good protection to functional coating layers from damage during compression. Hence it can be concluded that this approach is a very effective and potent strategy for manufacturing of MUPS tablets. Whereas very low viscous polymers PEG 6000 not able to protect functional coating layers of pellets from damage during compression.

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CONFLICTS OF INTERESTS

Declared none

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