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Original Article

THE INFLUENCE OF MAGNESIUM STEARATE, PURIFIED TALC AND COMBINATION OF BOTH ON TERNARY/QUATERNARY INTERACTIVE MIXTURE OF FREELY AND POORLY WATER-SOLUBLE DRUG

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ABSTRACT

Objective: This research purposed to describe and evaluate the influence of magnesium stearate (MgSt), purified talc (talc) and combination of both (MgSt-PT) on ternary/quaternary mixture of freely and poorly water-soluble drug.

Methods: Chlorpheniramine maleate (CPM) and prednisone (PDN) were used as the drug model of freely and poorly water-soluble drug, respectively. Compatibility studies between drugs and lubricants were carried out using Fourier transform infrared spectroscopy (FTIR). Ternary/quaternary interactive mixture of drugs, lubricants and carriers were conducted using granules of lactose-starch (1:1) as carriers with particle size 250 – 425 µm. Characterizations were conducted by homogeneity of mixture, physical properties of granules and tablets and drug releases. The results were analyzed statistically using one-way analysis of variance (ANOVA) with 95% of confidence interval level and dependent method for drug release.

Results: Homogeneity of binary mixture within drug and carrier was achieved in 60 minutes with 20 revolutions per minute. MgSt, talc and combination of both provided stable ternary/quaternary interactive mixture. MgSt affected the reduction of compactibility, prolong the disintegration time, retardation the drug release and talc improved flowability.

Conclusion: Talc provided more preferable effects than MgSt, and combination of both lubricants showed desirable physical properties of tablet. MgSt, talc and combination of both provided no significant effect on physical properties and drug release of CPM as freely water-soluble drug and the significant effect was observed on PDN as poorly water-soluble drug.

Keywords: Magnesium stearate, Talc, Interactive mixture, Drug release, Disintegration time.

INTRODUCTION

Solid-solid mixing is a fundamental process in the manufacture of solid dosage form. Stable and homogeneity of the mixture can be ensured the drug content uniformity [1,2]. Interactive mixture is a common processing operation in the pharmaceutical mixing using interactive constituent usually fine drug particle and carrier, in interactive mixture inter-particulate force is present because at least one of the constituent. Usually fine drug particles adhere to a coarser constituent in the carrier particle [3].

Formation the interactive mixture depend on the optimum mixing condition, i. e. type of mixer, mixing time, size distribution of carrier particle, surface of the carrier and adhesion force between fine particle drug and carrier determine the successful on interactive mixing. Carrier particles must be greater than drug particle to achieve the adhesion force [4-6].

Lubricant, flowing agent and anti-adherent agent such as talc and MgSt have been widely used in pharmaceutical formulation to enhance the powder flowability [7]. MgSt is the most widely used as the lubricant on pharmaceutical formulation as hydrophobic material, usually was added to reduce the friction between granules and die wall during the compression process [6]. This lubricant is commonly used in the range of 0.25-1% (w/w) for tablet dosage form formulation [8]. Pingali et al. have been reported that the mixing order of lubricant (MgSt) and glidant (colloidal silica) affected the hydrophobicity thus retarded drug release and prolonged disintegration time [9]. Enhancement the MgSt concentration prolonged the disintegration time. Using MgSt as lubricant with concentration 0.1 and 5% was to be not significant difference on tensile strength using granules of chitin-Mg silicate and Avicel® PH200 [10]. MgSt affected the increasing of bulk density and tapped density, the drug release was not significantly affected and the effect of sodium stearate provided higher drug release using the poorly water-soluble drug (indomethacin) [11]. MgSt improved the dispersibility of salbutamol sulfate as freely water-soluble drug and the dispersion of interactive mixture depend on particle size of MgSt and the concentration of MgSt [12].

Inorganic material such as talc is a hydrous magnesium silicate sometime containing small amount of aluminum silicate [8]. Talc lubricated the granules and produced the tablet with higher powder flow, enhance tablet hardness and reduce the disintegration time compared to MgSt. Difference source manufacture of talc provided showed the significant difference on glidant efficiency [13]. Talc in concentration 1% (w/w) provided similarity with 0.25% (w/w) of MgSt and produce tablet more hardness and less fragile and talcsuitable for lubricant at concentration 0.5-3% up to 5% (w/w) on aspirin tablet [14]. Lubricant and glidant were added in interactive mixture affected the stability and agglomeration [4,5].

Hence, this research was to describe and evaluate the effect of MgSt, talc and combination of both on ternary/quaternary interactive mixture and physical properties of tablets using difference drug solubility such as CPM as freely water-soluble drug and PDN as poorly water-soluble drug.

MATERIALS AND METHODS

Materials

CPM and PDN (micronized form) were obtained from Iffars Pharmaceuticals Labolatories (Surakarta, Indonesia), starch from *Manihot utilisima* (PIM Pharmaceuticals, Indonesia), lactose (DFE Pharma), MgSt (Peter Greven, Germany) and talc were purchased from Bratachem Chemicals (Surakarta, Indonesia) and all other chemicals were of pharmaceutical grade. Hydrochloric acid, potassium bromide and ethanol were purchased from Merck (Darmstadt, Germany) was of analytical grade and demineralized water.

Methods

Drug-excipients compatibility studies

Drug and lubricant compatibility studies was conducted using FTIR Shimadzu 8400S (Kyoto, Japan) to determine the interaction between CPM and PDN with MgSt, talc and MgSt-PT. The pure drug and lubricants (in equal ratio) with total amount of 1.5 mg and potassium bromide 150 mg was compressed using hydraulic pressure with compression force 6kN for 5 minutes. Pellets were scanned in the range of wave number 400 – 4000 cm^{-1} with resolution 4 cm^{-1} and 1000 times iteration.

Tablet formulation

CPM as freely water-soluble drug and PDN as poorly water-soluble drug were used as drug model. MgSt, talc and combination of both were used as lubricant with total amount 1% of tablet weight and granules from starch and lactose in equal amount was used as carrier to adjust the weight of tablets (100 mg). Amount of lubricants, CPM and PDN were added according to Table 1.

Preparation of carrier (host)

Granules of lactose and starch were used as carrier. Equal amount of lactose and starch (1:1) with total amount 500 g were mixed using Erweka AR400 cube mixer for 10 minutes with 20 rpm and was followed by addition of 10% (b/v) of starch paste to the blend until elastic mass of wet granules were achieved. Mass of wet granules were passed through 40 mesh sieve. Wet granules were dried in oven for 8 hours and temperature at 50^{o}C. Granules were used as carrier under size of 40 mesh sieve (425 μm) and over size of 60 mesh sieve (250 μm).

Table 1: Composition of tablet formulation

Composition	Formula code (mg)					
	F1	F2	F3	F4	F5	F6
CPM	4	4	4	-	-	-
PDN				5	5	5
MgSt	1	-	0.5	1	-	0.5
Talc	-	1	0.5	-	1	0.5

Preparation of tablet

Tablets were formulated according to Table 1. The direct compressed method was employed for tablet preparation. The time of mixing process was determined based on coefficient of variation (CV) of drug content. The binary mixture between drug and carrier were mixed in cube mixer at 20 rpm, and sample with 20 points in different places were withdrawn and determined the drug content using Hitachi 150-20 spectrophotometer every 30 minutes interval until coefficient of variation (CV) less than 5% was achieved, then followed by addition of lubricant for 5 minutes at 20 rpm.

Physical properties of ternary/quaternary mixture characterization

Physical properties of ternary/quaternary mixture were characterized by flowability and compactibility. Flowability was conducted using Erweka flowmeter. Moreover flow rate and angle of repose was computed automatically. Compactibility testing was conducted using the single punch with deepness of upper and lower punch 4.0 and 7.0 mm, respectively. Compactibility was described by crushing force of tablet and was tested using Vanguard YD-1 hardness tester.

Tablet compression

The tablet compression process used KorschXP-1 (Germany) single punch tablet machine. The weight of tablets were arranged 100 mg and tablets were compressed with the same compression force with deepness of upper and lower punch 4.5 and 7.0 mm, respectively.

Physical properties of tablet

Physical properties of tablets were conducted by weight variation (n=20 tablets), friability testing (n=20 tablets) using Pramec friability tester, hardness (n=10 tablets) using Vanguard YD-1 hardness tester, tablet disintegrating time (DT) (n=6 tablets) using Erweka ZT-2 disintegration tester.

***In vitro* drug release**

The drug releases were determined using Erweka TDT-06 dissolution tester type apparatus II (paddle method), a 900 ml of water as dissolution medium, temperature was maintained at 37±0.5^{o}C with stirring rate 50 rpm. Aliquots of 5 ml were withdrawn at 2, 5, 10, 15, 20, 25, 30, 45 and 60 minutes with replacement of 5 ml of the fresh medium. All the samples were analyzed directly at maximum wavelength of PDN and CTM, i. e. 254and 262 nm, respectively using Hitachi 150-20 UV-Vis spectrophotometer.

Drug release profiles

Drug releases were characterized based on dependent model, i. e. Dissolution efficiency during 10 and 60 minutes was abbreviated with $DE_{10}$and DE_{60}, respectively. Cumulativeamount of drug release at 2, 5 and 30 minutes were abbreviated with Q_2,Q_5 and Q_{30}, respectively. Similarity factor, difference factor and multivariate analysis of variance (MANOVA) with 95% of confidence intervals (p=0.05) was employed to compare the drug release profiles.

Statistical analysis

The results (flowability, compactibility, CV of drug content, physical properties of tablet and drug release) were analyzed statistically using analysis of variance (ANOVA).

RESULTS AND DISCUSSION

The preliminary study revealed that incompatibility studies between drugs (PDN and CPM) with lubricants (MgSt and talc) are presented in Fig. 1. FTIR spectra of CPM and physical mixture with lubricants are shown in Fig. 1a. The principal peaks of CPM were at wave number 1587.42 cm^{-1} assigned carbonyl stretching vibration of maleate and 1666.50 cm^{-1} assigned C-O stretching vibration of maleate. Peak at wave number 648.08 cm^{-1} assigned C-Cl vibration and 1091.71 cm^{-1} assigned C-N vibration of aliphatic tertiary amine. Peaks at wave number around the 1400 – 1500 cm^{-1} were assigned as ring vibration. FTIR spectra of PDN and physical mixture with lubricants are shown in Fig. 1b. The principal peak of PDN was at wavenumber 1618.28 and 3361.93 cm^{-1} due to the C=O stretching and OH stretching vibration, respectively. The characteristic peaks of PDN were assigned at wavenumber 1710.86 cm^{-1} and the strong peak at 1666.50 cm^{-1} due to C=O and C=C stretching vibration from cyclohexadiene, respectively. The other peaks below 1000 cm^{-1} assigned C-H deformation vibration. FTIR spectra of PDN and CPM and physical mixture with lubricants showed that there were compatible between drugs and lubricants. There was no significant shift of the principal peaks CPM and PDN with presence of lubricants from native CPM and PDN spectra, thus indicated that no chemical interaction between drug and lubricants.

Homogeneity of mixture was achieved until the CV of drug content in samples less than 5% [4,5]. Preliminary study to achieve homogeneity of mixture is presented in Fig.2. The homogeneity of binary interactive mixture between drugs and carrier was achieved in 60 minutes of mixing time using cube mixer with 20 rpm. At the initial time (30 min) of mixture, the CV of drug content was higher than 60 min of mixing time. Interactive mixture need more time than

random mixture to achieve the homogeneity. Interactive mixture provided stable mixture without segregation rather than random mixture, thus the interactive mixture was used in low dose of drug to ensure the homogeneity. Among than PDN and CPM, CPM showed that CV of drug content was lower than PDN mixture, this was affected by shape, size and particle distribution of PDN and CTM. Addition of lubricants as ternary/quaternary mixture provided stable mixture without segregation that was shown by the CV of drug content (Table 2) less than 5%. MgSt, talc and combination of both not affected the homogeneity of interactive mixture, there was no significant difference statistically ($p<0.01$) for CPM tablet and PDN tablet, respectively. Talc provided influence on reduction the homogeneity (increasing CV) than MgSt, their combination showed that MgSt improved homogeneity the ternary mixture. Previous work showed that MgSt improved the dispersion the drug to the carrier on interactive mixing[12].

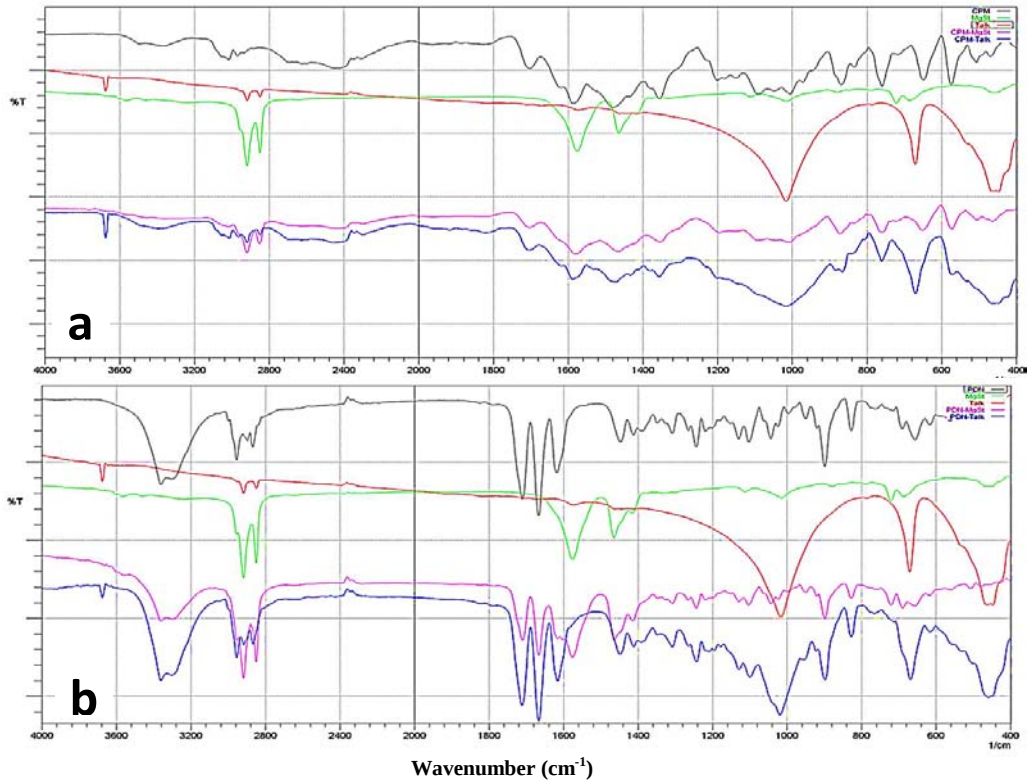

Fig. 1: FTIR spectra of CPM (a) and PDN (b) (black band = drug, green band = MgSt, red band = talc, purple band = drug-MgSt and blue band = drug-talc)

Table 2: Physical properties of granules and tablets (mean ±SD)

Formula code	Flow rate (gram/sec)	Compactibility (N)	CV (%)	Hardness (N)	Friability (%)	DT (sec)
F1	27.17±0.29	17.75±0.87	4.08±0.93	28.83±2.17	0.419±0.085	56.92±4.68
F2	30.02±0.44	22.92±1.08	3.48±0.14	32.83±2.08	0.358±0.116	27.92±4.44
F3	29.35±0.81	20.42±1.08	3.66±0.33	31.00±2.52	0.414±0.119	45.33±3.65
F4	24.86±0.27	17.42±1.24	3.39±0.63	30.00±1.48	0.408±0.081	57.00±3.59
F5	27.23±0.34	22.58±1.51	2.78±0.69	34.42±1.21	0.321±0.060	27.33±3.28
F6	26.56±0.44	21.25±1.22	3.35±0.74	31.50±1.12	0.343±0.093	39.42±6.22

Table 3: Drug release properties of CPM and PDN tablets (mean ±SD)

Formula code	Q_2 (%)	Q_5 (%)	Q_{30} (%)	DE_{10} (%)	DE_{60} (%)
F1	50.30±5.76	66.64±4.41	84.00±2.47	57.83±4.25	78.93±1.82
F2	44.64±7.91	68.99±3.69	80.95±1.93	57.18±4.11	76.62±2.28
F3	51.49±1.53	66.25±3.11	81.14±1.83	57.92±1.95	77.11±1.74
F4	29.39±4.33	50.01±1.99	86.74±3.99	46.94±2.47	80.06±3.64
F5	18.75±4.39	38.57±2.76	80.28±1.85	35.06±2.87	70.29±2.25
F6	23.92±2.39	45.69±4.46	81.77±1.37	40.35±2.53	72.62±2.18

The effect of MgSt, talc and combination of both on physical properties of granules and tablet are shown in Table2. Among both of lubricants, talc affected on increasing flowability than MgSt. Granules using CPM had lower flowability than granules using PDN. Mechanism talc in increasing the flowability reduces the friction of interparticle of granules. Talc as the anti-adherent agents which avoid the mass of tablets adhere in the upper punch on compression process and enhance the flowability. MgSt reduce the friction within

the mass of tablets and wall of compression room and as aid process in the tablet compression [6]. MgSt affected the reduction compactibility, thus MgSt coating the granules and reduce the interactive contact surface on the tablet compression process and tablet became soft after compaction. Similar result have been reported by Uchimoto et al. (2011) that MgSt reduced the inter particle bonding by coating the carrier surface [15]. Talc provided compactibility and flowability higher than MgSt, thus combination both of lubricant improved compatibility and flowability than MgSt alone as lubricant. The compactibility was shown by the crushing force of tablet in the same condition of tablet compression process. The flowability was shown by flow rate of the ternary/quaternary mixture, flow rate more than 10 gram/sec and angle of repose less than 30^{o} show the preferable flowability [16].

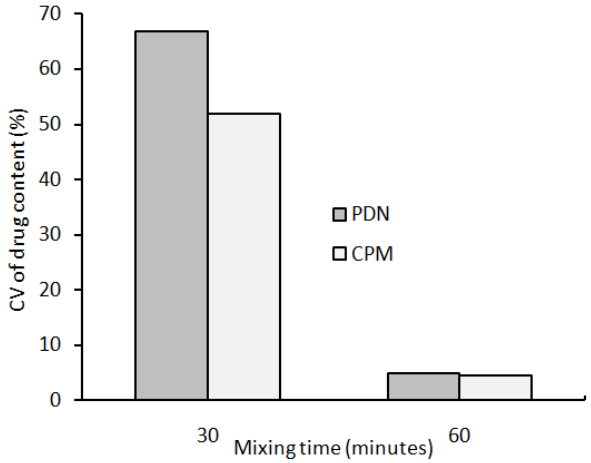

Fig. 2: Variation coefficient of homogeneity mixture using 30 minutes interval

Talc as powder flow agent improved the flowability than MgSt [17], thus combination of both (MgSt-PT) provide desirable of powder flow and dispersibility. Hardness was affected by lubricant, MgSt reduced hardness and talc increased hardness and combination both of lubricant improved the hardness tablet than MgSt alone as lubricant. PDN tablet showed higher hardness than CPM tablet in the same condition of compression process, that significant difference statistically ($p<0.01$) was observed. Friability of tablet less than 0.8% more preferable, thus all formulations had friability within 0.321 – 0.419%. Friability of tablet based on hardness of tablet, increasing hardness tablet reduce the friability. The effect of MgSt on tablet friability was affected by hardness, although combination both of lubricant reduced friability of tablet. MgSt, talc and combination of both provided no significant effect on friability statistically ($p>0.01$) in CPM tablet and PDN tablet, although hardness was affected by lubricants.

The influence of MgSt, talc and MgSt-PT on DT of ternary/quaternary mixture are presented in Table 2. All lubricants and combination of both showed significant effect on DT ($p<0.01$), moreover difference of drug solubility provided significant effect statistically ($p<0.01$). Lubricant act as coating of the granules and had hydrophobic properties, thus reduce the water-uptake and inhibit imbibition of water to the tablet [8,9]. MgSt more hydrophobic material than talc, thus formulation using MgSt showed increasing DT than using talc as lubricant and combination of both reduced the DT than MgSt alone as lubricant.

The effect of MgSt, talc and MgSt-PT on drug release profile of CTM as water-soluble drug and PDN as poorly water-soluble drug from tablet dosage form are presented in Fig. 3. Difference solubility of drug affected the drug release profile. Lubricant inhibit the imbibition of water to the tablet due to the hydrophobicity, thus MgSt had more hydrophobic than talc and combination of both lubricant showed improving the drug release especially at initial time than MgSt alone as lubricant. Uchimoto et al. (2010) have been reported that increasing the MgSt concentration as lubricant affected the reduction of drug release [18]. The effect of MgSt, talc and combination of both was assessed with dependent method using similarity and difference factor. Multiple comparisons were used in drug release at initial time (Q_2 andQ_5) and drug release during 30 minutes [19]. The similarity (f_2) and difference factor (f_1)were applied to compare drug release profile is shown in Fig. 4. f_2 showed that tablet using CPM as drug model had similar drug release profile with the f_2 value more than 50 [20,21]. This difference of lubricant provided no significant effect in drug release pattern. Hence, the drug release of all formulas in CPM tablet were affected by the solubility of drug and the lubricant affected the drug release at initial time, MgSt more hydrophobic than talc thus the drug release at initial time using talc higher than MgSt as lubricant. Similarity drug release profile between MgSt and combination MgSt-PT on PDN tablet was found with f_2 value more than 50 and f_1 less than 15. Thus, based on fit model MgSt, talc and combination of both not affected the drug profile release in water soluble drug, although in poorly water-soluble drug similarity was found on MgSt and combination between MgSt and talc.

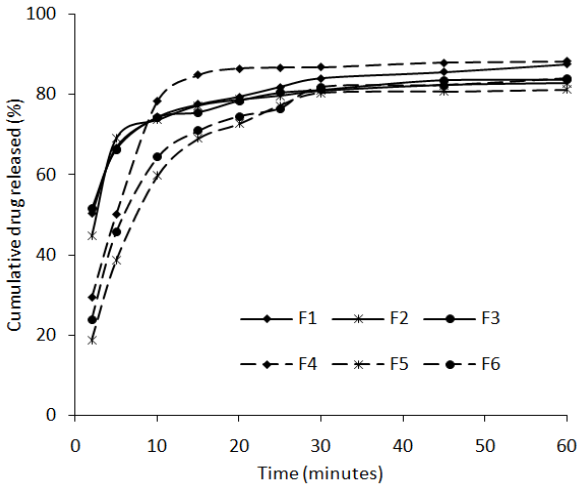

Fig. 3: Drug release profiles of CPM and PDN tablets

Based on the dependent method to compare the drug release, i. e. Q_2, Q_5, Q_{30}, DE_{10} and DE_{60} are shown in Table 3 and Table 4 for multiple comparisons of Q_2 and Q_5. Cumulative drug release above 30 minutes showed no significant difference among all formulations, thus MgSt, talc and combination of both provided no significant effect on Q_{30} statistically ($p>0.05$). Lubricant inhibits the imbibition of water in initial time and after tablet liberation, the lubricants provide no effect on drug release. Based on multiple comparisons of Q_2 and Q_5 are presented in Table 4, MgSt, talc and combination of both provided no meaningful difference in the formulation using CPM as drug model. CPM as freely water-soluble drug, the drug release based on solubility and the lag time after tablet liberation and no significant effect on delay or reduction the drug release in initial time was observed. The previous work was reported that freely water soluble drug (captopril) release from the dosage form after tablet liberation with burst release due to increasing the surface area [22]. Using PDN as poorly water-soluble drug showed the difference on Q_2 and Q_5, thus MgSt, talc and combination of both provided significant effect on drug release especially at initial time ($p<0.01$ and $p<0.05$). MgSt provided reduction on drug release at initial time lower than talc and combination of both, thus talc as flow agent provided more preferable effect than MgSt, although MgSt can be reduce the ejection force in compression proses because act as lubricant that reduce of friction within compressed mass and die. Addition of poorly water-soluble constituent in ternary component such as dibasic calcium phosphate, calcium sulfate and talc increase the dissolution rate and de-agglomeration of indomethacin [23].

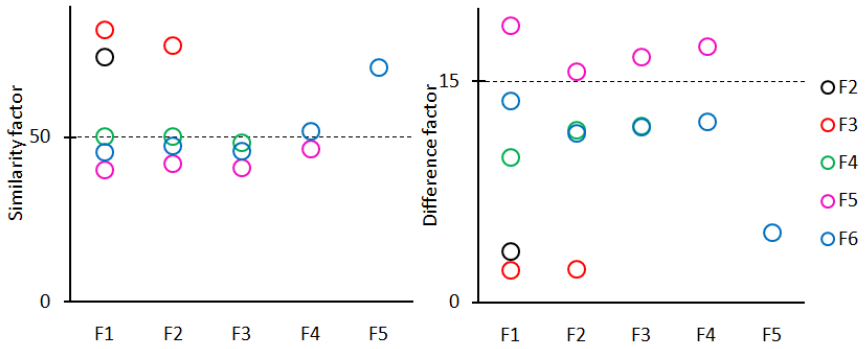

Fig. 4: Similarity and difference factor of CPM and PDN tablet

Table 4: Multiple comparisons of Q_2 and Q_5 by t-Least Significance Difference test

Comparison (I)-(J)	Q_2				Q_5			
	|I-J|	Sig.	95%CI Low	Up	|I-J|	Sig.	95%CI Low	Up
F1-F2	5.66***	0.053	-0.08	11.39	2.35	0.256	-1.79	6.50
F1-F3	1.19***	0.676	-6.92	4.55	0.39	0.848	-4.54	3.75
F1-F4	20.91**	0.000	15.17	26.64	16.63**	0.000	12.49	20.78
F1-F5	31.55**	0.000	25.82	37.28	28.07**	0.000	23.93	32.22
F1-F6	26.39**	0.000	20.65	32.12	20.96**	0.000	16.81	25.10
F2-F3	6.84*	0.021	1.10	12.58	2.75**	0.186	-1.40	6.89
F2-F4	15.25**	0.945	9.51	20.98	18.99**	0.000	14.84	23.13
F2-F5	25.89**	0.000	20.16	31.63	30.43**	0.000	26.28	34.57
F2-F6	20.73**	0.000	14.99	26.46	23.31**	0.000	19.16	27.45
F3-F4	22.09**	0.000	16.36	27.83	16.24**	0.000	12.09	20.39
F3-F5	32.74**	0.000	27.00	38.47	27.68**	0.000	23.53	31.83
F3-F6	27.57**	0.000	21.83	33.31	20.56**	0.000	16.42	24.71
F4-F5	10.64**	0.001	4.91	16.38	11.44**	0.000	7.29	15.59
F4-F6	5.47***	0.060	-0.26	11.21	4.32*	0.042	0.18	8.47
F5-F6	5.16***	0.076	-0.57	10.89	7.12**	0.001	2.97	11.26

|I-J| = |mean difference|, CI = confidence interval, sig. = significance (p-value), low = lower bound, up = upper bound. *= $p < 0.05$, **= $p < 0.01$, ***= not significant difference

CONCLUSION

The influence of MgSt, talc and combination of both on physical properties of ternary/quaternary interactive mixture of CPM as freely water-soluble drug and PDN as poorly water-soluble drug have been studied. The outcome of this study provides mechanistic reason the effect of difference lubricant and combination of both using drug with difference solubility (freely and poorly water-soluble drug). MgSt was the most dominant factor affected on the reduction the compactibility, prolong the disintegration time and retardation the drug release. Talc provided more preferable than MgSt and combination both of lubricant showed desirable physical properties of tablet. MgSt, talc and combination of both provided no significant effect on CPM as freely water soluble drug, and significant effect was found on PDN as poorly water-soluble drug.

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CONFLICT OF INTERESTS

Declared None

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