Design and Assessment of Chlorpheniramine Maleate Sublingual Tablets Using Novel Ternary Phase Superdisintegrants

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Abstract: Sublingual tablets are gaining popularity over conventional tablets due to their convenience in administration and suitability for elderly and children who have swallowing difficulties. The aim of this study was to formulate Chlorpheniramine Maleate (CPM) sublingual tablets to achieve rapid onset of action. CPM is a first generation antihistamines, undergoes first pass metabolism in liver. Sublingual dosage forms bypass the metabolism of CPM in liver and so improve the drug bioavailability. The novel ternary phase developed by co-processed superdisintegrants via solvent evaporation method using crospovidone, croscarmellose and sodium starch glycolate in different ratios (1:1:1, 3:1:1, 1:3:1and 1:1:3) were prepared. The pre-compression parameters (angle of repose, Hausner ratio and Carr's index) of the prepared co-processed superdisintegrants were evaluated in comparison to physical mixture of superdisintegrants. The developed co-processed formulae were compared with those the corresponding physical mixtures and individual superdisintegrant sublingual tablets. The tablets were evaluated for its disintegration time, wetting time, *in-vitro* dispersion time as well as hardness, weight variation, friability, drug content and *in-vitro* dissolution study. Among all the designed formulations, the formulations CP1 and PM1 containing 4% w/w co-processed and physical mixture of superdisintegrant respectively (1:1:1 mixture of crospovidone, croscarmellose and sodium starch glycolate) were considered to be best formulations, which showed the shortest disintegration time (6.29 and 6.31 sec), *in-vitro* dispersion time (18.67 and 18.83 sec) and wetting time (12.47 and 12.58 sec) respectively. As well as these promising formulae showed highest drug release (100 and 97.52 %) within two min. Finally, the promising formulae were compared with CPM sublingual tablet prepared using commercially available co-processed mixture of excipients containing superdisintegrant (Pharmaburst^{TM}500). There were significance differences in disintegration time, *in-vitro* dispersion time, wetting time and *in vitro* drug release (p<0.001) using ANOVA-one way test.
[Asmaa M. Elbakry, Ghada H. Elosaily, Ghada E. Yassin and Alaa A. Zaky. **Design and Assessment of Chlorpheniramine Maleate Sublingual Tablets Using Novel Ternary Phase Superdisintegrants.** *J Am Sci* 2014;10(5):125-134]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 17

Keywords: Chlorpheniramine Maleate, co-processed superdisintegrants, sublingual tablets, crospovidone, croscarmellose, sodium starch glycolate and Pharmaburst^{TM}500.

1. Introduction

Although oral route of drug administration is considered to be the most effective and acceptable form due to its better therapeutic efficacy, many patients particularly children and the elderly population find it inconvenient to ingest conventional solid dosage forms due to an impaired ability to swallow. This leads to patient noncompliance and potentially prolonged duration of treatment [(1-3)]. To overcome this weakness, the sublingual tablets that dissolve in the saliva and are swallowed without water have been developed [(4)]. Besides improving the acceptability and compliance of patients, sublingual mucosa and the abundance of blood supply at the sublingual region allow excellent drug penetration to achieve high plasma drug concentration with rapid action. In addition,first pass metabolism can be overcome by fast dissolving sublingual drug delivery systems and quick drug delivery into the systemic circulation can be obtained. Also the drug can be directly absorbed into the systemic circulation by passing the enzyme degradation in the gastro intestinal tract and liver [(5-7)].

Chlorpheniramine maleate (CPM) is a first generation alkylamine H_1receptor antagonist used to prevent the symptoms of allergic condition such as rhinitis and urticaria. CPM is slowly absorbed from the GIT with peak plasma concentration occurring about 2.5-6 hours after oral administration. About 70% of CPM is bound to plasma protein [(8)].

In recent years drug formulation scientists have recognized that single excipient do not always provide the requisite performance to allow certain active drug to be manufactured adequately [(9)]. Therefore, the excipients with multiple characteristics built into them to improve the flowability, superior compressibility

and rapid disintegration ability was developed [10]. One such approach for improving the functionality of excipients is co-processing of two or more excipients. Co-processing excipients could lead to formation of excipients with superior properties compared with physical mixtures of components or with individual components [11, 12].A large number of co-processed diluents are commercially available as Ludipress (Lactose monohydrate, polyvinylpyrrolidone and crospovidone), Ran Explo-C (Microcrystalline cellulose, silica and crospovidone), Ran Explo-S (Microcrystalline cellulose, silica and sodium starch glycolate), Starcap1500 (corn starch and pregelatinized starch) and pharmaburst™500 (co-processed sugar alcohol with crospovidone) [13]. The widely used superdisintegrants are crospovidone, croscarmellose sodium and sodium starch glycolate. In particular, crospovidone has better compressibility with high capillary activity. Sodium starch glycolate was chosen because of its high swelling capacity. While, croscarmellose sodium worked via wicking and swelling mechanism [14-16]. Therefore, a blend of swelling and wicking types of superdisintegrant may prove to be effective because the medium required for swelling will be brought into the tablet more easily if a wicking type of superdisintegrant is also present [17].

The concept of formulating sublingual tablets of CPM using ternary phase co-processed superdisintegrants to improve the water uptake with shortest wetting time and thereby decrease the disintegration and dissolution time.

The aim of the study was to clarify the comparison between ternary phase co-processed and physical mixture of superdisintegrants in different ratios. On the other hand, the work was further extended to compare between the best formulae prepared via ternary phase co-processed and physical mixture with pharmaburst (commercial co-processed superdisintegrants).

2. Material and Methods

2.1. Material

Chlorpheniramine Maleate, crospovidone, croscarmellose sodium, sodium starch glycolate and avicel PH 102 were received as a gift samples from Adco, Egypt. Pharmaburst™500 was a gift sample from Sigma Company, Egypt. cellactose was a gift sample from Future Company, Egypt. Talc, magnesium stearate, mannitol and sodium saccharin were purchased from El Gomhouria Co.

2.2. Methods

2.2.1. Preparation of Physical mixture and Co-processed superdisintegrants

The physical mixture of crospovidone, croscarmellose and sodium starch glycolate was prepared by mixing them together in glass pestle mortar. The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of crospovidone, croscarmellose and sodium starch glycolate (in the ratio of 1:1:1, 3:1:1, 1:3:1& 1:1:3) was added to 30 ml of isopropyl alcohol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirred on a magnetic stirrer. The temperature was maintained between 65ºC and 70ºC. The stirring was continued till most of isopropyl alcohol evaporated. The wet coherent mass was granulated through # 44-mesh sieve. The wet granules were dried in a hot air oven at 60ºC for 20 minutes. The dried granules were sifted through # 44-mesh sieve and stored in airtight container till further use [18].

2.2.2. Preparation of sublingual tablets by direct compression method

Sublingual tablets of CPM were prepared by direct compression. Compositions of various formulations are shown in Table 1. All the ingredients (except granular directly compressible excipients) were passed through # 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 100mg using 8mm round flat punches using single punch Erweka tablet compression machine. The total weight of the formulation was maintained 100mg.

2.2.3. Pre-compression parameters

All the batches of co-processed superdisintegrants or blend were evaluated for various parameters like angle of repose, bulk density, tapped density, Carr's compressibility index and Hausner ratio and results reported in Table 2

2.2.3.1. Angle of repose (θ)

Angle of repose was determined using fixed funnel method. The co-processed superdisintegrants or blend was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed [19].

$\theta = \tan^{-1} (h / r)$

Where, θ is the angle of repose. h is the height of the pile and r is the of the base pile

2.2.3.2. Bulk Density

Apparent bulk density was determined by pouring co-processed superdisintegrants or blend into a graduated cylinder. The bulk volume and the weight of the powder were determined. The bulk density was calculated using the formula [19, 20].

$$\rho b = M/Vb$$

Where, ρb is the bulk density, Vb and M are the bulk volume and weight of the powder respectively.

2.2.3.3. Tapped Density

The measuring cylinder containing known mass of co-processed superdisintegrants or blend was tapped for a fixed time. The minimum volume (Vt)

occupied in the cylinder and weight (M) of the co-processed or blend was measured. The tapped density (ρt) was calculated using the formula [19].

$$\rho t = M/Vt$$

2.2.3.4. Carr's index

It indicates powder flow properties. It is expressed in percentage and is given by

$$I = \frac{\rho t - \rho b}{\rho t} \times 100$$

Where, ρt is the tapped density of the powder and ρb is the bulk density of the powder.

2.2.3.5. Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula [19].

$$hausner\ ratio = {}^{\rho t}/_{\rho b}$$

Where, ρt is the tapped density. ρb is the bulk density. Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

2.2.4. Evaluation of tablets

All the tablets were evaluated for different parameters as hardness, friability, weight variation, disintegration time, wetting time, water absorption ratio, drug content uniformity and *in-vitro* drug release study.

2.2.4.1. Weight variation

Weight variation test was performed for twenty tablets from each batch using electric balance and average values were calculated [21].

2.2.4.2. Thickness

The thickness of three randomly selected tablets from each formulation was determined in mm using micrometer screw gauge. The average values were calculated

2.2.4.3. Hardness

Tablet hardness was measured by Pharma Test PTB 311 hardness tester. A tablet was placed in the hardness tester and load required to crush the tablet was measured. It was expressed in Kg/Cm^2 [22].

2.2.4.4. Friability

Friability is a crucial parameter for evaluation of sublingual tablets. Pharma Test friabilator is used to determine the friability by following procedure. Pre-weighed tablets were placed in a plastic chamber friabilator that revolves at 25 rpm. The tablets were rotated in the friabilator for 4 minutes. At the end of test tablets were dusted and reweighed; the loss in the weight of tablet was the measure of friability and was expressed in percentage as [23]:

% Friability=Loss in weight/Initial weight×100

2.2.4.5. Drug content uniformity

For the content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 4 mg of CPM was weighed and dissolved in suitable quantity of phosphate buffer PH 6.8, and the solution was filtered. The CPM content was determined by measuring the absorbance at 261 nm (using UV-vis Spectrophotometer, Shimadzu 1700) after appropriate dilution with phosphate buffer. The drug content was determined using standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

2.2.4.6. Wetting time

The initial process in the disintegration of a sublingual tablets involves water uptake and wetting of the tablet. So determination of wetting time is also important. A Petri-dish containing 6 ml of distilled water was taken and a tissue paper folded twice was placed in it. A tablet was carefully placed on the surface of the tissue paper in the petri dish. Time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time [24, 25].

2.2.4.7. Water absorption ratio

A pre weighed tablet (W_a) was placed in a Petri dish in the similar way as described in the wetting time test. After the tablet was absorbed water completely. It was removed and weight was noted (W_b). Water absorption ratio R is calculated as [24,25]:

$R = (W_a - W_b) / W_b \times 100$

2.2.4.8. *In-vitro* Dispersion Time

Tablet was placed in a beaker containing 10ml of buffer solution (pH 6.8) and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed [26].

2.2.4.9. Disintegration Time (DT)

Disintegration times of the prepared sublingual tablets were determined with six tablets in distilled water at 37 ± 0.5°C using a disintegration tester (Copley DTG 1000). The time in seconds taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was determined. All results are presented as mean value ± SD ($n = 6$) [26].

2.2.5. *In-vitro* drug release study

In-vitro release rate of CPM sublingual tablets was carried out using USP dissolution testing apparatus (Paddle method) (Hanson SR8-plus80, USA). The dissolution test was carried out using 500 ml of phosphate buffer PH 6.8, at 37 ± 20ºC and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 2, 4, 6, 8, 10and 15min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered and analyzed by UV spectrophotometer at 261nm. The percentage drug release was calculated using an equation obtained from the calibration curve.

2.2.6. Kinetic modeling of drug release

The release kinetics of CPM from prepared sublingual tablets was evaluated by employing the

Korsmeyer peppa's equation[27]: $M_t/ M_\infty = k\ t^n$, where M_t is the amount of the drug released at time t, M_∞ is the amount of the drug released after infinite time, k is the kinetic constant incorporating structural and geometric characteristics of the tablet and n is the diffusional exponent indicative of the mechanism of drug release. When n is ≤ 0.5, the drug is released from the polymer with a Fickian diffusion mechanism. If 0.5 < n < 1 this indicates anomalous or non-Fickian release. While if n= 1 this indicates Case II transport. Lastly, when n is > 1.0, Super Case II transport is apparent. Kinetic studies were performed by adjusting the release profiles to Higuchi, First and Zero order equations.

2.2.7. Statistical analysis for the obtained results

Statistical analysis for the obtained results was carried out by using ANOVA test followed by the Tukey-Kramer multiple comparisons test to determine if the differences between the results of the investigated samples are significant or not.

3. Results and Discussion

3.1. Preparation of CPM sublingual tablets

The formulations and composition of new ternary phase of co-processed superdisintegrants, as well as the physical mixture, individual superdisintegrants, Pharmaburst and drug without superdisintegrant were presented in Table 1.

Table 1: Formulations composition of CPM sublingual tablets prepared by direct compression method

Ingredients (mg/tab)	Formulation code												
	F_0	F_1	F_2	F_3	F_{PM1}	F_{PM2}	F_{PM3}	F_{PM4}	F_{CP1}	F_{CP2}	F_{CP3}	F_{CP4}	F_{Ph}
CPM	4	4	4	4	4	4	4	4	4	4	4	4	4
Superdisintegrants	-	-	-	-	4	4	4	4	4	4	4	4	-
Crospovidone	-	4	-	-	-	-	-	-	-	-	-	-	-
Croscarmellose	-	-	4	-	-	-	-	-	-	-	-	-	-
SSG	-	-	-	4	-	-	-	-	-	-	-	-	-
Pharmabrust	-	-	-	-	-	-	-	-	-	-	-	-	14
Mannitol	10	10	10	10	10	10	10	10	10	10	10	10	-
Cellactose	20	20	20	20	20	20	20	20	20	20	20	20	20
Avicel PH 102	61.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5
Sodium saccharin	1	1	1	1	1	1	1	1	1	1	1	1	1
Mg. Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	100	100	100	100	100

PM-Physical Mixture of crospovidone, croscarmellose and sodium starch glycolate in different ratios (1:1:1, 3:1:1, 1:3:1, 1:1:3).

CP- Co-processed Superdisintegrants of crospovidone, croscarmellose and sodium starch glycolate in different ratios (1:1:1, 3:1:1, 1:3:1, 1:1:3). F_0- Control formulation (without superdisintegrants). F_{Ph}- formulation containing pharmaburst, and SSG- Sodium starch glycolate

3.2. Pre-compression parameters

Co-processed superdisintegrants were prepared by solvent evaporation technique using crospovidone, croscarmellose and sodium starch glycolate in the ratios of 1:1:1, 3:1:1, 1:3:1& 1:1:3. The co-processed superdisintegrants were evaluated for their flow and compression properties in comparison with physical mixture. The angle of repose of co-processed and physical mixture of superdisintegrants was found within (22.64 –25.28º), which indicate excellent flow in comparison to the individual superdisintegrants. The angle of repose of crospovidone, croscarmellose and sodium starch glycolate was 43.02º, 40.28º and 33.18º, respectively. Carr's index was in the range of 14.35-16.28%, and Hausner's ratio was in the range of 1.10-1.17. So the prepared ternary phase of co-processed and physical mixture superdisintegrants possessed good flow properties (table2).

Table 2: Pre-compression parameters of CPM powder, pharmaburst, crospovidone, croscarmellose sodium, sodium starch glycolate, co-processed superdisintegrants and physical mixture of superdisintegrants

Code	Angle of repose (degree)	Carr's index %	Hausner ratio
CPM powder	45.86±2.60	35.53±1.21	1.95±0.14
Pharmaburst	27.54±0.10	16.20±1.73	1.16±0.08
Crospovidone	43.02±0.13	33.04±1.52	1.49±0.03
Croscarmellose	40.28±0.19	27.95±1.36	1.32±0.08
SSG	33.18±0.17	20.03±0.23	1.25±0.04
PM_1	24.38±0.12	16.28±0.92	1.13±0.01
PM_2	24.54±0.10	14.92±1.49	1.14±0.02
PM_3	22.64±0.09	15.63±0.42	1.16±0.01
PM_4	25.28±0.29	14.35±0.50	1.15±0.01
CP_1	24.00±0.16	15.98±0.71	1.10±0.01
CP_2	22.07±0.19	15.42±1.57	1.14±0.02
CP_3	24.09±0.16	14.74±0.50	1.13±0.01
CP_4	25.21±0.12	15.50±0.30	1.17±0.00

CP- Co-processed Superdisintegrants of crospovidone, croscarmellose and sodium starch glycolate in different ratios (1:1:1, 3:1:1, 1:3:1, 1:1:3).

PM-Physical Mixture of crospovidone, croscarmellose and sodium starch glycolate in different ratios (1:1:1, 3:1:1, 1:3:1, 1:1:3).

3.3. Evaluation of tablets

Sublingual tablets of CPM containing individual superdisintegrant, pharmaburst (commercially available co-processed mixture of excipients containing superdisintegrant), co-processed and the physical mixture of superdisintegrants and control formulation (F_0) were prepared as shown in Table1. All the tablets were evaluated for different parameters as hardness, friability, weight variation, disintegration time, wetting time, water absorption ratio, drug content and *in-vitro* release study. All the tablets maintained hardness in the range 3.05-3.45 Kg. The loss in the total weight of the tablets due to friability varied from 0.41% to 0.72% which is an indication of good mechanical resistance of the tablets. Thickness of the tablets ranged from 2.05-2.89 mm. The drug content of the different formulations was within the acceptable limits (98.67-100.13%). The weight variation of the tablets was within the range. The result of the *in-vitro* dispersion time for the formulations that contain the co-processed, the physical mixture of superdisintegrants and F_2 (contain crospovidone only) were in the range of 18.57-28.67 sec. That was promising and facilitating faster dispersion in the mouth when compared to the control formula (F_0, 119.33 sec.). On the other hand, F_2 and F_3 showed longer in-vitro dispersion time of 55.33 and 51.00 sec., respectively (Table 3).

Table 3: Post formulation characteristics of CPM sublingual tablets

Formulation Code	Thickness (mm)	Hardness (Kg)	Friability (%)	Weight variation (mg)	In-vitro dispersion time (sec)	Drug content (%)
F_0	2.89±0.06	3.09±0.18	0.72±0.02	100.23±1.28	119.33±3.30	99.27±0.49
F_1	2.13±0.06	3.26±0.14	0.71±0.02	100.60±0.47	26.33±6.85	98.67±0.50
F_2	2.26±0.02	3.12±0.05	0.71±0.06	103.30±0.24	55.33±2.49	99.13±0.17
F_3	2.14±0.03	3.31±0.21	0.72±0.04	100.53±0.66	51.00±5.35	98.97±0.25
F_{PM1}	2.24±0.02	3.11±0.09	0.53±0.04	100.33±0.47	18.83±1.18	100.10±0.94
F_{PM2}	2.28±0.07	3.25±0.25	0.52±0.04	102.33±0.47	18.57±2.49	98.83±0.21
F_{PM3}	2.06±0.04	3.42±0.33	0.56±0.02	99.33±0.940	28.67±2.87	99.00±0.29
F_{PM4}	2.24±0.01	3.05±0.24	0.58±0.02	102.67±0.94	25.83±1.65	99.47±0.61
F_{CP1}	2.05±0.02	3.12±0.17	0.41±0.01	101.17±0.62	18.67±1.70	100.13±0.29
F_{CP2}	2.14±0.05	3.39±0.30	0.46±0.01	100.33±0.94	19.17±1.84	99.80±1.04
F_{CP3}	2.05±0.01	3.37±0.36	0.50±0.01	101.33±0.47	20.93±1.64	99.63±0.54
F_{CP4}	2.15±0.02	3.37±0.22	0.51±0.02	100.33±1.70	21.67±2.49	99.47±0.71
F_{ph}	2.36±0.09	3.45±0.08	0.62±0.02	101.00±0.82	43.33±2.05	99.07±0.40

The water absorption ratio and the wetting time which are important criteria for understanding the capacity of disintegrates to swell in presence of little amount of water were found to be in the range of 91.60-171.02% and12.47-46.33 sec. (Figure 1A and 2A).

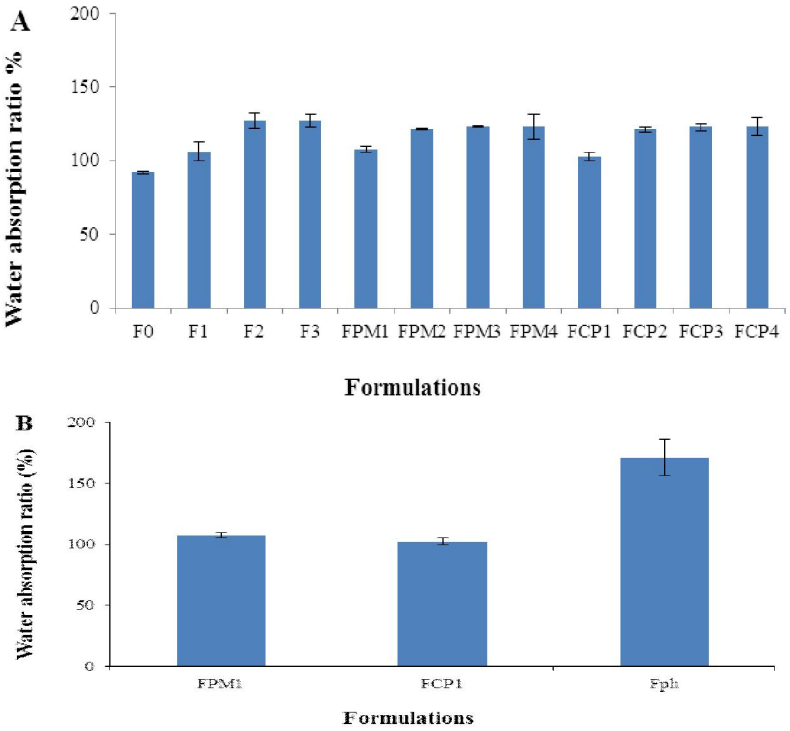

Figure 1. (A) water absorpation ratio of CPM sublingual formulations. (B) water absorpation ratio of PM1, CP1 and ph of CPM formulae

The formulations contain the co-processed superdisintegrants, the physical mixture and F_1 showed the lowest wetting time. While, the control formula F_0 showed the highest wetting time (46.33 sec). In contrast, the formula CPM-pharmabrust (F_{ph}) showed longer in vitro dispersion and wetting time (43.33 and 32.43 sec.) respectively and higher water absorption ratio 171.02% (Figure 1B and 2B).

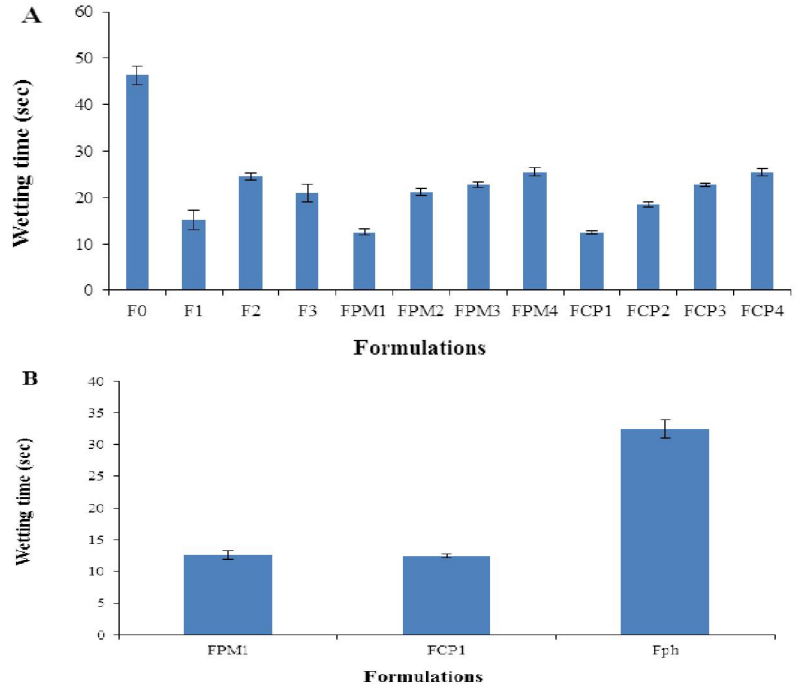

Figure 2. (A) wetting time of CPM sublingual formulations. (B) wetting time of PM1, CP1 and ph of CPM formulae

The disintegration time of CPM sublingual tablets were presented in Figure 3A and B. The control formula F_0 showed the highest disintegration time (47.62 sec). F_{CP1} and F_{PM1} (1:1:1 mixture of crospovidone, croscarmellose and sodium starch glycolate) showed the lowest disintegration time 6.33 and 6.29 sec. respectively. We notice the disintegration and the wetting time increasing in the following ascending order

$F_{CP1} < F_{CP2} < F_{CP3} < F_{CP4}$

$F_{PM1} < F_{PM2} < F_{PM3} < F_{PM4}$

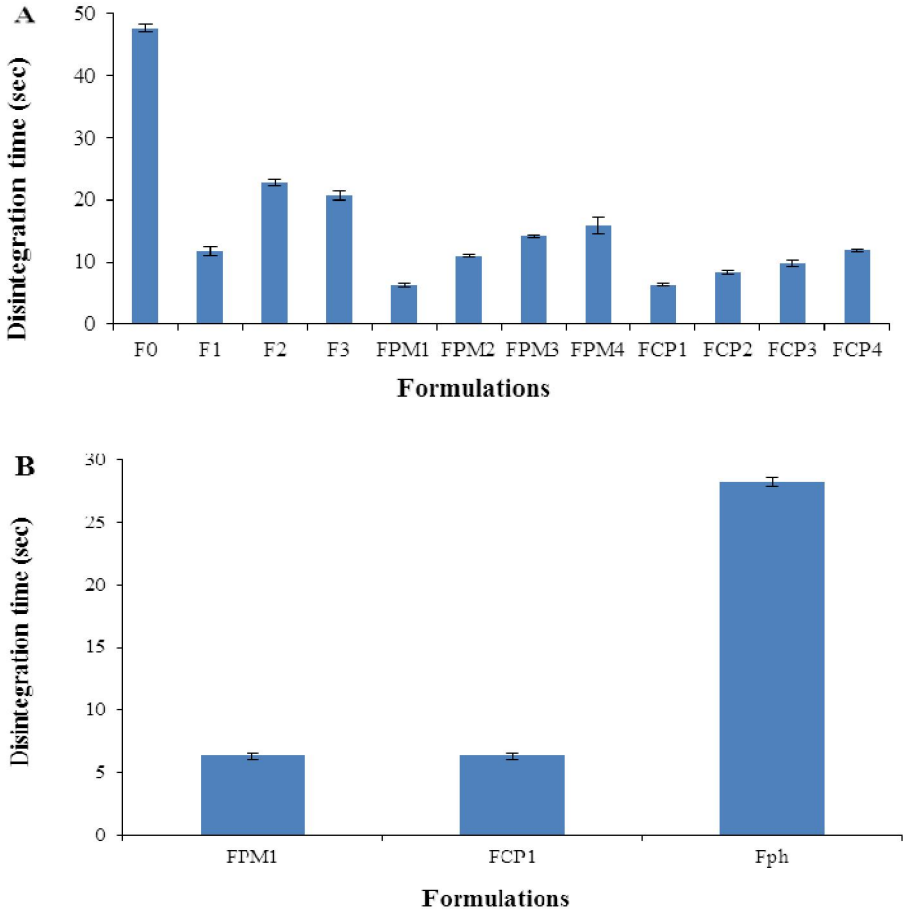

Figure 3. (A) Disintegration time of CPM sublingual formulations. (B) Disintegration time of PM1, CP1 and ph of CPM formulae

Indicating the best ratio for mixing of these superdisintegrants is 1:1:1 and this ratio showed better results than each superdisintegrant alone. This could be attributed to the advantage of the combination between different superdisintegrants having different mechanisms. In particular, sodium starch glycolate has spherical shape particle and generally spherical shaped particles more likely to absorb water and retain it rather than transfer it to the next particle (mechanism of disintegration is rapid absorption of water and swelling only [28]). In other words, the water transferring rate between particles is slower than the swelling rate of individual particle. Moreover, the crospovidone and croscarmellose play an important role to uptake a liquid and transfer it to next particle (mechanism of disintegration for both is swelling and wicking in addition to deformation for crospovidone as it is highly compressible [28]). So the combination of these ternary phase superdisintegrants is much more useful to prepare sublingual tablets [29]. Moreover, our ternary phase superdisintegrant showed lower disintegration time than F_{ph} formula which disintegrate after 28.2 sec (Figure 3B).

3.4. *In- vitro* drug release study

The cumulative percent of CPM released as a function of time from the formulations ranged between 49.8% and 100% within two minutes (Figure 4A and B). Dissolution for the control formula with no superdisintegrant (F_0) has the slowest release (49.8%).

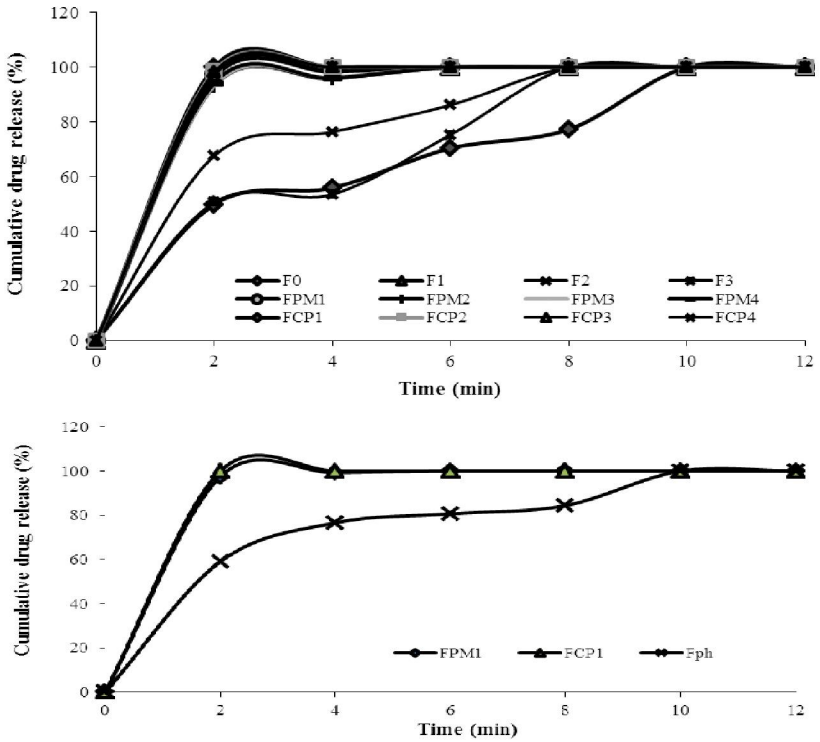

Figure 4. (A) in vitro release profiles of CPM sublingual formulations. (B) in vitro release profiles of PM1, CP1 and ph of CPM formulae

The drug dissolution from co-processed and physical mixture formulations was higher than formulations containing single superdisintegrants (F_2 and F_3). While the drug release from F_{ph} (containing pharmaburst) was 59% within two minutes. The highest release was observed from F_{CP1}formulation (100 % via two minutes). The rapid drug dissolution might be due to easy break down of particles due to the presence of ternary phase co-processed superdisintegrants[30].

3.5. Kinetic modeling of drug release

The *in-vitro* release data were fitted to Korsmeyer peppa's release model and interpretation of release exponent values (n) enlightens us in understanding the release mechanism (Table 4). The release exponent values of the formulations obtained were from 0.0011 to 0.4156. Based on these values we can say that the formulations exhibited Fickian release. These results are in agreement with a result by Mahesh *et al*[31]. All formulations showed higher (r) values drug release followed Higuchi model kinetics.

Table 4: Kinetics of in-vitro release from different formulations of CPM sublingual tablets

Code	(n) value	r	Zero-order kinetic		Higuchi model		Possible mechanism Of drug release
			r	k	r	k	
F_0	0.3902	0.9605	0.9374	4.3040	0.9537	23.3676	Higuchi model, Fickian
F_1	0.0200	0.9026	0.7338	0.2389	0.8246	1.4323	Higuchi model, Fickian
F_2	0.2228	0.9550	0.8650	2.6097	0.9205	14.8202	Higuchi model, Fickian
F_3	0.4156	0.9246	0.8611	4.3777	0.9042	24.5293	Higuchi model, Fickian
F_{PM1}	0.0126	0.8868	0.7016	0.1449	0.7967	0.8784	Higuchi model, Fickian
F_{PM2}	0.0386	0.9068	0.7588	0.4740	0.8416	2.8055	Higuchi model, Fickian
F_{PM3}	0.0373	0.9077	0.7551	0.4545	0.8399	2.6978	Higuchi model, Fickian
F_{PM4}	0.0332	0.9009	0.7633	0.4136	0.8419	2.4344	Higuchi model, Fickian
F_{CP1}	0.0011	0.7782	0.5811	0.0001	0.6805	0.0006	Higuchi model, Fickian
F_{CP2}	0.0064	0.7782	0.5811	0.0684	0.6805	0.4274	Higuchi model, Fickian
F_{CP3}	0.0082	0.7782	0.5811	0.0883	0.6805	0.5521	Higuchi model, Fickian
F_{CP4}	0.0128	0.7782	0.5811	0.1404	0.6805	0.8772	Higuchi model, Fickian
F_{ph}	0.2672	0.9715	0.9145	3.0474	0.9528	16.9431	Higuchi model, Fickian

3.6. Statistical analysis for the obtained results

Table 5 showed the statistical analysis for the obtained results using ANOVA test followed by the Tukey-Kramer multiple comparisons test. There was significance difference between F_0 (control formula) and F_{PM1}& F_{CP1}. While, there was no significance difference between F_{PM1}, $F_{CP1}$and F_1except in the in-vitro release results at two minutes. The statistical analysis showed also significance difference between F_{PM1}, $F_{CP1}$and F_2 and F_3. Moreover, there was also significance difference between F_{ph} (pharmaburst) and F_{PM1}& F_{CP1}which indicate superior efficacy of our new ternary phase superdisintegrants over commercially available pharmaburst. Both co processed and physical mixture of superdisintegrant (F_{CP1} and F_{PM1}) didn't show any significance difference except in the in-vitro release results at two minutes.

Table 5.Tukey-Kramer multiple comparisons test of different formulations of CPM sublingual tablets

Code	Significance				
	***In-vitro* dispersion time**	**Water absorption**	**Wetting time**	**Disintegration time**	***In-vitro* release**
F_0vs F_{PM1}	***	NS	***	***	***
F_0vs F_{cp1}	***	NS	***	***	***
F_1vs F_{PM1}	NS	NS	NS	***	NS
F_1 vs F_{CP1}	NS	NS	NS	***	***
F_2vs F_{PM1}	***	NS	***	***	***
F_2 vs F_{CP1}	***	*	***	***	***
F_3vs F_{PM1}	***	NS	***	***	***
F_3 vs F_{CP1}	***	**	***	***	***
F_{ph}vs F_{PM1}	***	***	***	***	***
F_{ph}vs F_{cp1}	***	***	***	***	***
F_{ph}vs F_0	***	***	***	***	***
F_{CP1}vs F_{PM1}	NS	NS	NS	NS	***

*** Significant at $p < 0.001$; ** Significant at $p < 0.01$; * Significant at $p < 0.05$; NS, not significant.

Conclusion

In the present study CPM sublingual tablets prepared with novel ternary phase superdisintegrants was successfully developed and evaluated. Among all the formulations, $F_{CP1}$and F_{PM1}containing 4% w/w of the co-processed and the physical mixture of superdisintegrants respectively (1:1:1 mixture of crospovidone, croscarmellose and sodium starch glycolate) were found to be promising compared with other formulations. They were shown an in-vitro dispersion time of 18.67 and 18.83 sec., wetting time of 12.47 and 12.58 sec., water absorption ratio of 102.54 % and 106.95 %, disintegration time of 6.33 and 6.29 sec. and *in-vitro* release 100 % and 97.52 % at two minutes respectively.Furthermore, F_{CP1} and F_{PM1} had superior flow and compression properties as well as improved disintegration and dissolution rate than commercial available co-processed superdisintegrant pharmaburst (F_{ph}). The advantages of our new ternary phase superdisintegrants are easy adaptability, economically in industry and the possibility of bypassing the existing patents in the areas of quick disintegration and dissolution. Whereas, there was no significance difference between $F_{CP1}$and F_{PM1} so in the industrial scale the physical mixture will be more applicable, time saving and economic than the co-processing.

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4/11/2014