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Research Article

Effects of superdisintegrants on formulation of mouth dissolving dexamethsone tablets

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ABSTRACT

Dysphagia is the main drawback of conventional dosage forms such as tablets. This has lead to treatment failure and high rate of incompliance. Mouth dissolving tablet dosage forms are developed to overcome dysphagia. This study aims to develop mouth dissolving dexamethasone tablets which are able to disintegrate and dissolve rapidly in saliva without the need of water. MDTs of dexamethasone were prepared by using natural and synthetic superdisintegrants at different concentration. Direct compression technique was used to develop the tablets. The prepared tablets were evaluated with various physiochemical parameters like thickness, hardness, friability, weight variation, wetting time, water absorption ratio, disintegration time, *in vitro* dispersion time and *in vitro* dissolution. Drug release kinetics was also studied.The prepared mouth dissolving dexamethasone tablets were found to be better in term of more rapid drug release as compared to current marketed dexamethasone tablets. Drug is releasing from tablets following first order kinetics and Fickian diffusion. Mouth dissolving tablets of dexamethasone was able to disintegrate rapidly in saliva and achieved rapid and complete drug release.

Keywords: Croscarmellose sodium; Guar gum; Dexamethasone; Mouth dissolving tablets; Superdisintegrants.

INTRODUCTION

Difficulty swallowing or dysphagia is the most common complain of different age groups, which lead to low patient compliance and thus ineffective treatment outcome. In order to overcome dysphagia and improve patient compliance (Ciorabai EM *et al*., 2008), mouth dissolving formulations are developed (Goel H *et al*., 2008). This type of delivery system is ideal for drugs that have high first pass metabolism. Besides that, mouth-dissolving tablet is also suitable for patients with variety of medical conditions such as stroke, Parkinson's disease and other neurological disorders (Mangal M *et al*., 2012). Dexamethasone is a synthetic corticosteroid that is widely used to reduce inflammation. In perioperative setting, dexamethasone is frequently utilized to prevent postoperative-induced nausea and vomiting (PONV), reduce airway and cerebral edema (Ramakrishna S *et al*., 2011). It is also used in management of acute and chronic pain. A comparative study showed that dexamethasone is more effective at preventing PONV compared to ondansetron. The use of dexamethasone is also shown to be more cost effective (Rowe R *et al*., 2012). This study aimed to prepare dexamethasone mouth dissolving tablets with different concentration of croscarmellose sodium (synthetic) and guar gum (natural).

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MATERIALS

Dexamethasone, Croscarmellose sodium and guar gum were purchased from Sigma-Aldrich Malaysia. Other excipients such as mannitol, sucralose, starch, vanillin and magnesium stearate used and all other reagents used were of analytical grade.

METHODS

Preparation of mouth dissolving tablets of dexamethasone by direct compression method (Pawar H *et al*., 2014)

Mouth dissolving dexamethasone tablets were prepared by direct compression method. The formula for preparing the tablets is shown in Table 1. All the raw materials were accurately weighed and individually passed through 60# mesh screen prior to mixing. The ingredients were mixed in geometrical order using a mortar and pestle. Finally, the powder mixture was compressed into 150mg tablets by using manual 7mm

Table 1: List of ingredients used in formulation of mouth dissolving dexamethasone tablets

Ingredients (mg)	Formulation code					
	CS1	CS2	CS3	GG1	GG2	GG3
Dexamethasone	0.75	0.75	0.75	0.75	0.75	0.75
Croscarmellose sodium	1.5	3.0	4.5	-	-	-
Guar gum	-	-	-	1.5	3.0	4.5
Mannitol	128.25	126.75	125.25	128.25	126.75	125.25
Sucralose	3.0	3.0	3.0	3.0	3.0	3.0
Starch	12.5	12.5	12.5	12.5	12.5	12.5
Magnesium stearate	3.0	3.0	3.0	3.0	3.0	3.0
Vanillin	1.0	1.0	1.0	1.0	1.0	1.0
Total weight	150	150	150	150	150	150

Table 2: Physiochemical evaluation parameters of dexamethasone MDTs

Evaluation parameters	Formulation code					
	CS1	CS2	CS3	GG1	GG2	GG3
Thickness (mm)	2.69±0.08	2.64±0.01	2.75±0.04	2.67±0.06	2.72±0.04	2.72±0.02
Hardness (kg/cm2)	2.53±0.06	2.67±0.12	3.00±0.10	2.93±0.23	2.70±0.17	2.60±0.10
Friability (%)	0.75	0.63	0.85	0.98	0.73	0.91
Weight Variation (mg)	143.8±1.5	143.7±2.0	146.5±5.0	147.9±2.2	146.7±3.2	148.6±1.5
Water absorption ratio (%)	28.8	38.42	50	70.7	83.34	93.81
Wetting time (seconds)	52±10	43±7	26±8	47±9	45±7	53±6
Disintegration time (seconds)	55±4	47±4	36±5	39±8	44±5	38±5
In vitro dispersion time (seconds)	59±4	46±6	46±12	56±9	53±9	34±4

For all parameters, n=3; *n=10; $^{+}$n=2

Table 3: Determination coefficient and kinetic constant, diffusional exponent for Korsemeyer-Peppas model

Formulation	Determination Coefficient, r^2				Kinetic Constant, k	Diffusional Exponent, n	Order of Release
	Zero order	First order	Higuchi Model	Korsemeyer-Peppas Model			
CS1	-0.923	0.923	0.493	0.918	0.604	0.136	Fickian Diffusion
CS2	-1.068	0.962	0.419	0.919	0.660	0.111	Fickian Diffusion
CS3	-0.674	0.901	0.610	0.981	0.517	0.168	Fickian Diffusion
GG1	-0.964	0.955	0.474	0.942	0.631	0.128	Fickian Diffusion
GG2	-1.000	0.945	0.454	0.868	0.649	0.127	Fickian Diffusion
GG3	-1.202	0.920	0.342	0.910	0.742	0.084	Fickian Diffusion

single-punch tablet compression machine. The composition of MDT is shown in table 1.

Compatibility studies

Compatibility between drug and superdisintegrant was studies by Fourier Transform Infrared Spectrophotometer (FTIR) and differential scanning calorimeter (DSC). The results are shown in fig 1-6.

Physiochemical evaluation of mouth dissolving tablets of dexamethasone

Tablets were randomly selected from each formulation and subjected to post compression parameters as per US pharmacopoeia (Pabari R *et al.*, 2012). The results are shown in table 2.

Wetting time and water absorption ratio (Jeevanandham S *et al.*, 2010)

A piece of tissue paper folded twice was placed in small Petri-dish containing 9mL of water. A pre-weighed tablet was placed on the tissue paper. Wetting time was recorded when tablet was completely wetted by water. The wetted tablet was re-weighed and the water absorption ratio was determined by following equation.

R (%) = [(Weight after wetting-Weight before wetting)/Weight before wetting] x 100

The results are shown in table 2 and fig 7.

***In vitro* dispersion time**

A tablet was placed in a petri dish containing 9mL of phosphate buffer pH6.8 (mimic saliva pH). The time for complete tablet disintegration was recorded. The results are shown in table 2.

***In vitro* drug release studies** (Jeevanandham S *et al*., 2010)

USP type-II dissolution apparatus (paddle type) at 50rpm was used to study dissolution profile of prepared MDTs. 900mL of phosphate buffer pH 6.8 was used as dissolution medium. Temperature for dissolution medium was maintained at 37±0.5ºC. 5mL aliquots of dissolution medium were withdrawn at specific time interval (5, 10, 15, 20, 25, 30, 45, 60 minutes) and the withdrawn volume was replaced with similar amount of fresh dissolution medium. The collected samples were filtered and analysed by UV-Visible spectrophotometer at 239nm. The concentration of the drug was determined from standard calibration curve. Procedures were repeated for marketed dexamethasone tablets by using 500mL 0.01M HCl as dissolution medium. The results are shown in fig 8.

Drug Release Kinetics

Kinetic models were used to describe the release kinetics of the drug. Determination coefficient for each model was determined. Kinetic constant, diffusional exponent of Korsemeyer Peppas were calculated from the plot. Determination coefficients of different drug release kinetics are shown in table 3.

DISCUSSION

Based on the infrared spectra obtained it is concluded that there is no drug polymer interaction between dexamethasone and superdisintegrants used. This is because the combination spectra retained the same characteristic peaks of pure dexamethasone as well as for croscarmelloase sodium (CCS) and guar gum.

When individual thermogram of dexamethasone and superdisintegrants were compared to the combination thermogram, no significant change in melting point is observed. Thus, dexamethasone, CCS and guar gum are compatible to each other fig 1-6.

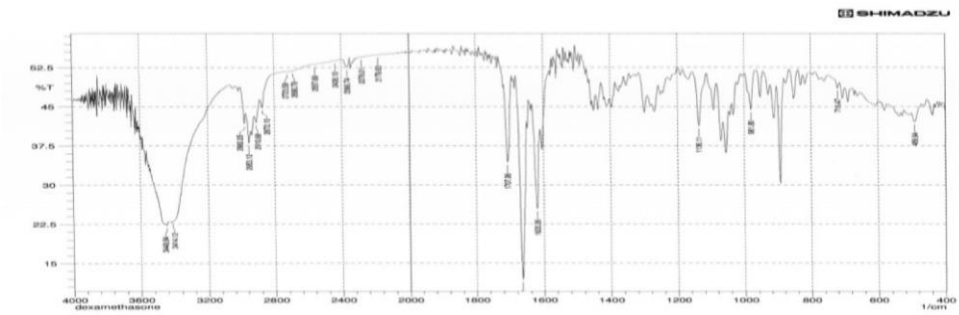

Figure 1: FTIR spectrum of pure dexamethasone

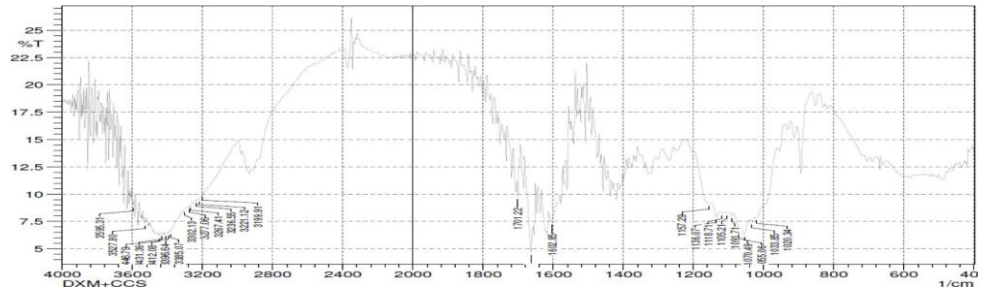

Figure 2: FTIR spectrum for combination of dexamethasone and croscarmellose sodium

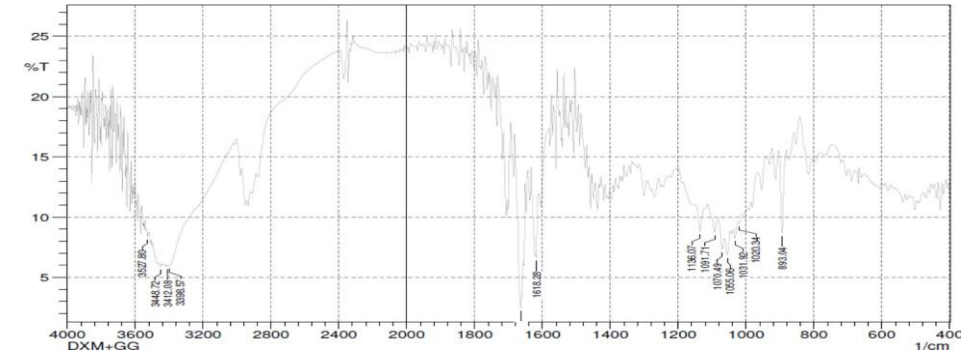

Figure 3: FTIR spectrum for combination of dexamethasone and guar gum

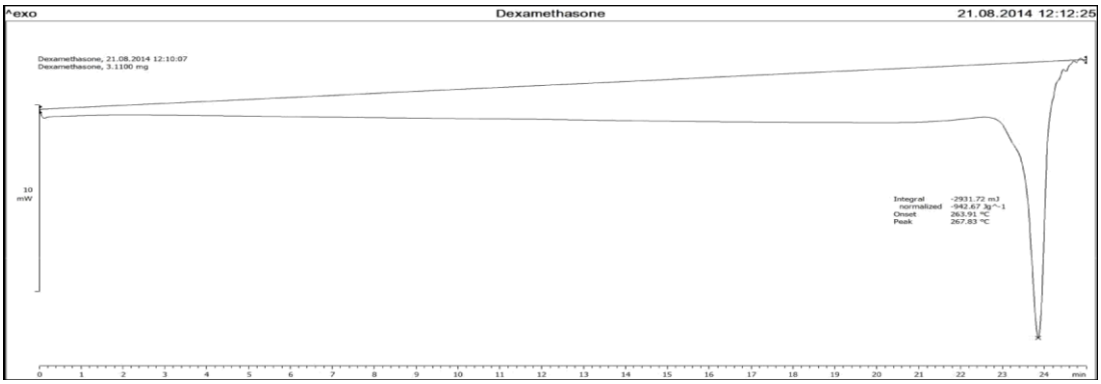

Figure 4: DSC thermogram of pure Dexamethasone showed sharp peak

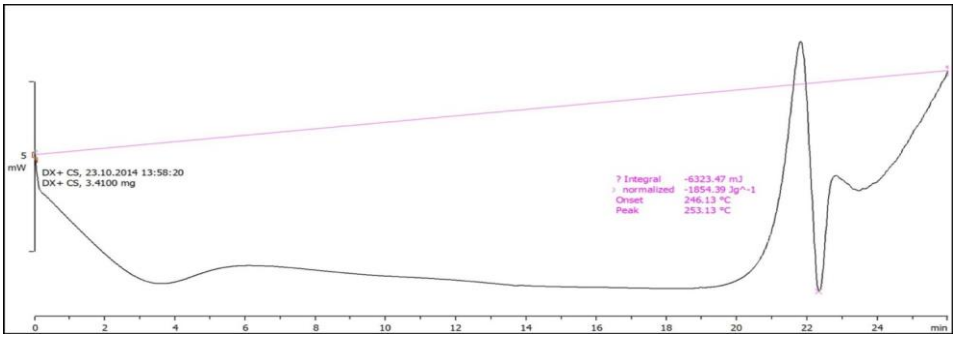

Figure 5: DSC thermogram of dexamethasone with at croscarmellose sodium

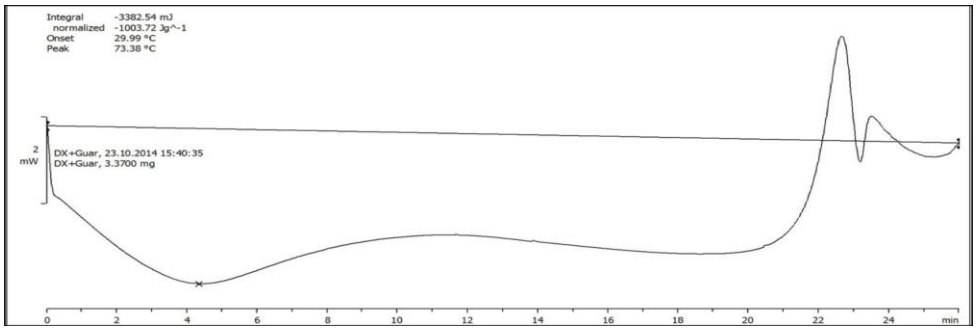

Figure 6: DSC thermogram of Dexamethasone (253.13°C) with guar gum (73.38°C)

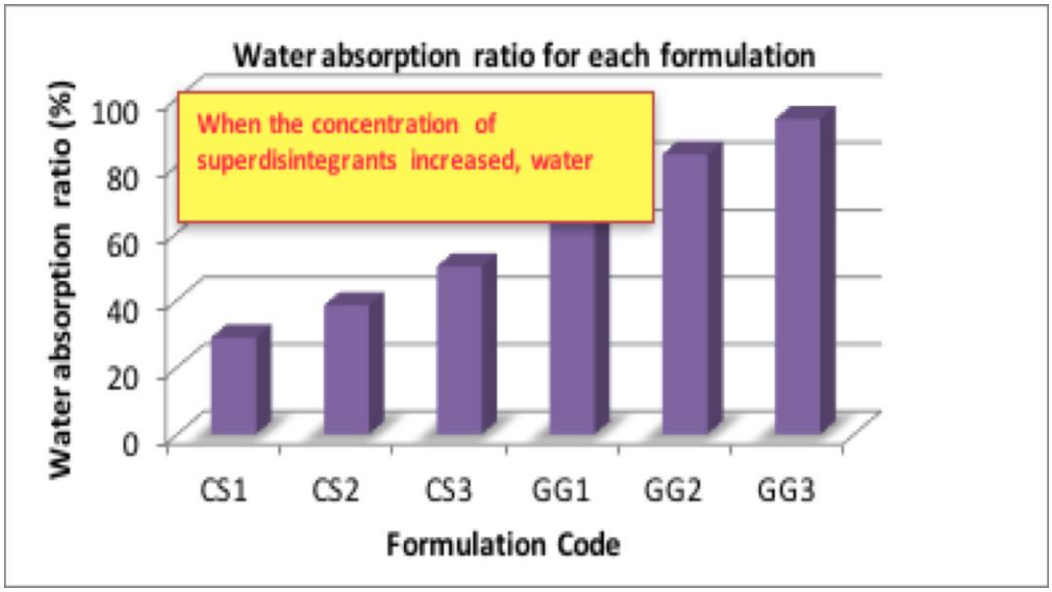

Figure 7: Water absorption ratio for MDT containing croscarmellose sodium and guar gum at different concentration (1%, 2%, 3% w/w)

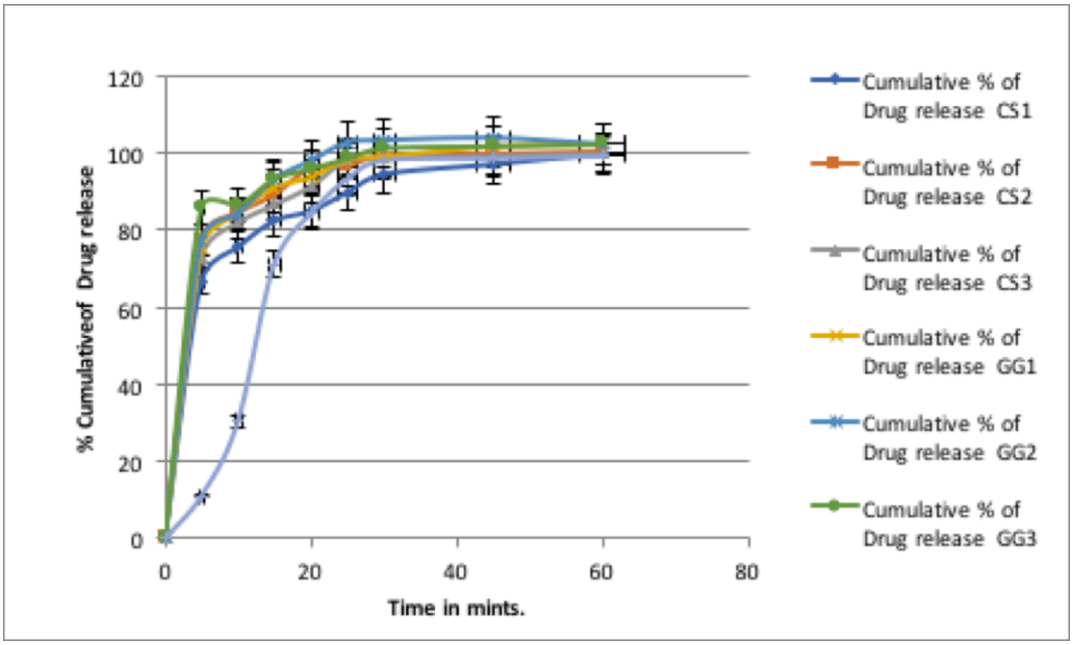

Figure 8: Graph of percentage drug release for MDT containing

All compressed tablets appeared white, odourless and round shaped with smooth surface. The results for post-compression parameters are shown in table 2. The hardness of dexamethasone MDTs was adjusted to 2.5-3.0kg/cm^2.

The batches CS1, CS2 and CS3 were prepared using CCS at different concentration of 1%-3% w/w to study its effect on disintegration time of dexamethasone MDTs. Based on the *in vitro* disintegration time and dispersion time shown in table 2, all formulations have disintegration time, *in vitro* dispersion time of less than 60 seconds. It is observed that, the disintegration time of tablets was reduced with successive increase in concentration of superdisintegrants. This suggested that disintegration time is concentration-dependent. The main reason for quick disintegration is the porous tablet structure. Porosity of the tablet enables the saliva to penetrate through the tablet easily (Pabari R *et al*., 2012) and facilitates the wicking of CCS through capillary action (Mangal M *et al*., 2012). Wicking breaks the inter-particulate bonds causing tablet to disintegrate. In case of guar gum, penetration of saliva into tablet's pore leads to swelling of guar gum that creates a sufficient hydrodynamic pressure for rapid and complete disintegration of tablets (Pabari R *et al*., 2012).

According to the literature, wetting time indicates the ease of tablets to disintegrate in buccal cavity. It is observed that all formulations have a wetting time of less than 60 seconds. CS3 has the lowest wetting time compared to CS1 and CS2. This indicated that the porosity of CS3 is greater than CS1 and CS2. Based on the overall wetting time (Table 3), guar gum is found to be less porous compared to croscarmellose sodium because formulations containing guar gum has longer wetting time.

In vitro dissolution studies were carried out for all formulations. All mouth dissolving dexamethasone tablets produced showed good drug release in relative short time. More than 50% of the drug is released from formulation in less than 5 minutes. Complete drug release is achieved at 25-30 minutes. Mouth dissolving dexamethasone tablets are not available in the market. Therefore, the prepared tablets were compared to the marketed tablet of equivalent strength (0.75mg). Drug release profile of marketed dexamethasone tablets was determined and compared with the best formulation CS2 and GG3. CS2 and GG3 showed more than 85% drug release within 15 minutes, whereas marketed product only showed about 71.25% of drug release at 15 minutes. Comparative dissolution profile of formulation CS2, GG3 with marketed product is shown in figure 8. Due to fast tablet disintegration, drug release is increased, which contribute to a more rapid onset of action.

Based on the deterministic coefficient value obtained in table 3, all formulations were found to be following first order release kinetic and Fickian diffusion. Thus, the release of dexamethasone from tablet is a concentration-dependent process.

CONCLUSIONS

In conclusion, mouth dissolving dexamethasone tablets can be successfully formulated by using croscarmellose sodium and guar gum as superdisintegrants. Comparative studies of best MDT formulations with marketed product suggested that, mouth dissolving dexamethasone tablets release drug more rapidly than conventional tablets.

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