Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2010; 2(1): 36-39

Research Article ISSN 0975 1556

Effect of Combination of Surfactant and Super Disintegrating Agent on *In-vitro* Disintegration and Dissolution Release Profile of Medroxyprogestrone Acetate Tablet

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ABSTRACT
The effects of selected surfactants and superdisintegrants on the disintegration behavior of selected model drug with varying combinations of excipient were evaluated. All formulations were made with fixed disintegrant concentration and equal drug load using a model formulation. Tablets were made by wet granulation and were compressed to equal hardness. In-vitro disintegration time and dissolution studies were carried out in dissolution media specified high performance liquid chromatography method. The use of Crosscarmellose sodium (Ac-di-Sol) significantly improved the disintegration time and dissolution of the drugs in the model formulation with or without surfactant, when compared with the other formulation. Crosscarmellose sodium (Ac-di-Sol) with combination of surfactant and disintegrating agent can be effectively used as a tablet disintegrant to improve the disintegration time and dissolution of either soluble or poorly soluble drugs.

Keywords: *In-vitro* disintegration time, Dissolution release profile, Medroxyprogestrone acetate, Superdisintegrating agent, High performance liquid chromatography.

INTRODUCTION

In spite of the increased focus and interest generated in the area of controlled release and targeted drug delivery system in recent years, tablet dosage forms that are intended to be swallowed whole, disintegrate, and release their medicaments rapidly in the gastrointestinal tract still remain the formulation of choice from both a manufacturing as well as a patient acceptability point of view. Thus, a drug given in the form of a tablet must undergo dissolution before being absorbed and eventually transported into systemic circulation. For most of the tablet dosage forms, disintegration precedes drug dissolution. Superdisintegrants such as crosscarmellose sodium, sodium starch glycolate (SSG), and crospovidone are now frequently used in tablet formulations to improve the rate and extent of tablet disintegration and thus improve the rate of drug dissolution. The behavior of superdisintegrants in various tablet formulations has been investigated by many researchers. [1-5] The majority of this research has been directed at the function-related properties of the superdisintegrants with special emphasis on correlating these properties to disintegrant efficiency and drug release. The research focus in recent years has shifted to the formulation of both fast dissolving and disintegrating tablets that are swallowed and tablets that are intended to dissolve in the oral cavity. [6-8] However, some research has also focused on using substantially higher amounts of super disintegrating agent with the aim of either improving the dissolution or stabilizing the formulations. The choice of combination of disintegrating agent, super disintegrating agent and surfactants for a tablet formulation depends largely on the nature of the drug being used. For example, the solubility of the drug component could affect the rate and mechanism of tablet disintegration. Water-soluble materials tend to dissolve rather than disintegrate, while insoluble materials generally tend to disintegrate if an appropriate amount of disintegrant is included in the formulation. Further, in an in vitro dissolution test conducted by using a given method, the drug-excipient interaction could result in a decreased or apparent incomplete drug release from the dosage form. In an earlier study, it was reported that dissolution of phenylpropanolamine HCl from tablets containing crosscarmellose sodium showed only 60 % of apparent amount of drug released, while the release from the corresponding control tablet (without any disintegrant) and a tablet with pregelatinized starch as the disintegrant showed almost complete release. In the present study, an attempt has been made to investigate the effect of tablet

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superdisintegrants alone and their combination with same amount of disintegrant on the disintegration time and dissolution behavior of medroxyprogestrone acetate as model drug. Tablets from each batch were tested for different evaluation parameters.

MATERIALS AND METHODS

Active drug medroxyprogestrone acetate and other excipients such as dicalcium phosphate, microcrystalline cellulose (Avicel 102), crosscarmellose sodium (Ac-di-Sol), aerosol, polyvinylpyrilidone K-30 and polyplasdone XL were provided as a gift sample from Plethico Pharmaceutical Pvt. Ltd., Indore, India. Lactose anhydrous, sodiumlauryl sulphate and isopropyl alcohol were purchased from Thomas baker chemicals Ltd., Mumbai, India.

Preparation of tablet

Medroxyprogestrone acetate tablet was prepared according to Table 1. All the excipients without magnesium stearate, purified talc, aerosil and crosscarmellose sodium were mixed at time of blending of mass. The prepared granules were compressed with single punch compression machine using 7.1 mm circular; concave with break line punches (Table 2).

Evaluation of tablet

Visual inspection of appearance

This was assessed under standard laboratory lighting. Each of 10 tablets per condition as examined for colour, texture and appearance.

Theoretical average weight

Each of 10 tablets per condition was weighed separately on an analytical balance, accurate to five decimal places, and the mass recorded. The weight increase or decrease in relation to that of tablets stored under condition A were recorded as a percentage and expressed as the mean of 10 tablets.

Disintegration time

Each of six tablets per condition was placed separately in the six cylinders of the disintegration apparatus with water (37° ± 0.5°C) as the medium. Disintegration time was recorded as the time point corresponding to the breakdown of all six tablets.

Hardness test

Each of 10 tablets per condition was placed in turn on the platform of a manually hardness tester (pfizer).

Friability test

The total mass of 10 tablets was determined before and after placing those in the clean drum of a friability tester (Roche friabilator) operated at 25 rotations per minute for four minutes. [9]

Dissolution test

The dissolution medium, 900 ml 0.1 N HCl with 0.5 % sodiumlauryl sulphate and thermo stated to 37.0 ± 0.5°C, was placed in each of six vessels of a dissolution test apparatus I.P. Type I with paddle speeds of 50 rotations per minute (rpm). The dissolution medium was sampled at different time intervals. The samples were filtered with filter paper (filter pore size 0.45 µm) and assayed by using the HPLC protocol described below. Dissolution was deemed acceptable where the concentration of medroxyprogestrone acetate released at 30 minutes was NLT 75 % of the total content.

High performance liquid chromatography (HPLC) variables:
Column: 150 × 3.95 µm Novapack C18
Mobile phase: Acetonitrile 600 ml + Water 400 ml
Dilution Factor: Std. 70 mg in 140 ml stock solution + dilute with water to 250 ml
Flow rate: 1
Injection volume: 20
Detector: UV 254
Chromatogram:
Retention time: 8.267 (Table 3 and Fig. 1)

High performance liquid chromatography assay

Sample preparation: Grind tablets to a fine powder; weigh out amount equivalent to about 10 mg medroxyprogestrone acetate, add 10 ml acetonitrile sonicate for 5 min, filter with whatman filter paper (0.45 µm), inject a 20 µl aliquot.
HPLC variables:
Column: 150 × 3.95 µm Novapack C18
Mobile phase: Acetonitrile 600 ml + Water 400 ml
Dilution Factor: Std. 25 mg in 25 ml Acetonitrile [10]
Flow rate: 1
Injection volume: 20
Detector: UV 254
Chromatogram:
Retention time: 8.508.
Formulae: sample Area * potency * Std. wt. * Avg. wt.
(Table 4 and Fig. 2)

RESULT AND DISCUSSION

The objective of the present study was to investigate the effect of superdisintegrating agent with or without surfactant and fixed concentration of disintegrating agent on the disintegration time and dissolution behavior of model drug limited aqueous solubility.

Table 1: Formulae of medroxyprogestrone acetate tablet 10 mg

S. No.	Name Of Ingredient	Uses
1.	Dry Mixing/Granulation	
A	Medroxyprogesterone Acetate USP	Active drug
B	Dibasic Calcium Phosphate	Diluent
C	Lactose (anhydrous)	Diluent
D	Avicel pH 102	Diluent
E	Sodium Lauryl Sulphate	Surfactant
F	Crosscarmellose Sodium (Ac-di-Sol)	Super disintegrant
G	Polyplasdone XL (Crosspovidone XL)	Disintegrant
H	Polyvinyl pyrilidone K-30	Binder
I	Iso Propyl Alcohol	Solvent
2.	Blending/Lubrication	
A	Purified Talc	Lubricant
B	Magnesium Stearate	Lubricant
C	Aerosil(Colloidal silicon Dioxide)	Glident
D	Crosscarmellose Sodium (Ac-di-Sol)	Guper disintegrant

Table 2: Formulations of medroxyprogestrone acetate tablet 10 mg

Formulation code	Drug (mg)	D C P (mg)	Lactose (mg)	Avicel pH 102 (mg)	S L S (mg)	Ac-di-Sol (mg)	P X L (mg)	PVP K-30 (mg)	I P A (ml)
F1	10.14	30	31	35.46	12	5	12	16	q.s.
F2	10.14	61	-	35.46	12	5	12	16	q.s.
F3	10.14	30	31	35.46	24	5	-	16	q.s.
F4	10.14	61	-	35.46	24	5	-	16	q.s.
F5	10.14	30	31	35.46	-	17	12	16	q.s.
F6	10.14	61	-	35.46	-	17	12	16	q.s.

D C P (Di basic calcium phosphate); S L S (Sodium lauryl sulphate); P X L (Polyplasdone XL or Crosspovidone XL); Ac-di-Sol (Crosscarmellose sodium); I P A (Iso propyl alcohol)

Table 3: HPLC data of standard solution of medroxyprogestrone acetate at dissolution study

Parameter	STD
TOTAL	605876
MEAN	121175.2
STDEV	2291.678
RSD	1.691211

Table 4: HPLC data of standard and sample solution of medroxyprogesterone acetate at assay

Prameter	STD	Sample
Total	56672505	21553800
Mean	11334501	10776900
STDEV	22332.408	173928.469
RSD	0.19703	1.6139007
Mg found	10	9.62
Assay		96.2 %

Medroxyprogestrone acetate used as model drug in present study with or without combination of crosscarmellose sodium, polyplasdone XL, PVP K30 and sodium lauryl sulphate. Combination of superdisintegrating agent, surfactants and disintegrating agent (F1) showed best result with respect to better dissolution and disintegration time period than other formulating tablet (Fig. 3 and 4). During preparation of medroxyprogestrone acetate tablet a number of variability used such as concentration of diluents and combination of diluents to identify best formulation. Formulation F1 was prepared by combination of lactose and dibasic calcium phosphate (1:1) with microcrystalline cellulose (Avicel pH 102) showed hardness 7.1 kg/cm^2 and 0.0 or 0.1 % friability.

Table 5: Characterization of medroxyprogestrone acetate tablet (10 mg)

Evaluation parameters	Limits	F1	F2	F3	F4	F5	F6
Description	White circular, biconvex with break line on one side	Complies	Complies	Complies	Complies	Complies	Complies
Identification	Identification by HPLC	Complies	Complies	Complies	Complies	Complies	Complies
Theortical average weight (mg)	±7.5 %	161.56	163.45	166.57	162.84	164.25	163.17
Hardness (kg/cm^2)	5-8	7.1	6.9	6.8	6.6	6.5	7.0
Friability (%)	NIL	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
Disintegration Time (min)	NMT 15 min	5.20	6.05	6.48	5.55	6.30	6.38
Assay (%)	95-105	101.72	100.59	96.77	97.85	100.01	95.12
Dissolution (%; After 30 min)	NLT 75	94.27	87.25	90.65	89.54	91.84	88.46

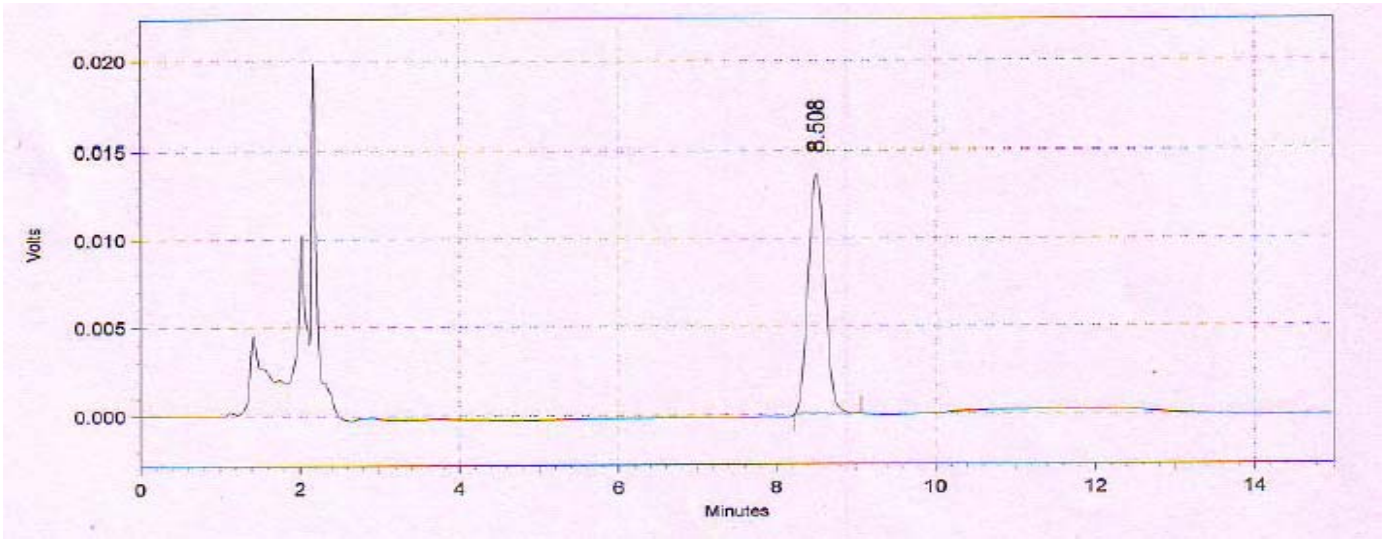

Fig. 1: Chromatogram of dissolution profile of medroxyprogesterone acetate tablet 10 mg
Sample I D: Medroxyprogestroneacetate 10 mg 40°C with 75% RH
Injection Volume: 20 l
Detector: 254 nm

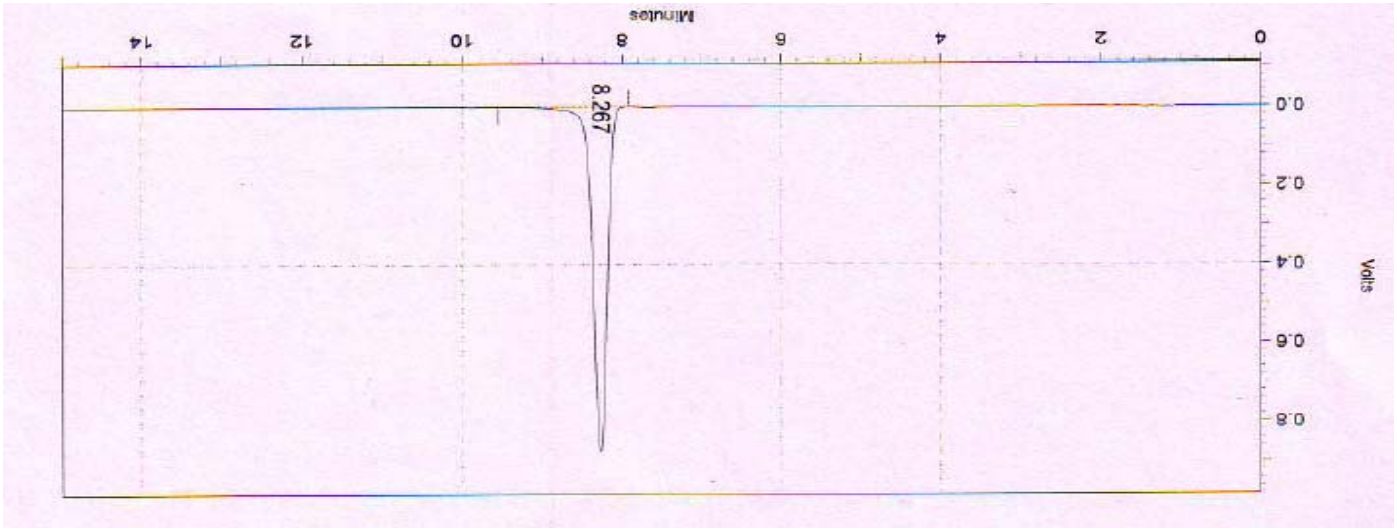

Fig. 2: Chromatogram of assay of medroxyprogesterone acetate tablet 10 mg

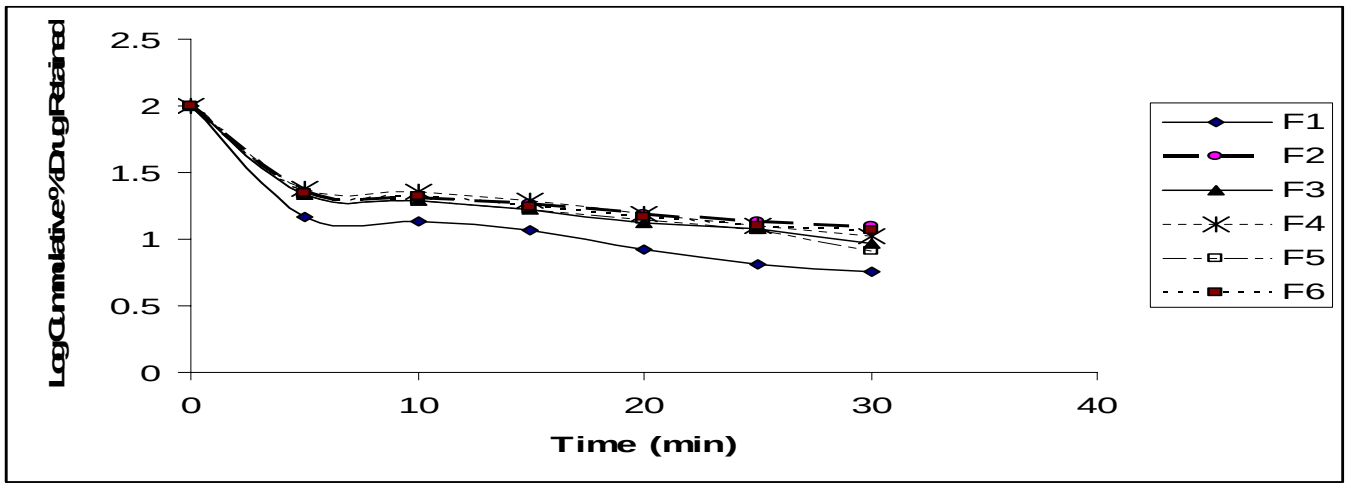

Fig. 3: in-vitro dissolution profile of medroxyprogestrone acetate tablet (10 mg)

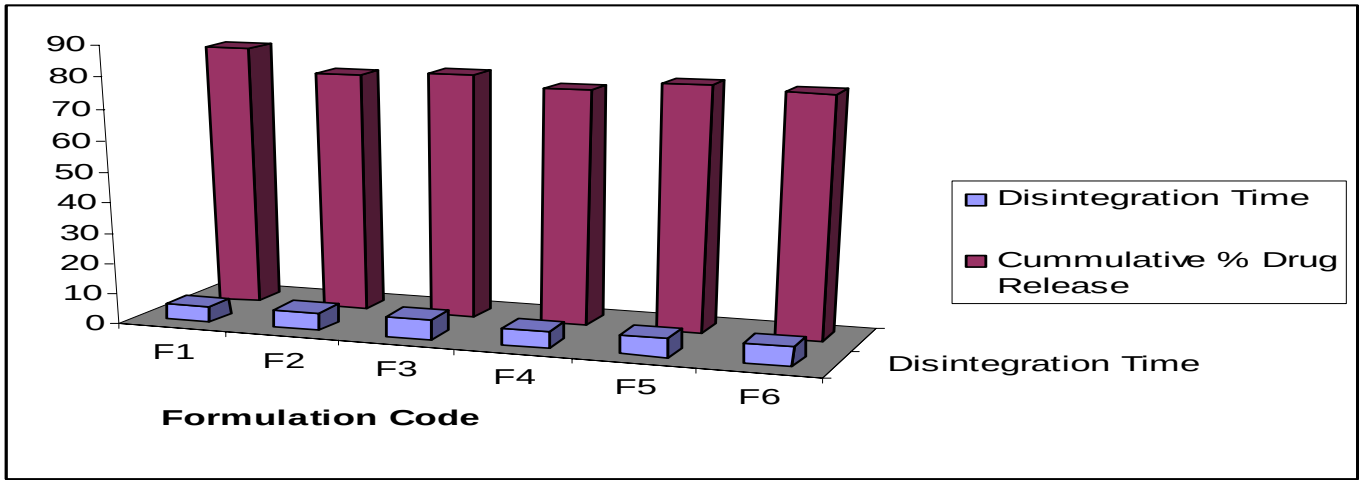

Fig. 4: Co-relation between in-vitro dissolution profile and disintegration time of various formulations

Hardness and friability of all formulations were showed in Table 5; relatively equal tablet hardness values are shown for all formulations of the model drug with various combinations of superdisintegrating agent and disintegrating agents. No significance effect was observed in variability of combination of various diluents and their concentration. The overall results point that Ac-di-Sol is more effective with surfactant sodiumlauryl sulphate and crospovidone XL in enhancing disintegration time as well as dissolution profile.

CONCLUSION

In this study, a comprehensive evaluation of the dissolution rates and disintegration time of medroxyprogestrone acetate tablet with varying combination of superdisintegrating agent and surfactant was performed. In general, crosscarmellose sodium and, more specifically, polyplasdone XL with sodiumlauryl sulphate as surfactant demonstrated a more rapid dissolution rate for the model drug. Since combination of superdisintegrating agent with surfactant and disintegrating agent crosspovidone XL shows better effect than other combinations; thus formulae of such prepared formulation can be used in future tablet technology.

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