Research Article

Formulation development and evaluation of Methylprednisolone dispersible tablets

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Received: 7 June 2018 Revised: 6 July 2018 Accepted: 12 July 2018

Abstract

Objective: The objective of this study was to enhance the solubility of methylprednisolone by choosing micronized form of drug and to enhance patient compliance by formulating it as dispersible tablets. **Materials and methods:** Methylprednisolone dispersible tablets were prepared by direct compression method using micronized form of drug. The concentration of magnesium stearate and superdisintegrants such as croscarmellose sodium and sodium starch glycolate were varied and the concentration of other excipients was kept constant. Formulated dispersible tablets were evaluated for uniformity of dispersion, *in vitro* dispersion time, wetting volume, *in vitro* disintegration time, *in vitro* dissolution profile, wetting time and water absorption ratio. **Results:** Results showed that no significant drug-polymer interactions in FTIR studies. Among all the formulations F3 containing croscarmellose sodium showed superior micromeritic properties along with excellent *in vitro* disintegration time of 45sec and 100% drug release within 20min as compared to other formulations. Stability study on optimized F3 formulation showed that there is no significant change during study period. F3 formulation was found to be stable. **Conclusion:** Thus for better patient compliance and reduced developmental cost micronisation and superdisintegrants addition turns out to be a best option.

Keywords: Dispersible tablets, Methylprednisolone, Croscarmellose Sodium and Sodium Starch Glycolate

Introduction

Many patients have difficulty in swallowing tablets and capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population are affected by this problem, which results in a high incidence of noncompliance and ineffective therapy (Tiwari and Rajabi-Siahboomi, 2008). The demand for solid dosage forms that can be dissolved and suspended in water, chewed, or rapidly dissolved in the mouth is particularly strong in the pediatrics and geriatric markets, with further application to other patients who prefer the convenience of a readily administered dosage form. The changes in various physiological functions associated with aging including difficulty in swallowing make administration of the current dosage forms, like capsules and tablets impractical to such patients and have become the object of public attention (Rasenak and Muller, 2002; Reddy et al, 2002).

In the present research, an attempt has been made to formulate alternative dosage form that has advantages of both solid and liquid dosage forms. Solid oral dosage forms are most convenient, from patient as well as from manufacturing chemist's perspective. They ensure uniformity of dosage, are more robust and have less microbial issues when compared to liquid dosage forms. However immediate release tablets cannot act as a substitute for suspensions. Thus there is a need for a formulation, which overcomes the problems associated with the swallowing of solid dosage forms and acts as a viable substitute for suspensions (Brown D, 2001; Kuchekar et al, 2003).

Methylprednisolone is used to suppress the immune system and decrease inflammation. Conditions in which it is used include skin diseases, rheumatic disorders, allergies, asthma, croup, COPD, certain cancers, multiple sclerosis, and as add-on therapy for tuberculosis. The rate and extent of dissolution of the active ingredient from any dosage form often determines the rate of extent of absorption of the drug. A problem associated with dosage forms of selected

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DOI: https://doi.org/10.31024/ajpp.2018.4.4.20

corticosteroid is its poor dissolution characteristics with water solubility of about 120mcg/ml at 25°C. which is a rate limiting step in the process of drug absorption. Drug with poor water solubility have been shown to be unpredictably and slowly absorbed compared with drugs of higher solubility. Therefore, a better oral formulation can be developed by increasing the water solubility of the drugs. (Raghunathan, 1985) For better patient compliance and reduced developmental cost micronisation and superdisintegrants addition turns out to be a best option. Thus dispersible tablets were formulated using direct compression technique by dry mixture of drug having a reduced particle size and to enhance disintegration superdisintegrants are added. These agents are added to tablet formulations to promote the breakup of the tablet into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. Dispersible tablet formulation with good taste and flavor increase the acceptability of bitter drug methylprednisolone by various groups of population.

Fast dispersible tablets are categorized into two types: **Dispersible tablets -**These types of tablets disintegrate quickly in the water to produce the suspension (Pilgaonkar et al., 2008).

Second is **Mouth dissolving tablets** are differentiated by dissolving in mouth.

Materials and methods

Materials

Methylprednisolone (Micronized), Lactose monohydrate (DCL 11), Microcrystalline cellulose (Avicel PH 102), Croscarmellose sodium, Sodium starch glycolate, Aspartame, Trusil orange, Colloidal silicon dioxide and Magnesium stearate.

Preparation of formulations

Composition of 5 different formulations of methylprednisolone dispersible tablets were prepared by following method. All the materials were individually dispensed and weighed. The sifted Methylprednisolone, Lactose spray dried DCL11, Microcrystalline cellulose PH (102), Croscarmellose sodium, Colloidal silicon dioxide, Trusil Orange, and Aspartame was loaded into polybag and mixed well for 10minutes. To the above blend sifted Magnesium stearate was added and mixed for 2mins. By direct compression the final lubricated blend is compressed in a 16 station compression machine with 8.00mm punch size, round shape and standard concave punch with plain on both the surface.

Compatibility study of drug and excipients using Fourier Transform Infrared Spectroscopy

The spectra were recorded for pure drug and the physical mixture of drug and excipients at the scanning range of 4000-400 cm-1using FTIR spectrophotometer (Shimadzu, Japan).

Evaluation of powder blends (Aulton, 1998; Martin et al., 1991; Sharma and Gupta, 2009; Indian Pharmacopoeia, 2007)

Bulk density

Accurately weighed 50 gm of blend, previously passed through 20# sieve was transferred into 100 ml graduated cylinder. Carefully the powder is leveled without compacting, and the unsettled apparent volume is observed.

Bulk density = Weight of the powder/Bulk volume of powder

Tapped density

Accurately weighed 50 gm of the blend was transferred into 100 ml graduated cylinder. Initial volume was observed. The cylinder was tapped initially 500 times from a distance

Table 1. Composition of Dispersible tablets of Methylprednisolone with corresponding formulations

Ingredients	F1	F2	F3	F4	F0
	mg/tab				
Methylprednisolone	16.00	16.00	16.00	16.00	16.00
Lactose (DCL 11)	133.50	133.50	131.5	131.5	134.5
MCC (Avicel PH 102)	40.00	40.00	40.00	40.00	40.00
CCS	2.00	-	3.00	-	-
SSG	-	2.00	-	3.00	-
Colloidal silicon dioxide	3.00	3.00	3.00	3.00	3.00
Trusil Orange	1.00	1.00	1.00	1.00	1.00
Aspartame	2.50	2.50	2.50	2.50	2.50
Magnesium stearate	2.00	2.00	3.00	3.00	3.00
Tablet weight	200.00mg				

of 14 + 2 mm and measured the tapped volume to the nearest graduated units. The tapping was repeated for additional 750 times. Again the tap volume was measured to the nearest graduated unit. The tapped bulk density in gm/ml was calculated by the following formula

Tapped density = Weight of powder taken/ Tapped Volume

Compressibility Index

The propensity of the powder to be compressed is measured by compressibility and it also helps in measurement of settling property and interparticulate interaction.

Compressibility index (%) = $\rho t - \rho o X 100 / \rho t$

Where,

ρt = Tapped density gram/ml,

ρo = Bulk density gram/ml.

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material.

Hausner ratio= Tapped density/ Bulk density

Angle of repose

The angle of repose of blend was determined by funnel method. Accurately weighed powder blend was taken in a funnel. Height of the funnel was adjusted in such ways that tip of the funnel just touches the apex of the powder blend. The powder blend was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\tan(\theta) = h/r$$

Where, h – height of the powder cone.

r- radius of the powder cone.

Evaluation of dispersible tablets (Subrahmanyam, 2004; Rajesh et al., 2010; Gosai et al., 2008; Furtado et al., 2009; Singh and Singh, 2009; Radke et al., 2009)

a) Physical appearance: The tablets are inspected for smoothness, absence of cracks, chips, and other undesirable characteristics.

b) Weight variation test: 20 tablets are randomly selected from each formulation and their average weight is calculated using digital balance. Individual weight of each tablet is also calculated using the same digital balance and compared with the average weight of a tablet. The allowed percentage deviation in Weight variation is given in table.

Table 2. Percentage Weight variation of prepared tablets

Average weight of tablet (mg)	% Difference
80 mg or less	10%
More than 80mg or Less than 250mg	7.5%
250mg or more	5%

c) Hardness: Tablet should be hard enough to withstand packing and shipping. Schluenzier hardness tester is used for the determination of hardness of tablets. The hardness of 10 tablets is noted and the average hardness was calculated. It is expressed in N or kg/cm^2.

d) Thickness: Thickness was determined for 20 pre weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm.

e) Percentage friability: The tablets are rotated in the Roche friabilator which subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25rpm and dropping the tablets at a height of 6inches in each revolution for 100 revolutions. The tablets that loose less than 1% weight are considered to be compliant.

$$\% \text{ Friability} = (W1-W2)/W1x100$$

f) Uniformity of dispersion: This test is applicable only to dispersible tablets. In this method, two tablets are placed in 100ml of water and stirred gently until completely dispersed. A smooth dispersion must be obtained which passes through sieve screen with nominal mesh aperture of 710µm (sieve no. 22).

g) *In vitro* dispersion time: This test is unofficial parameter applicable only to dispersible tablets. In this method, tablet was added to 10ml of water and time required for complete dispersion is measured. Three tablets from each formulation are randomly selected and dispersion time is performed.

h) *In vitro* disintegration studies:

Dispersible tablets must disintegrate within 3min when examined by the disintegration test for tablets as per the compliance in the pharmacopoeia.

i) Wetting Volume: The tablet is placed in the center of the Petri dish and with the help of 5 ml pipette; distilled water is added drop wise on the tablet. The volume required to completely disintegrate the tablet is noted as the wetting volume.

j) Wetting Time: A piece of tissue paper (12cmx10.75cm) folded twice is placed in a Petri dish (10 cm diameter) containing 10 ml of water. Containing Eosin, a water soluble dye, was added to Petri dish. A tablet was carefully placed on the surface of the tissue paper and allowed to wet completely. The time required for water to reach upper surface of the tablet was noted as a wetting time.

k) Water Absorption Ratio: A piece of tissue paper folded

twice is placed in a small Petri dish (10 cm diameter) containing 6 ml of water. A tablet is put on the tissue paper and allowed to wet completely. The wetted tablet is then reweighed.

Water absorption ratio, R is determined using following equation,

$R = 100\,(Wa - Wb)/Wb$

Where,

Wa = weight of tablet after water absorption

Wb = weight of tablet before water absorption.

l) *In vitro* dissolution studies (By UV method)

In vitro dissolution studies were performed in distilled water with volume of 900ml using USP apparatus Type –II (paddle) at temperature of 37±0.5°C.

Stability study

In any rational design and evaluation of dosages forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection. During the stability studies the product is exposed to normal condition of temperature and humidity. However the studies will take a longer time and hence it would be convenient to carry out accelerated stability studies, were the product is stored under extreme condition of temperature and humidity (Indian Pharmacopoeia, 1996). In the present study, stability studies were carried out on optimized formulation and the closely packed samples were stored for 3 months in the stability chamber which was maintained at 40±2°C and 75±5% RH. The tablets were analyzed for physical characterization and drug release and statistically drug release.

Statistical Analysis

The statistical analysis for stability studies was carried out by Student's t-test by using ANOVA (SPSS 16.0 software).

Results and discussion

Compatibility study of drug and excipients using Fourier Transform Infrared Spectroscopy

In the present investigation, FT-IR spectra of Methylprednisolone showed sharp characteristic peaks. All the above characteristic peaks appear in the spectra of

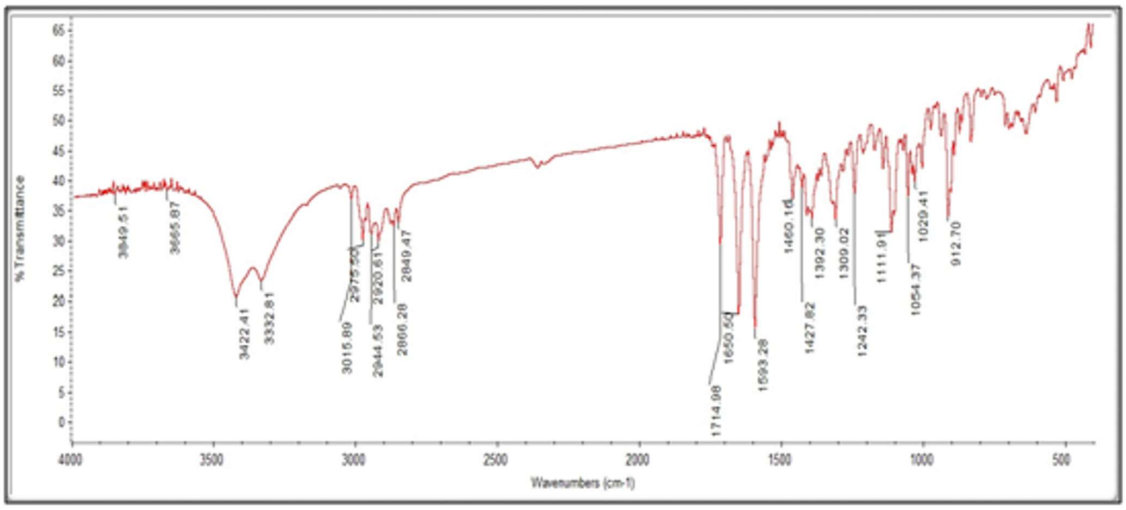

Figure1. IR spectra of Methylprednisolone

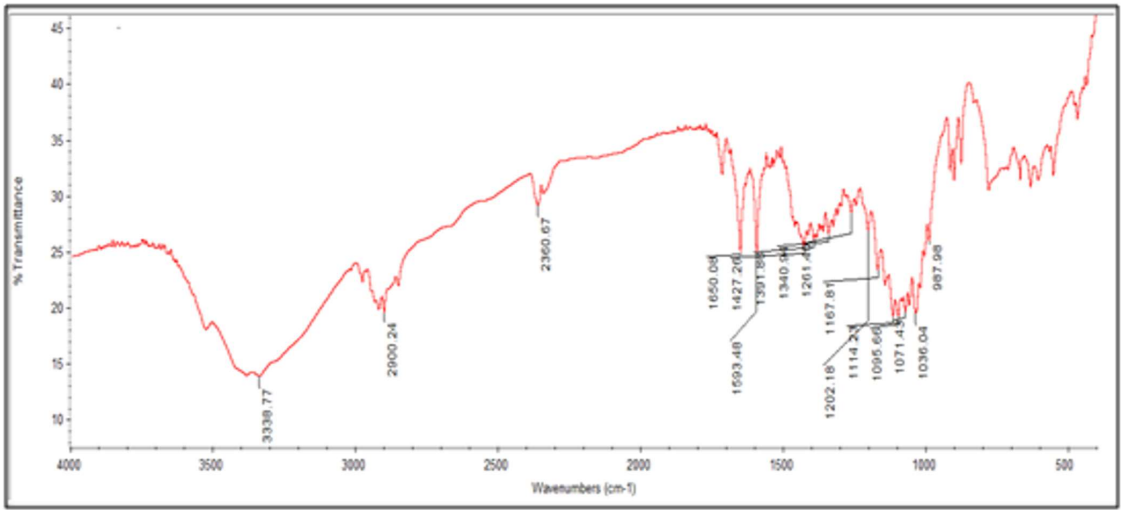

Figure 2.IR spectra of Physical mixture

formulation at same wave number indicating no modification or interaction between the drug and excipients. FT-IR spectroscopy was used as means of studying drug excipient compatibility and confirmed undisturbed structure of Methylprednisolone in figure.1 and figure 2, which indicate no drug-excipient interaction.

Characterization of Methylprednisolone dispersible powder blend

Each formulation blend of drug and excipients were evaluated for various parameters as explained earlier. Bulk density was found in the range of 0.452-0.496 g/cm3 and tapped density between 0.523-0.569 g/cm3 as shown in table 3. Using these two densities data compressibility index and hausner's ratio was calculated.

The powder blends of all the formulations had compressibility index between 12.16 and 12.93 which indicating good flowability of the powder blend. Hausner's ratio for all formulation was less than 1.16, indicated good flowability. The compressibility flowability correlation data indicated an excellent flowability of all powder blends, the good flowability of the blend was also evidenced with angle of repose which is between 25.2 and 27.26. The results are shown in table 4.

Characterization of Methylprednisolone dispersible tablet

Methylprednisolone dispersible tablets were prepared in five formulations with varying concentration of two superdisintegrants croscarmellose sodium (Ac-Di-Sol), sodium starch glycolate and MCC (Avicel) as diluents.

Post-compression parameters such as thickness, hardness, friability, weight variation, amount of drug content, wetting time, wetting volume; water absorption ratio, dispersion time and disintegration time are shown in table 5, 6, 7. The hardness was found to be in the range of 68-77 N for all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. Thickness of all formulations varied from 3.73 to 3.83 mm. In all the formulations the friability values are less than 1% and complies the IP limits. Friability of the tablets was found below 0.78 - 0.84 % indicating good mechanical resistance of tablets. All the tablets passed weight variation test as the percentage weight variation was within the Pharmacopeial limits. The weight of all the tablets was found to be uniform with low standard deviation values indicating efficient mixing of drug, disintegrants and excipients.

All the batches pass the Uniformity of dispersion as per IP and the Dispersion time of all the batches tablet was within

Table 3. Evaluation of physical properties of tablet blends

Formulation code	Bulk density* (g/ml)	Tap density* (g/ml)	Compressibility index* (%)	Hausner's ratio*	Angle of repose*
Pure drug	0.527±0.03	0.637±0.02	17.26±0.19	1.21±0.009	40.20±0.56
F1	0.469±0.01	0.536±0.01	12.50±0.30	1.14±0.003	27.26±0.31
F2	0.462±0.01	0.526±0.01	12.16±0.33	1.14±0.004	25.56±0.81
F3	0.471±0.02	0.541±0.01	12.93±0.11	1.15±0.02	25.70±0.37
F4	0.496±0.02	0.569±0.01	12.82±0.30	1.15±0.003	26.77±0.73
F5	0.452±0.03	0.523±0.02	13.57±0.51	1.16±0.02	26.42±0.55

*Average of 3 determinations ±standard deviation

Table 4. Evaluation of physical properties of tablet formulations

Formulation code	Weight variation* (mg)	Hardness* (N)	Thickness* (mm)	Friability* (%)
F1	200.12±0.25	74±3	3.73±0.04	0.84±0.001
F2	200.05±0.11	75±2	3.81±0.06	0.83±0.003
F3	200.12±0.23	68±3	3.83±0.04	0.78±0.03
F4	199.59±0.33	69±2	3.80±0.05	0.79±0.005
F5	200.21±0.41	77±1	3.75±0.07	0.80±0.03

*Average of 3 determinations ±standard deviation

Table 5. Evaluation of physical properties of tablet formulations

Formulation code	Uniformity of dispersion*	Dispersion time* (sec)	Disintegration time* (sec)
F1	Passes	45±0.13	81±3
F2	Passes	55±0.12	93±2
F3	Passes	25±0.22	48±3
F4	Passes	33±0.16	55±2
F5	Passes	More than 3min	More than 3min

*Average of 3 determinations ±standard deviation.

Table 6. Evaluation of physical properties of tablet formulations

Formulation code	Wetting volume* (ml)	Wetting time* (sec)	Water absorption ratio*
F1	3.5±0.05	34.17±0.11	76.57±0.29
F2	3.7±0.04	39.73±0.18	67.31±0.13
F3	2.4±0.08	26.66±0.24	104.63±0.38
F4	2.9±0.04	28.66±0.27	81.31±0.33
F5	More than 5ml	More than 3min	-

*Average of 3 determinations ±standard deviation.

the range of 25-55 sec. Water absorption ratio of all formulations was found between 67.31 and 104.63%. This resulted in fast wetting of tablets of all formulations as reflected from wetting time ranging between 26.66-39.73 sec. Wetting volume for all the batches was within the range of 2.-3.7 ml except F5. The Dispersion time of all the batches tablet was within the range of 25-45sec except F5, The results of wetting time and disintegration time of all the tablets were found to be within the prescribed limits and satisfy the criteria of Dispersible tablets. It was observed that when Ac-Di-Sol is used as Superdisintegrants, the tablets disintegrate rapidlywithin less time due to easy swelling ability of Ac-Di-Sol when compared to Sodium starch glycolate. Among the formulations F3 containing Ac-Di-Sol 3 mg was found to be the best as compared to other formulations as this formulation showed good hardness, low friability, least wetting time (26.66 ± 1.24 sec.) and disintegration time of (48±13 sec.), which is an ideal characteristic of a dispersible type tablets.

In the study, the relatively larger fragments generated by tablets containing sodium starch glycolate were not small enough to pass through the screen of the disintegration vessels. Accordingly a longer disintegration time and a larger variation were observed, especially when the sodium starch glycolate was used at the lower concentration.

Tablets formulated with Ac-Di-Sol rapidly disintegrate into more or less uniform fine particles, while tablets formulated with sodium starch glycolate appeared to disintegrate much more slowly into more or less uniform coarser particles.

In-vitro dissolution study

The drug release at the end of 20 minutes was found to be 74.583, 77.12, 99.896 and 86.356% with Ac-Di-sol and SSG. The percentage drug release of all the batches was found to be between 74.583 to 99.896% in Table 7, this was within the acceptable limits.

The cumulative percentage of the drug released for formulation batch F3 found by the dissolution test shows the better drug release of 99.896 % at the end of 20 minutes. Indicates good bioavailability of the drug from these formulations.

Kruskal-Wallis test showed that there was a highly statistical difference (P=0.009) in % drug release between F1- F5 and it was concluded that F3 showed better drug release among all the formulations.

Table 7. *In Vitro* Drug release

Time in hours	% Cumulative drug release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	45.251	42.321	60.153	50.852	16.326
10	55.631	52.693	75.321	63.285	22.365
15	66.021	64.239	90.281	74.258	28.652
20	75.583	77.121	99.896	86.356	34.785
25	85.698	84.231	100	98.985	39.989
30	95.893	91.698	100	100	45.698
35	100	99.894	100	100	53.563
40	100	100	100	100	60.896
45	100	100	100	100	67.235

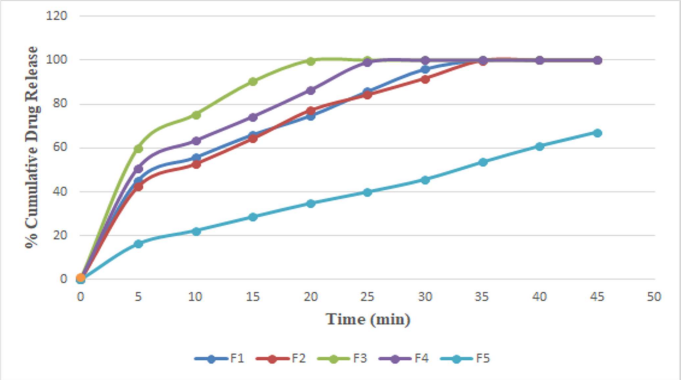

Figure 3. *In vitro* Drug Release Profile

Ac-Di-Sol when comes in contact with water gets inflated immediately burst out there by releasing the drug in the short duration of time. The tablets showed not less than 75 % drug release in 20 minutes in distilled water except F5. Comparative dissolution profile of all Batches (F1-F5) is given in figure 3.

It was observed that as the concentration of superdisintegrants increased the drug release also increased. With reference to the type of superdisintegrants, the release rate was found to follow the order: Ac-Di-sol > SSG.

Stability study

Stability study was carried out on optimized F3 formulation. The color of the tablets was similar before and after stability studies. Physical characterization does not show any significant change at 40°C ± 2°C / 75 ± 5 % RH after 90 days. This indicated that the tablets not absorb moisture from the environment. Dissolution profile of optimized F3 batch before and after stability study is shown in figure 4 and table 9 and statistical method used is ANOVA by (SPSS 16.0 software).

In the ANOVA the p value for initial, first month and third month is 0.998 which is greater than 0.05. Hence there is no significant difference between the drug release during the study period. Thus the F3 formulation was found to be stable.

Table 8. Stability Compilation for Methylprednisolone dispersible tablets

Test Parameters	Acceptance criteria	Initial results	Condition - 40 ±20°C & 75±5% RH	
			1st month	3rd month
Appearance*	White colored round shaped tablets, plain on both sides.	Complies	Complies	Complies
Average weight* (mg)	200mg ± 7.5% (185.00mg – 215.00mg)	200.12±0.23	199.89±0.19	199.78±0.21
Hardness* (N)	NLT 30N	68±1	69±2	67±2
Disintegration Time* (Sec)	NMT 3minutes	48±13	49±9	47±8
Fineness of Dispersion*	A smooth dispersion is obtained which passes through a sieve screen with a nominal mesh aperture of 710µ (sieve number 22)	Complies	Complies	Complies
Dissolution*	NLT 70% of the labeled amount of Methylprednisolone	100%	100%	100%

*Average of 3 determinations ±standard deviation.

Table 9. *In vitro* drug release study of F3 batch before and after stability study

Time in hours	% Cumulative drug release* ± SD		
	Initial	1st month	3rd month
0	0	0	0
5	60.153	59.891	57.213
10	75.321	75.012	74.123
15	90.281	89.989	87.836
20	99.896	99.759	98.623
25	100	100	100

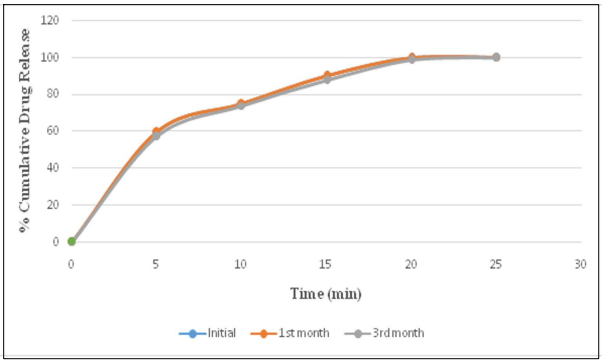

Figure 4. *In vitro* drug release study of F3 batch before and after stability study

Conclusion

Among the formulations F3 containing Ac-Di-Sol showed superior micromeritic properties along with excellent in vitro disintegration time and drug release as compared to other formulations. It was concluded that superdisintegrants addition technique is a useful method for preparing dispersible tablets by direct compression. The In-vitro study shows formulation F3 was well suited to dispersible tablet formulation due to the disintegration time of just 45 sec, which is formulated by using superdisintegrant croscarmellose. Stability study on optimized F3 formulation shows that there are no significant changes during study period. Thus F3 formulation was found to be stable.

Acknowledgement

The authors of the manuscript are very much thankful to Mother Theresa Post Graduate and Research Institute of Health Sciences, Puducherry.

Declaration of interest

The authors of the manuscripts report no declaration of interest. The authors are alone responsible for the content and writing of the paper.

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