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Development and Evaluation of Mouth Dissolving Films of Sumatriptan Succinate for Better Therapeutic Efficacy

Buchi N. Nalluri*, B. Sravani, V Saisri Anusha, R. Sribramhini, K.M. Maheswari
Department of Pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada-520010, AP, India.

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ABSTRACT

The present investigation was undertaken with an objective of formulating mouth dissolving films (MDFs) of an anti-migraine drug, Sumatriptan Succinate (SUM) to enhance convenience and compliance to the elderly and pediatric patients for better therapeutic efficacy. Film former, Hydroxy Propyl Methyl Cellulose along with film modifier/solubilizing agents, Polyvinyl pyrrolidone K30 (PVP K30) and Sodium Lauryl Sulphate (SLS) were used to formulate MDFs. The MDFs were prepared by wet film applicator technique and were evaluated for *in vitro* dissolution characteristics, *in vitro* disintegration time, and their physico-mechanical properties. MDFs with 13% (w/w) of HPMC E5 gave better dissolution properties when compared to HPMC E15. MDFs with PVP K30 and SLS gave superior dissolution properties when compared to MDFs without PVP K30 and SLS. The dissolution properties of MDFs with PVP K30 were superior when compared to MDFs with SLS. Overall, SUM MDFs showed good mechanical properties like tensile strength, folding endurance and % elongation and dissolution properties. These results suggest that the HPMC is an excellent film former which gives rapid drug release.

INTRODUCTION

The oral cavity is the most prominent site of drug delivery for a long period of time. In 1847 Sobrero found that nitroglycerine was absorbed from the oral cavity (Ponchel, 1993). Since then various active substances have been investigated for local or systemic use. Recent developments in the formulation technology have presented viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or non-compliant patients. Novel bioadhesive mucosal dosage forms including adhesive tablets, gels, patches and more recently the use of polymeric films for oral cavity delivery, also known as mouth dissolving films (MDFs) gained attention in formulation research. MDFs, a new and novel drug delivery system for per oral delivery of the drugs, were developed based on the technology of the transdermal patch (Arun Arya et al; 2010). The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. Various film formers like Polyvinyl alcohol, Polyvinyl pyrrolidone (PVP), Maltodextrin, Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Propyl Cellulose (HPC), Methyl Cellulose (MC), Sodium Carboxy Methyl Cellulose (Na CMC), Chitosan and some natural gums have been used in the production of films (Dinge & Nagarsenker, 2008). SUM, an anti-migraine drug is structurally similar to serotonin and hence induces activation of 5-HT1 receptors. Bioavailability is approximately 15% primarily due to presystemic metabolism and partly due to incomplete absorption. The elimination half- life is approximately 2.5 hours (Martindale, 1999). It was selected as a model drug based on the low oral bioavailability, first pass effect and the need of quick onset of action for better therapeutic efficacy when compared to existing marketed dosage forms. Very few reports were published on the orally disintegrating tablets of SUM (Sheshala et al; 2011) and no work has been published on the MDFs of SUM. Hence, the main aim of this work is to develop a novel, fast dissolving drug product on the technology platform of a small and thin drug loaded film i.e. MDF for SUM in order to have quick onset of action for better

* *Corresponding Author*
Buchi N. Nalluri, Professor and Director for PG Studies and Research, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada-520010, AP, India. Tel: +91-9618394959

therapeutic efficacy. In this work, the effect of nonionic micelles of triton X 100 on the spectroscopic and acid–base properties of LST K is described. The absorption spectrophotometry were used to quantify the LST K/Triton X 100 binding constant and Triton X 100/water partition coefficient, by applying the mathematical models that consider partitioning of the drug between the micellar and aqueous pseudo-phases.

MATERIALS AND METHODS

Sumatriptan Succinate (Gift sample from Aurobindo Pharmaceuticals Pvt Ltd, Hyderabad), Hydroxy Propyl Methyl Cellulose E5, E15, (Loba Chemie, Mumbai), Methanol (Loba Chemie, Mumbai), Sodium Lauryl Sulphate (Merck, India), PVP K30 (Dr. Reddy's Laboratories, Hyderabad), Pine apple flavor (Darwin Laboratories, Vijayawada), Aspartame (Darwin Laboratories, Vijayawada). All other reagents of analytical grade were used.

Preparation of Artificial Saliva

Artificial saliva was prepared as per the method reported (Na & Faraj, 2005). Sodium chloride-0.844g; Potassium chloride-1.2g; Calcium chloride dihydrate-0.193g; magnesium chloride hexahydrate-0.111g; potassium phosphate dibasic-0.342g. These ingredients were added one by one to 500ml of distilled water and then the volume was made up to 1000ml using the same. The pH was adjusted with 0.1N hydrochloric acid to 5.7.

Preparation of SUM MDFs

Films were prepared as per formula given in Table 1 to a batch size of 5g. Drug was dissolved in the mixture of solvents (water and methanol) in a beaker and other ingredients were added one by one and finally polymer HPMC was added and mixed thoroughly and the mixture was sonicated for 5 minutes to remove entrapped air bubbles and casted on a glass plate with a wet film applicator set at 10 mil thickness (250µm) and it was dried at 40ºC for 60min in hot air oven. Then the dried films were peeled off from the glass plate, cut into appropriate sizes, and stored in desiccator until use.

Morphological Properties

Properties such as homogeneity, color, transparency and surface of SUM MDFs were tested visually. All the formulations were stored at room temperature (25 ± 3°C) with relative humidity of approximately 65 ± 5% and were tested periodically every month for a period 6 months. The results are given in Table 2.

Drug Content

1cm^2 film was taken in to a 10mL volumetric flask and dissolved in 5mL of methanol and then final volume was made up with methanol. Samples were suitably diluted with artificial saliva and the absorbance was measured at 282 nm. The estimations were carried out in triplicate. The data was given in Table 2.

Variation of Mass

Mass of 2×2.5cm^2 film from different batches of the formulations was noted on electronic balance. The results are given in Table 3.

Thickness

The thickness of film was evaluated using screw gauge with range 0-10mm and revolution 0.001mm. Anvil of the thickness gauge was turned and the film was inserted after making sure that pointer was set to zero. The film was held on the anvil and the reading on the dial was noted down. The average of 3 readings was taken and the data was given in Table 2.

Tensile Strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks (Doaa Ahmed El-Setouhy and Nevine Shawky Abd El-Malak, 2010). It is calculated by the load at rupture divided by the cross-sectional area of the film as given below:

$$\text{Tensile strength} = \frac{Loadatfailure \times 100}{FilmThicknes \times filmwidth}$$

It was measured using Shimadzu AG-100kNG (Winsoft tensile and compression testing). The film of size 3×2 cm^2 and free of physical imperfections was placed between two clamps held 10 mm apart. The film was pulled by clamp at a rate of 5mm/min. Whole experiment was carried out in triplicate. The values were given in Table 3.

Percent Elongation (%E)

When stress is applied the film sample stretches and is referred to as strain. Strain is basically the deformation of the film divided by the original dimension of the film. Generally elongation of the film increases as the plasticizer concentration increases (Choudhary et al; 2011). Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement by using the following formula. The values were given in Table 3.

Percentage Elongation = [L-L0] X 100 / L0

Where, L = Final length, L0 = initial length

Young's Modulus

Young's modulus or elastic modulus is the measure of stiffness of film. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

$$\text{Young's Modulus} = \frac{Slope \times 100}{FilmThicknes \times CrossHeadSpeed}$$

Hard and brittle film demonstrates a high tensile strength and Young's modulus with small elongation. The values were given in Table 3.

Table. 1: Composition of different SUM MDFs.

Ingredients	Formulae (Amounts in mg)					
	F1	F2	F3	F4	F5	F6
SUM	50	50	50	50	50	50
HPMC E5	650	650	-	-	650	-
HPMC E15	-	-	650	650	-	650
PEG 400	50	50	50	50	50	50
SLS	-	2	-	2	-	-
PVP	-	-	-	-	2	2
Water	1679.5	1677.5	1679.5	1677.5	1677.5	1677.5
Methanol	2600	2600	2600	2600	2600	2600
Pineapple	10	10	10	10	10	10
Aspartame	10	10	10	10	10	10

Table. 2: Physico-mechanical properties of different SUM MDFs.

Formulae	Appearance*	DrugContent /cm^2 (mg) (n=3)	Thickness (µm) (n=6)	Disintegration Time (sec) Drop Method (n=3)	Disintegration Time (sec) Petri Dish Method (n=3)
F1	Homogeneous, transparent, colorless, both sides smooth Transparent	0.808 ± 0.003	130.6 ± 1.15	4.66 ± 0.50	30.33 ± 1.50
F2	Homogeneous, transparent, colorless, both sides smooth Transparent	0.806 ± 0.004	133.33 ± 1.52	3.33 ± 0.50	25.33 ± 1.52
F3	Homogeneous, transparent, colorless, both sides smooth Transparent	0.807 ± 0.005	131.33 ± 1.52	4.66 ± 0.50	36.66 ± 2.08
F4	Homogeneous, transparent, colorless, both sides smooth Transparent	0.825 ± 0.002	131.33 ± 1.52	4.00 ± 1.00	31.66 ± 1.52
F5	Homogeneous, transparent, colorless, both sides smooth Transparent	0.807 ± 0.003	132.00 ± 2.00	2.33 ± 0.50	9.33 ± 1.15
F6	Homogeneous, transparent, colorless, both sides smooth Transparent	0.807 ± 0.003	133.00 ± 2.60	3.30 ± 0.50	10.00 ± 2.00

* No change in properties even after 6 months of storage period

Table. 3: Physico-mechanical properties of different SUM MDFs.

Formulae	Mass variation (mg)	Tensile Strength (N/cm^2)	% Elongation (cm %)	Elasticity Modulus	Folding Endurance
F1	64.33 ± 0.57	3.23 ± 0.152	85.53 ± 3.60	3.38 ± 0.244	101
F2	64.66 ± 0.57	3.96 ± 0.152	88.83 ± 3.22	2.26 ± 0.0151	98
F3	64.66 ± 1.52	2.13 ± 0.251	81.43 ± 3.66	1.28 ± 0.102	115
F4	63.00 ± 1.00	2.91 ± 0.173	84.16 ± 3.18	2.76 ± 0.218	91
F5	63.66 ± 1.52	1.96 ± 0.208	94.06 ± 2.73	2.01 ± 0.285	144
F6	64.33 ± 1.52	3.01 ± 0.2	90.98 ± 3.12	2.36 ± 0.07	129

Table 4. Drug percent released for SUM.

Formulation	DP_{10} (Mean ± SD)		Mean 'k' (sec^{-1})	
	(Method I)	(Method II)	(Method I)	(Method II)
F1	34.93 ± 0.48	34.80 ± 1.14	0.055	0.032
F2	58.42 ± 0.61	54.19 ± 1.31	0.078	0.059
F3	29.94 ± 2.69	21.52 ± 1.99	0.029	0.039
F4	26.69 ± 0.54	47.96 ± 1.16	0.041	0.073
F5	100 ± 0.00	100 ± 0.00	0.460	0.921
F6	36.35 ± 0.24	51.60 ± 4.36	0.052	0.059

Folding Endurance

Folding endurance was determined by repeated folding of the film at the same place till the film breaks.

This gives an indication of brittleness of the film. The number of times the film is folded without breaking is computed as the folding endurance value (Basani Gavaskar et al; 2010). The values were given in Table 3.

***In vitro* Disintegration Studies**

Disintegration time gives an indication about the disintegration characteristics and dissolution characteristics of the film. Incase of MDFs the disintegration and dissolution procedures are hardly distinguishable. If the MDF disintegrates it concurrently dissolves in a small amount of saliva which makes it difficult to mimic these natural conditions and measures with an adequate method. However, in the present investigation two methods of disintegration were adopted.

Drop method

In the first method one drop of distilled water was dropped by a pipette onto the oral films. Therefore the films were placed on a glass slide and placed planar on a petridish. The time until the film dissolved and caused a hole within film was measured. The results are given in Table 2.

Petridish method

In this method 2ml of distilled water was placed in a petridish and one film was added on the surface of the water and the time required until the oral film dissolved completely was measured. Drug-loaded films were investigated under both methods. The results are given in Table 2.

Dissolution studies

As the MDFs are not official in any pharmacopoeia the following dissolution methods were used for testing the *in vitro* drug release profiles from MDFs.

Beaker Stirring Method (Method I)

The *in vitro* dissolution studies were conducted using 150mL glass beaker with 125mL of artificial saliva as dissolution medium. Film (2×2.5 cm^2) was placed on one side of the beaker using double-sided tape (Figure 1). Medium was stirred at a speed of 200rpm using magnetic stirrer bar. 5mL samples were withdrawn at 10, 20, 30, 40, 50, 60, 80, 100, 120sec time intervals and every time replaced with 5mL of fresh dissolution medium. The samples were analyzed by measuring UV absorbance at 282nm. The dissolution experiments were conducted in triplicate. Percent of SUM dissolved at different time intervals and various dissolution parameters are given in Table 4.

Dissolution Apparatus 5 (Method II)

The *in vitro* dissolution studies were conducted using 600mL of artificial saliva as dissolution medium with modified type 5 dissolution apparatus. A temperature of 37º C and 50 rpm were used. Each film with dimension (2×2.5 cm^2) was placed on a watch glass covered with nylon wire mesh (Figure 1). The watch glass was then dropped into dissolution flask. 5mL samples were withdrawn at 10, 20, 30, 40, *50*, 60, 80, 100, 120 sec time intervals and every time replaced with 5mL of fresh dissolution medium. The samples were analyzed by measuring absorbance at 282nm. The dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

Preparation and physical characterization of SUM MDFs

Initially placebo MDFs were prepared with different polymers like HPMC (E5, E15, and K4M), HPC, MC, Na CMC, PVP, Gelatin, and sodium alginate. Finally, from these trials made and results obtained, HPMC E5 and HPMC E15were selected for further development.

In the initial trials 100mg of drug was added to the formulation and the films were prepared. However, crystallization of the drug was observed over a period of time and hence, the drug amounts were adjusted to 50mg per batch. The SUM MDFs were prepared as per the formulae given in Table 1. Totally a 5g batch size of formulation gave approximately 100cm^2 film area. Different homogenous films of SUM were prepared; all the films are transparent, colorless, and soft with no spots found on them.

Morphological properties

SUM MDFs were visually tested for homogeneity, transparency, color and smoothness and the results were given in Table 2. All the formulations showed no change in the properties at the end of 6 month time period and especially no crystallization of the drugs was observed.

Drug content

Films of 1cm^2 were cut from different places of the whole films and SUM content was estimated. The results were given in Table 2. These results indicated a good uniformity of SUM within films and overall, good solubilization of SUM in the formulations.

Variation of mass

Films of 2×2.5cm^2 were cut from different batches and weighed. The results are given in Table 3. Same mass of film was obtained with three batches of films indicating reproducibility of preparation method and spreadability of the formulation.

Tensile Strength

MDFs should possess moderate tensile strength, high % elongation (% E), low EM, and high percent of drug release. The results revealed that all the films showed moderate tensile strength values, films of F5 and F6 showed highest % E compared with other formulae and F5 has lowest EM when compared with other formulae (Table 3). Based on the above results the MDF of formula F3 showing the highest dissolution rate and lowest *in vitro* disintegration rate is suitable for fast-dissolving dosage form.

Thickness

The thickness was measured with screw gauge at different places of MDFs in order to evaluate the reproducibility of preparation method. Around 50% of wet film thickness was lost during drying. The results are given in Table 2 and a good uniformity of thickness was observed.

Disintegration time

The results of disintegration time are given in Table 2. These results indicated that the E5 formulations disintegrated faster than the E15 formulations. The SUM MDF formulations with PVP disintegrated faster than the MDFs with and without SLS formulations. With Petri dish method F5 and F6 formulations disintegrated/dissolute faster than the other formulations.

***In Vitro* Dissolution Studies**

Totally 6 different formulations of SUM were prepared using HPMC E5 and HPMC E15 as film forming polymers with and without SLS and PVP K30. With Method I i.e. beaker stirring method, at the end of the 10sec the cumulative percent of SUM released is 39.43 ± 0.48 and 29.94 ± 5.69 respectively for F1 and F3 formulations. Complete SUM release was obtained at 60 and 120sec with the F1 and F3 respectively. The SUM release from F1 is significantly higher when compared to F3 and the comparative release profiles are shown in Figure 2**.** Effect of solubilizing and or wetting agents on SUM release was also tested. Both the SLS and PVPK30 were added to the formulations at 0.04% levels. The cumulative percent of SUM released at the end of 10sec is 58.42 ± 0.61 for F2 (E5 with SLS) whereas, with F4 (E15 with SLS) 26.69 ± 0.54 percent. Complete SUM release was obtained at 40 and 60sec with F2 and F3 respectively. The SUM release from F2 is significantly higher when compared to F4 and also when compared to F1 and F3. The comparative release profiles are shown in Figure 2.

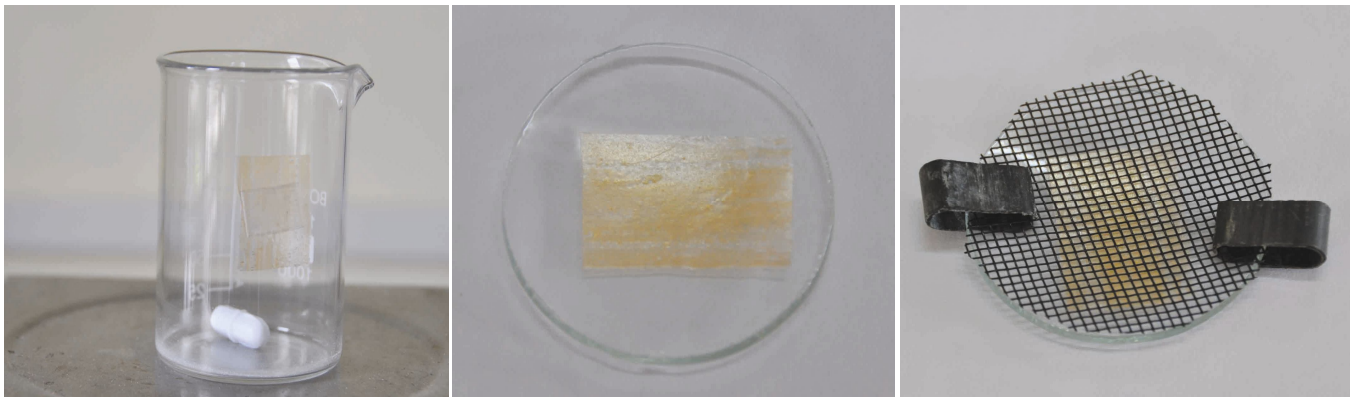

Fig. 1: Dissolution setups for Method I (beaker stirrer method) and Method II (Apparatus 5 method).

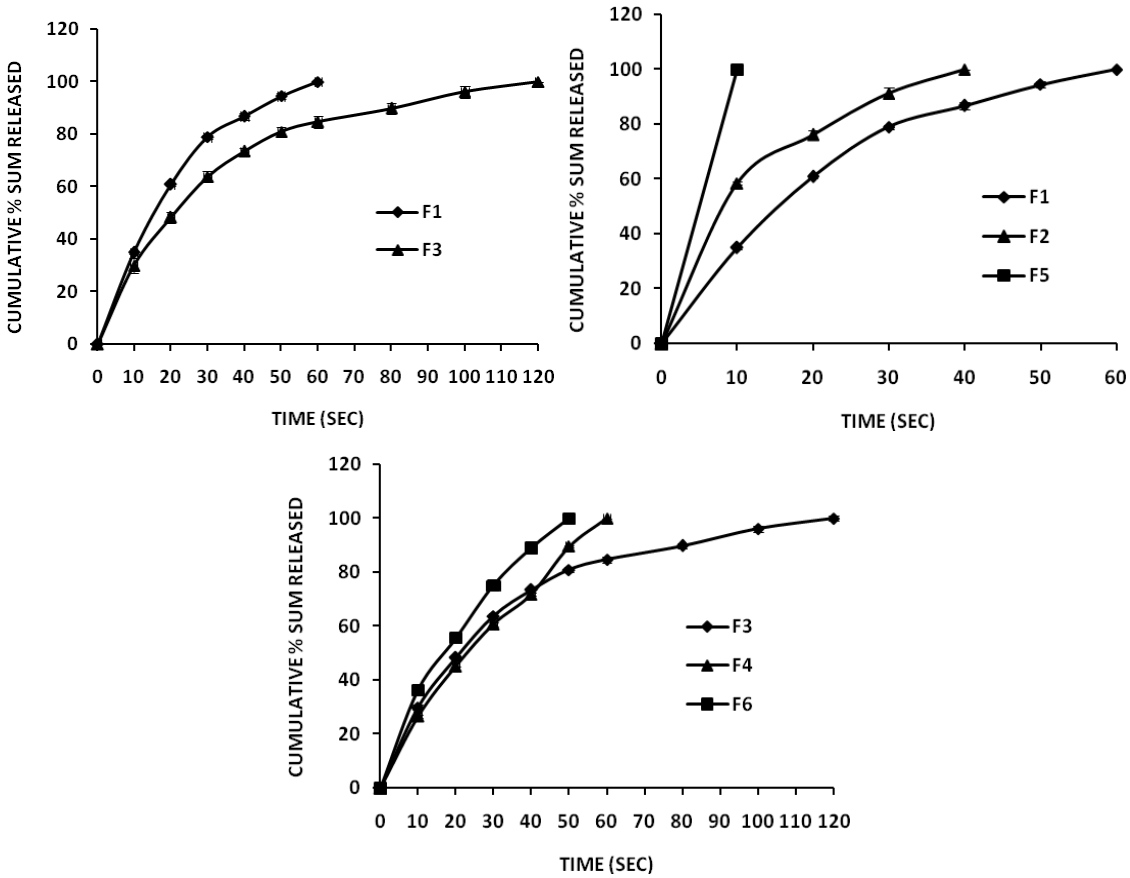

Fig. 2: Comparitive Dissolution Profiles of F1- F6 (Method 1).

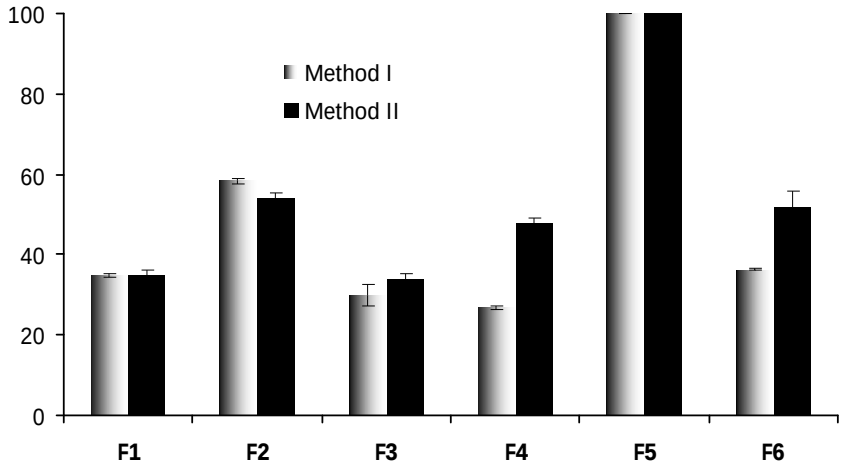

Fig. 3: Comparison of percent SUM released at 10sec with method I and II.

For F5 (E5 with PVPK30) at the end of 10sec complete dissolution of SUM was achieved whereas, with F6 (E15 with PVPK30) 36.35 ± 0.24 percent of SUM was released. The cumulative percents were significantly higher when compared to the formulations with SLS. In the case of F5 containing PVPK30 a complete SUM release was obtained within 10sec whereas and with F6 a complete SUM release was obtained at 50sec. The comparative release profiles are shown in Figure 2. Overall, the E5 formulations (F1, F2, and F5) with and without SLS and PVP gave superior dissolution properties when compared to E15 formulations (F3, F4, and F6). This could be due to the low viscosity of the HPMC E5 polymer when compared to E15 polymer. The formulations with PVP (F5 and F6) gave superior dissolution properties when compared to the SLS formulations (F2 and F4). The comparative release profiles are shown in Figure 2.

Dissolution studies were also carried out with type 5 dissolution apparatus where 600mL of dissolution medium was used (artificial saliva) for comparison. All the formulations followed similar dissolution behavior when compared to the Method I. For comparison the cumulative percent of SUM released at the end of 10sec (DP_{10}) by both dissolution methods were shown in Figure 3. The dissolution data was very well supported by the disintegration time data.

Drug Release Kinetics

The first order release rate constant 'k' (sec^{-1}) values for SUM MDFs calculated from Method I dissolution data were given in Table 4. When compared to the F1 the 'k' value was significantly higher for F2. The 'k' value for F4 is not significantly higher when compared to that of F3. Whereas, the 'k' values are significantly higher for HPMC E5 MDFs when compared to HPMC E15 MDFs. An 8.37 and 1.76 fold increase in 'k' values for F5 and F6 were obtained when compared to F1 and F3 MDFs. Based on the above results the MDF of formula F5 showing the highest dissolution rate and lowest *in vitro* disintegration rate is suitable for fast-dissolving dosage form.

CONCLUSION

The SUM MDFs were prepared using different film-forming materials showed satisfactory drug dissolution and acceptable physico-mechanical characteristics. Amongst 6 formulae, the film prepared using HPMC E5 and PVP K30 showed the highest dissolution rate, suitable *in vitro* disintegration time and satisfactory physico-mechanical properties.

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