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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS CONTAINING TASTE-MASKED MICROSPHERES OF DICLOFENAC SODIUM FOR SUSTAINED RELEASE

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Diclofenac sodium (DCS), a non-steroidal antiinflammatory drug used for posttraumatic pain and rheumatoid arthritis, has bitter taste. Thus formulating orally dissolving tablet containing taste-masked microspheres of diclofenac sodium is extremely advantageous and challenge. Taste-masked microsphers were prepared using Eudragit EPO (EEPO) in different ratios. The physicochemical properties of the prepared microsphers were evaluated. The prepared taste-masked microspheres were formulated in orally dissolving tablets (ODTs) using different superdisintegrants. The effect of superdisinitegrant on *in-vitro* release of drug was studied. The obtained data showed that the ratio of drug: polymer influenced both the microsphere size and the drug release from Eudragit EPO microspheres. Increasing this ratio resulted in increasing the size of microspheres and slowed the release of the drug in both 0.1 N HCl and phosphate buffer (pH 6.8). The orally dissolved tablets containing microsphere of a ratio 1: 4 drug to polymer exhibited acceptable hardness, friability, drug content and disintegration time 11 seconds. Moreover, the drug had sustained release rate from its-loaded orally dissolving tablets containing EEPo micropsheres. Orally dissolving tablets containing crosspovidone showed higher release as compared with other superdisintegrants. Furthermore, the orally dissolving tablets showed high degree of palatability in tested volunteers.

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Keywords: Diclofenac sodium. Eudragit EPPO. Microspheres. Orally dissolving tablets. In vitro release. Platabilty

1. Introduction

Design of an optimal formulation is required for administration of drugs having poor organoleptic properties to achieve acceptable degree of palatability. Regarding patient compliance, taste of oral formulations is very important especially in pediatric patients [1]. In recent decades, new dosage forms have been formulated by a variety of pharmaceutical researches. Most of these efforts have been focused on ease of medication [2]. Among the dosage forms developed to facilitate ease of medication, the orally dissolving tablets (ODTs), which are the most widely, used commercial products [3]. ODTs offer advantages of administration without water, ease of swallowing, rapid onset of action and convenience of dosing. When an ODT is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration.

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ODTs are desirable in case of local action in the mouth such as local anesthetic for toothaches, oral ulcers, cold sores or teething [4]. Also ODTs can be used to deliver sustained release multiparticulate system to patients, who cannot swallow intact sustained action tablets/capsules [5].

Diclofenac sodiumm, a phenylacetic acid derivative, is a potent non-steroidal analgesic and anti-inflammatory drug. Diclofenac sodium (DCS) is used for treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. DCS is practically insoluble in water but soluble in intestinal fluid [6]. Because of its short biological half-life (1-2 hours) and bitter taste, it is considered as an ideal candidate for its formulation as controlled ODTs delivery by preparation of taste-masked microsphere containing tablets. Thus, in the present study an attempt has been made to formulate ODTs containing taste-masked microsphers of diclofenac sodium for purposes of taste making and sustained release as well.

2. Materials and methods

2.1 Materials

Diclofenac sodium was purchased from Sigma-Aldrich Chemie Gmbh Munich, Germany. Microcrystalline cellulose (Avicel PH101) was purchased from Serva Feinbiochemica (Heidelberg, Germany). Spray dried mannitol (MannogemTM EZ), used as a filler for the orally disintegrating tablets, was kindly supplied by SPI, Grand Haven, USA. Croscarmellose sodium (CCS), Sodium starch glycolate (SSG) and Crospovidone (CPV) were kindely supplied by Riyadh Pharma, Riyadh, KSA. EEPO was purchased from Evonik Industries AG Pharma Polymers & Services, Darmstadt, Germany. Magnesium stearate was purchased from Riedel-de Haën, Seelze, Germany. Potassium dihydrogen orthophosphate, Sodium hydroxide, N-hexan, aceton, ethanol, and petroleum ether were purchased from Merck, Darmstadt, Germany. Light liquid paraffin was purchased from Winlab laboratory chemicals, UK. All other chemicals were of reagent grade and used without further purification.

2.2 Methods

Preparation of taste-masked microspheres

Solvent evaporation method [7] can be used for preparation of microsphers containing DCS. DCS was added to the solution of EEPO in acetone on a magnetic stirrer. The polymer drug solution obtained was injected into light liquid paraffin at a low stirring speed (200–600 rpm) of mechanical stirrer for about 3 h until all the acetone evaporated. N-Hexane/petroleum ether mixture (1:1) was added to the system for hardening of the microspheres and to accelerate settling. The formed microspheres were separated by decantation following filtration. The prepared microspheres were then washed with n-hexane and then dried in an oven maintained at 37°C for 24 hours. Various drug: polymer ratios were selected for the formulation of DCS loaded microspheres (Table 1).

Table 1: Composition of DCS microspheres

Batch No.	Diclofenac sodium (DCS) (mg)	Eudragit EPO (EEPO) (mg)
M_1	200	200
M_2	200	400
M_3	200	800

2.3 Characterization of Microspheres

Determination of % Encapsulation efficiency and % drug loading of DCS

DCS loaded microspheres (20 mg of each formula) were mixed with acetone-ethanol mixture (1:1) by vortex. Then, the mixture was sonicated in ultrasonic bath for 30 minutes. For extracting DCS, 10 ml of PBS was added to the mixture and mixed by vortex for 15 minutes. The organic solvent was removed by evaporation under vacuum. The remained aqueous dispersion was centrifuged at 12000 rpm for 45 minutes. The content of DCS in the supernatant was analyzed using HPLC mentioned below. Experiments were performed in triplicate. The % yield and % EE of DCS were calculated using the following two equations (Table 2).

$$\% DL = \frac{Weight\ of\ DCS\ in\ microspheres}{Weight\ of\ microspheres} * 100$$

$$\% EE = \frac{Actual\ drug\ loading}{Theoritical\ drug\ loading} * 100$$

Table 2: Palatability evaluation.

	Scale				After Effects
Effect	1	2	3	4	+
Taste	Bad	Acceptable	Good	Excellent	After taste
Mouth feel	Gritty	Acceptable	Good	Excellent	Numbness

2.4 Evaluation of flow properties of microspheres

The prepared microspheres were evaluated for flow properties including bulk density, tapped density, Carr's index, Hausner ratio and Angle of Repose (Table 3) [8].

Table 3: Evaluation parameters of microspheres

Batch No.	DCS:EEPO ratio	% DL ± S.D.*	% EE ± S.D.*
M_1	1:1	77.3 ± 0.83	64.03 ± 1.33
M_2	1:2	83.11 ± 0.79	71.32 ± 2.79
M_3	1:4	88.24 ± 0.48	80.43 ± 3.11

*Values are mean ± S.D., DSC, Diclofenac sodium and EEPO, Eudragit EPO

2.5 HPLC analysis

The amount of DCS was analyzed using HPLC system, which is composed of Waters HPLC system (Milford, MA, USA), equipped with a Dual Absorbance detector, a Binary HPLC pump, and a reversed-phase C18 column (4.6 ¥ 150 mm, Hypersil, Asheville, NC, USA). The HPLC system was monitored by Empower (Waters) software. The mobile phase was acetonitrile: water (60:40) and eluted at a flow rate of 1mL/min, injection volume, 20 µl and retention time (2.9 ± 0.2) min. Effluents were monitored at 279 nm.

2.6 Surface Morphology of prepared microspheres

The prepared DCS microspheres were morphologically examined by scanning electron microscopy (SEM) (Joel JSM 5400LV SEM, Japan) operated at 15kV. The samples were sputter coated with gold (SPI, sputter, USA) and images were then acquired using a scanning electron microscope.

2.7 Evaluation of flow properties

The prepared microspheres were evaluated for bulk density, tapped density, angle of repose, carr's index and hausner ratio (Table 4).

Table 4: Microsphere powder flowability

Batch No.	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of repose	Carr′s index	Hausner Ratio
M_1	0.62 ± 0.05	0.53 ± 0.06	35.98 ± 0.21	34.31 ± 0.45	1.11 ± 0.04
M_2	0.57 ± 0.11	0.52 ± 0.02	28.26 ± 0.42	31.23 ± 0.24	1.13 ± 0.03
M_3	0.56 ± 0.03	0.49 ± 0.27	21.33 ± 0.43	25.12 ± 0.36	1.01 ± 0.04

Values are mean ± SD (n=3)

2.8 Particle size measurements

The particle size of the prepared DCS microspheres was measured with a Malvern Mastersizer 2000® laser diffractometer using a dry sampling system (Scirocco 2000, Malvern Instruments, Malvern, UK) with a suitable standard operating procedure (SOP) (refractive index: 1.52, vibration feed rate: 25%, measurement time: 7 s, dispersive air pressure: 4 bar).

2.9Differential scanning calorimetry (DSC)

Thermal profile of pure DCS, EEPO and the prepared microspheres were investigated utilizing a differential scanning calorimetry (DSC-60, Shimadzu, Japan). Samples of (3-4 mg) were loaded in an aluminum pan and sealed with aluminum lids by a crimper. Each sample was then thermally scanned against an empty aluminum pan with lid covering range of 25-350 ^{o}C at heating rate of 10 ^{o}C/min under nitrogen purging at a rate of 40 ml/min. The thermal parameters of the scanned samples were obtained by using the TA-60WS thermal analysis software.

3.0 In vitro release study of microspheres

The *in vitro* release of DCS from microspheres (an amount equivalent to 50 mg of DCS) was carried out in a USP paddle type dissolution method (Apparatus II) in 900 ml of 0.1 N HCl and in phosphate buffer medium (pH 6.8) at 37±0.5ºC at a rotational speed of 50 rpm. At predetermined time intervals, 5 mL sample was withdrawn, filtered by 0.22 μ membrane filter and replaced with fresh medium in order to maintain the sink condition. The amounts of DCS released in dissolution media were determined by HPLC method as described above.

3.1. Preparation of taste-masked microspheres ODTs

Microspheres formula (M_3) that gave the best in vitro release results was selected for preparation of ODTs by direct compression technique. Avicel PH 101 was used as a directly compressible diluent. Mannitol was used as filler and also to impart cooling sensation in mouth. Croscarmellose sodium, Sodium starch glycolate and Crospovidone were used as superdisintegrants in a concentration of 5% of tablet weight. The corresponding amounts of DCS microspheres equivalent to 50 mg drug, avicel pH 101 and superdisintegrant (Table 5) were accurately weighed and mixed using Turbula mixer (Erweka, S2Y, Heusenstamm, Germany) for five minutes. Thereafter, the corresponding amount of mannitol was accurately weighed, added to the mixture and mixed for 10 min. Finally the amount of magnesium stearate was mixed with the powder in the turbula mixer for further 2 min. The powder was compressed into tablets weighing 200 mg using Korsh single punch machine with 9 mm shallow concave punches (Erweka, EKO, Germany).

Table 5: Composition of various DCS microspheres fast dissolving tablet formulations

Formula	Ingredients (mg)						
	Microsphere (DCS:EEPO 1:4)	MCC	Mannitol	CPV	SSG	CCS	Mg-stearate
T1	125	35.5	36.5	-	-	-	2
T2	125	35.5	36.5	10	-	-	2
T3	125	35.5	36.5	-	10	-	2
T4	125	35.5	36.5	-	-	10	2

Tablet weight 200 mg

3.2 Evaluation of ODTs

3.2.1 Hardness

Tablet hardness was determined with the Hardness Tester (Pharma test GmbH, Hainburg, Germany) for 10 tablets (with known weight and thickness) of each batch; the average hardness and standard deviation were reported (Table 6).

3.2.2 Tablet Friability

Friability of tablets was carried out using roche friabilator. Friability was evaluated from the percentage weight loss of 20 tablets tumbled in a Friabilator at 25 rpm for 4 minutes. The tablets were dedusted, and the loss in weight caused by fracture was recorded as the percentage weight loss. Friability should not more than 1% (Table 6).

% Friablity=100(1-W1/W2)

Where W1=Total weight of twenty tablets before friability
W2=Total weight of twenty tablets after friability

3.2.3 Tablet Disintegration

Disintegration of tablets was performed according to USP 36 [9] using disintegration tester (Electrolab, India). A minimum of 6 tablets of each product were tested. One tablet of each product was placed in each of the six tubes of the basket. Then the apparatus was operated using phosphate buffer pH 6.8 maintained at 37±2°C as a disintegration medium (Table 6).

3.2.4. Uniformity of dosage units

The uniformity of dosage units can be demonstrated either by content uniformity or weight variation according to USP 36 [9]. The content uniformity is based on the assay of the individual content of the drug substance in a number of individual dosage units to determine whether the individual content is within limits set. 10 tablets were taken and each tablet was assayed individually as stated in individual monograph. Individual tablets were placed in 50 ml volumetric flask and 1 ml of water was added and the flask was shaken till disintegration of the tablet occurs. Then 10 ml of ethanol was added and the flask was mechanically shaken for 30 minutes. The volume of the flask was completed to 50 ml with phosphate buffer pH 6.8. An aliquot was centrifuged at about 3000 rpm and 20 µl of the clear supernatant was injected to the chromatogram. Then, the amount of DCS was determined and the acceptance value was calculated (Table 6).

Table 6: Evaluation of ODTs

Formula	Hardness (Kp) ± SD	% Friability ± SD	Disintegration time (sec)* ± SD	Acceptance value
T_1	6.1 ± 0.91	0.85 ± 0.22	63 ± 2.21	5.7
T_2	5.2 ± 0.37	0.71 ± 0.44	19 ± 1.47	4.3
T_3	5.7 ± 0.29	0.62 ± 0.33	16 ± 1.89	5.9
T_4	5.4 ± 0.48	0.64 ± 0.46	11 ± 2.14	4.9

*Experiments were carried out in phosphate buffer (pH 6.8).

3.3 In vitro release study of ODTs

In vitro drug release was performed for ODTs according to the USP 36. A minimum of 6 tablets of each product were tested. The dissolution of DCS from tablets was monitored using an automated dissolution tester (LOGAN Instrument Corp, Somerset, NJ, USA) coupled to an automated sample collector (SP-100 peristaltic pump, Somerset, NJ, USA). The USP 34 (Apparatus II) paddle method was used at 100 rpm. The media used was phosphate buffer pH 6.8 maintained at 37± 0.5 °C. The amount of DCS released from each tablet (in the dissolution samples) was determined by HPLC method as previously mentioned.

3.4. Palatability studies

A taste panel consisting of 15 healthy male volunteers (25-45 years old) has tried a selected formula (T_4). The tested tablet was kept in mouth until disintegration, and then disgorged. The taste, its extent, after taste and other effects such as numbness if any were evaluated as shown in Table 7.

Table 7: Palatability evaluation of Formula T4

Volunteer No.	Taste	Mouth feel	After taste	Nubness
1	3	2	-	-
2	3	2	-	-
3	2	3	-	-
4	2	2	-	-
5	2	2	-	-
6	2	2	+	-
7	3	3	-	-
8	2	3	-	-
9	2	2	-	-
10	3	3	-	-
11	2	2	-	-
12	2	3	-	-
13	2	3	+	-
14	2	2	-	
15	3	2	-	

3.5. Statistical analysis

One way analysis of variance of means (ANOVA) was used for analysis of the difference in the release data of the prepared ODTs in phosphate buffer pH 6.8 using Microsoft 2010 excel package and confidence level was set at $p < 0.05$ (Table 8).

Table 8: Statistical analysis (One way ANOVA)

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	1988.771068	3	662.924	2.06118	0.132073	3.008787
Within Groups	7718.960299	24	321.623			
Total	9707.731367	27				

4. Results and discussion

4.1. Evaluation of microspheres

Microspheres containing different ratios of drug and polymer were prepared by solvent evaporation method.

4.1.1. Determination of % Encapsulation efficiency and % drug loading of DCS

Percentage entrapment efficiency and drug loading were determined for the prepared taste masked DCS microspheres (Table 3). Percentage entrapment efficiency was 64.03 ± 1.33, 71.32 ± 2.79 and to 80.43 ± 3.11 for the batches M_1, M_2 and M_3 respectively. Percentage drug loading was 77.3 ± 0.83, 83.11 ± 0.79 and to 88.24 ± 0.48 for the batches M_1, M_2 and M_3 respectively. From these results it was found that as the polymer weight ratio in the microspheres increases, % DL and % EE were found to be increased. This could be attributed to increased microsphere size by increasing polymer weight ratio [10]**.**

4.1.2. Differential scanning calorimetry

The DSC thermograms of pure DCS, pure EEPO and DCS loaded microspheres D_1, D_2 and D_3 are depicted in figure 1. The DSC thermogram of DCS shows an exothermic peak at 285.05 ºC followed by an endothermic peak at 292.97 ºC due to decomposition. From Fig. 1, it was found that the endothermic peak of DCS in the DCS loaded EEPO microsphere complex was shifted to lower temperatures of 259 ºC for the batch M_1, 253 ºC for the batch M_2 and 255 ºC for the batch M_3. This could be attributed to formation of a complex between the drug and the polymer [11]. Increasing the polymer weight ratio (M_3) resulted in shifting and broadening in DCS endothermic peak [12].

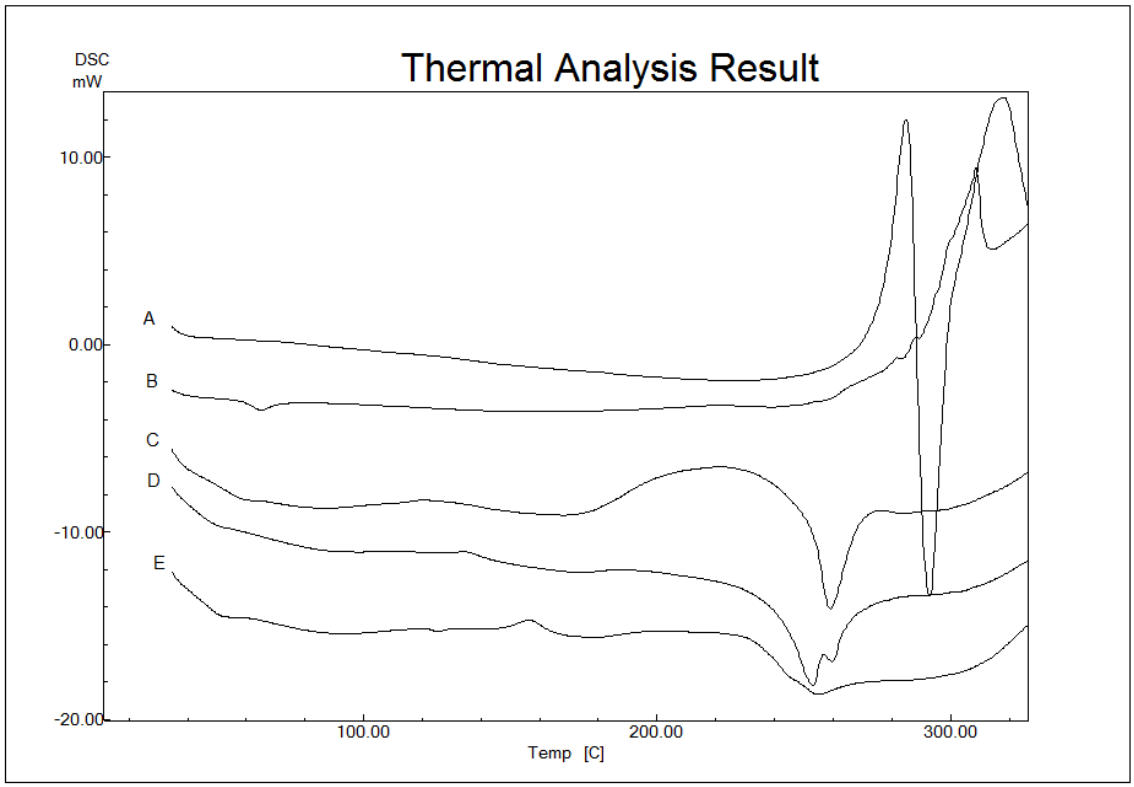

Fig. 1. DSC of pure DCS (A), pure EEPO (B), Drug-loaded microspheres M_1(C), M_2 (D) and M_3 (E).

4.1.3. Microspheres morphology

Fig. 2 exhibited the SEM of the prepared microspheres with different EEPO ratios. It was found that the prepared microspheres have spherical shapes but with different surface characteristics. The microspheres of batch M_1 have rough surface (Figure 1A). Microsphere of batch M_2 have smoother surface (Figure 1B), while the surface of batch M_3 microspheres is very smooth (Figure 1C).

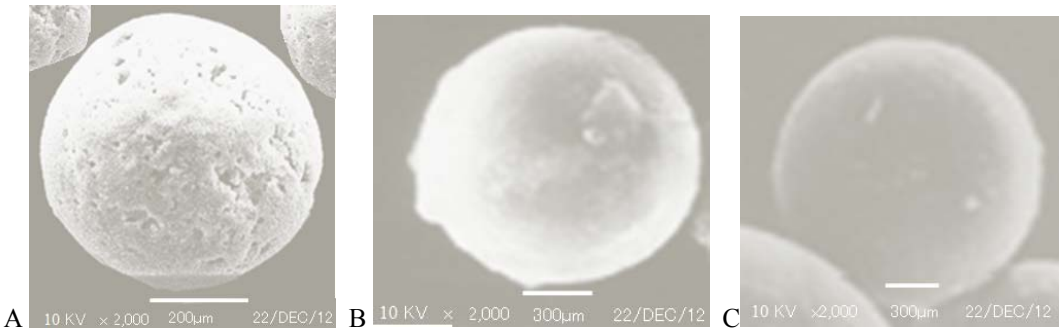

Fig. 2. Scanning electron micrograph of diclofenac sodium microspheres prepared with different ratio of Eudragit EPO; A = 1:1 ratio Eudragit, B = 1:2 ratio Eudragit. C=1:4 ratio Eudragit.

4.1.4. Evaluation of microspheres flowability

The prepared microspheres were evaluated for bulk density, tapped density, angle of repose, carr's index and hausner ratio. From the results of powder flow properties (Table 4), it was found that batches M_2 and M_3 have excellent flowability and batch M_1 has good flowability.

4.1.5. Measurement of microspheres particle size

Size distribution and average particle size of the prepared microspheres was measured with a Malvern Mastersizer 2000® laser diffractometer. The mean diameter of the prepared batches M_1, M_2 and M_3 microspheres was 463.086 µm, 557.066 µm and 627.599 µm respectively (Fig. 3a-c). This indicated that the particle size of the microspheres was increased by increasing the ratio of EEPO and this could be attributed to fusion between microparticles producing larger microparticles as the ratio of EEPO increased [13-14].

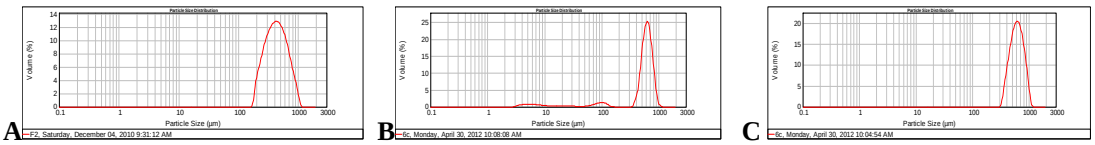

Fig. 3. particle size distribution of the prepared microspheres, A: M_1, B: M_2, C: M_3

4.2. In vitro release study of microspheres

Fig. 4 shows the in vitro release profiles of the taste-masked microspheres in 0.1 N HCl at 37 ºC. Although EEPO is soluble in acidic pH up to pH 5, It was found that the drug released is very slow for all batches M_1-M_3 up to 2 hours and this could be attributed to that DCS, the weakly acidic drug (pKa=4.0), is almost insoluble at acidic pH of the stomach [15]. The release of the drug was found to be decreased with increase EEPO ratio to the drug. This may be due to presence of small amount of drug close to the surface and the amount of the uncoated drug decreases with higher polymer concentration [16]. Also increasing microsphere size by increasing polymer weight ratio will increase the coat thickness leading to slow DCS release [17].

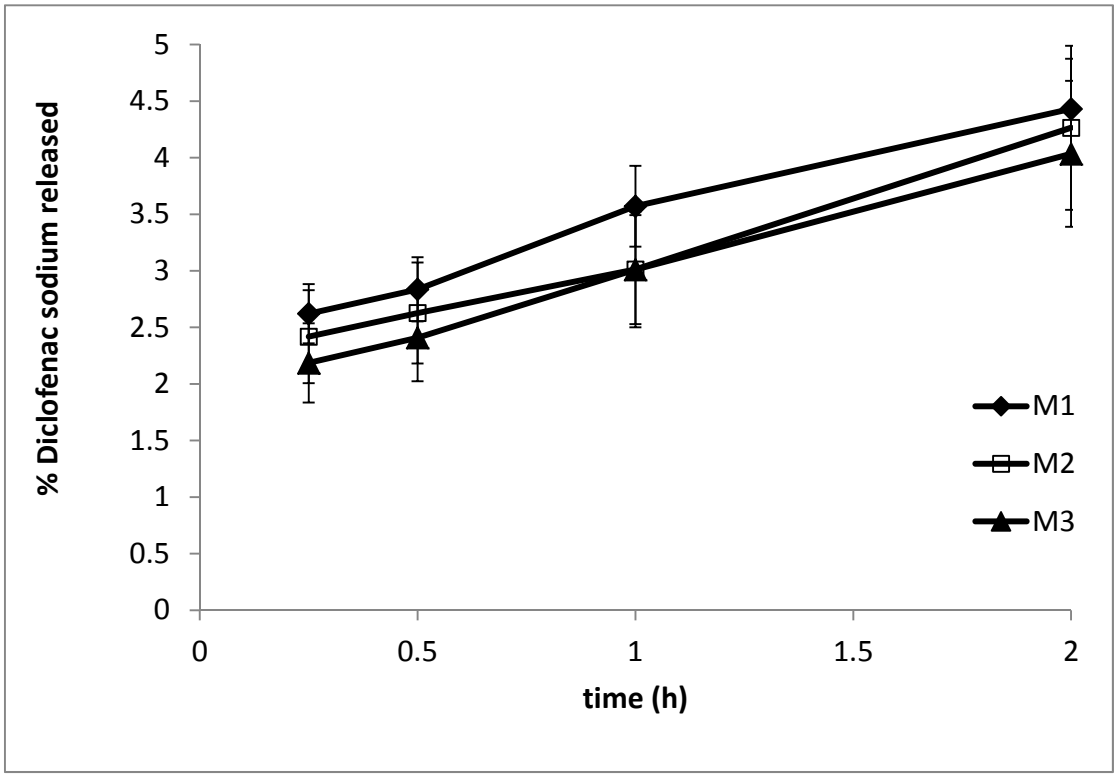

Fig. 4: Dissolution profiles of DCS taste-masked microspheres in 0.1 N HCl (pH 1.2). Each value represents an average of three determinations. (Mean ± SD, n = 3).

Fig. 5 illustrates the in vitro release profiles of the taste-masked microspheres in phosphate buffer pH 6.8 at 37 ºC. The data clearly show that drug release form all microspheres batches exhibits sustained release characteristics. This could be due to the fact that EEPO is insoluble in media with a pH greater than 5 but it becomes swellable and permeable allowing the slow release of DCS [18]. It was found that increasing the ratio of the polymer lead to decrease the drug release. This may be probably due to that the swelling and permeability nature of EEPO was decreased by increasing the polymer ratio [19].

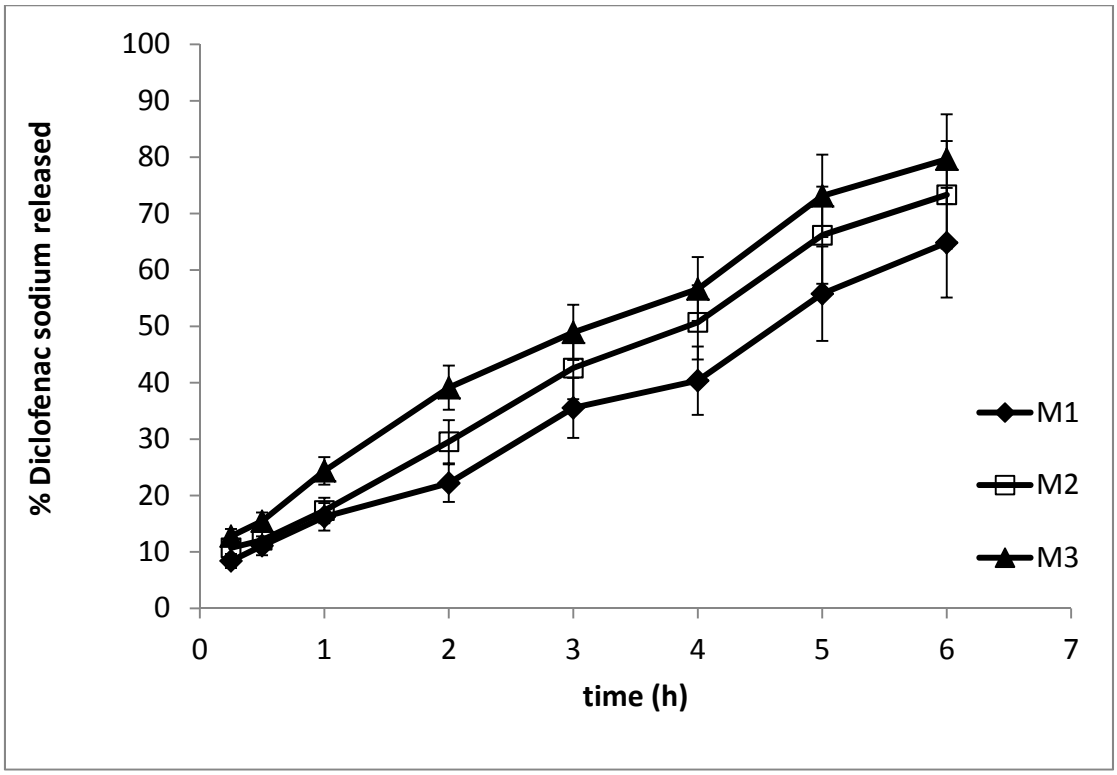

Fig. 5: Dissolution profiles of DCS taste-masked microspheres in phosphate buffer at pH 6.8. Each value represents an average of three determinations. (Mean ± SD, n = 3).

4.3. Evaluation of the prepared ODTs

4.3.1. Tablet hardness and friability

The results of hardness friability test of the prepared tablets are depicted in Table 6. The harness for all tablets was in the range 5.2 to 6.1 kp. According to the specification outlined in USP 36 [9], the friability value of tablets was less than 1%. All the prepared tablets passed this friability specification.

4.3.2. Uniformity of dosage units

The content uniformity of DCS tablets was performed and the acceptance value was calculated according to USP 36 [9]. It was found that the acceptance value for all formulae was less than 15 (The maximum allowed acceptance value, L1) as shown in Table 6.

4.3.3. Tablet disintegration

The mean disintegration times of the ODTs are shown in Table 6 and Fig. 6. T_1 Formula, which contains no superdisintegrant, showed the complete disintegration in 63 seconds. While formulae T_2-T_4 which contain superdisintegrants exhibit complete disintegration less than 20 seconds.

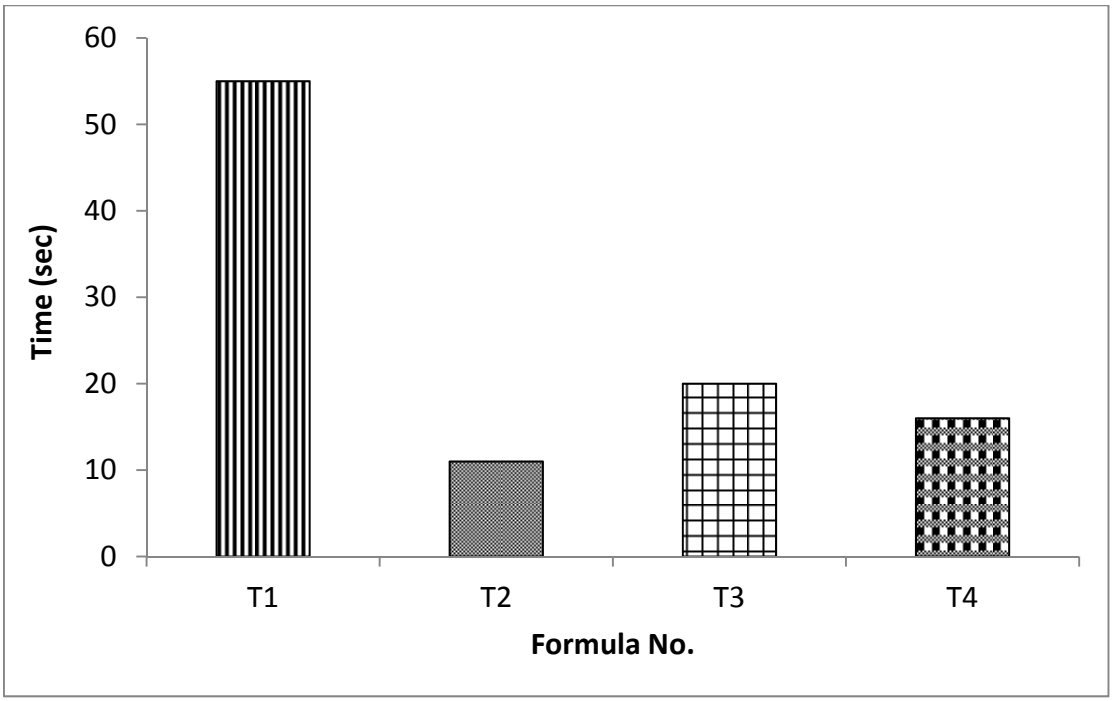

Fig. 6: In-vitro disintegration time of all formulations of DCS OTDs in phosphate buffer at pH 6.8

4.3.4. In vitro release of DCS ODTs

The release profiles of DCS from the prepared ODTs in phosphate buffer of pH 6.8 are shown in Fig. 7. From this figure, it was observed that all the formulations showed a gradient and sustained increase in the drug release. Moreover, it is obvious from Fig. 7 that, the release rate of the DCS from ODTs in phosphate buffer was slow compared to that from untabletted microspheres, where 39.97, 55.431, 60.962 and 68.893 % of the loaded drug were released after 6 hours from T_1, T_2, T_3 and T_4 formulae respectively. This may be due to the formation of a hydrophobic tortuous matrix during compression of the microsphere [20]. Regarding the effect of the type of superdisintegrant on DCS release from ODTs, it was found that the drug release was in the following order $T_4 > T_3 > T_2 > T_1$ (Fig. 7).This could be attribute to rapid swelling and disintegration of tablets containing CCS (T_4). While tablets prepared with SSG, disintegrate by rapid uptake of water followed by rapid and enormous swelling but more slowly due to formation of viscous layer. On the other hand tablets containing CPV show high capillary activity and pronounced hydration with a little tendency to gel formation and disintegrate rapidly into larger masses [21-22].

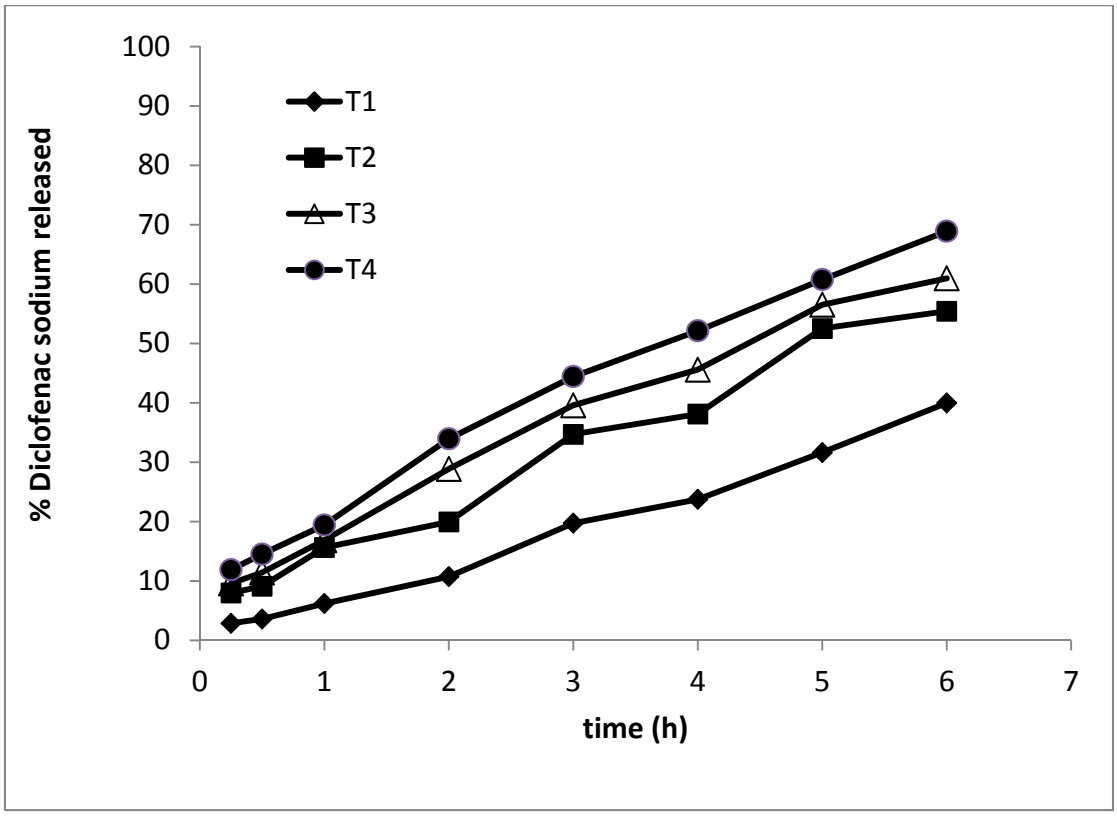

Fig. 7: Release profiles of DCS taste-masked ODTs in phosphate buffer at pH 6.8. Each value represents an average of three determinations.

4.4. Palatability Evaluation

Table 7 shows the results of palatability test. Taste evaluation results show that 66 % of response of the volunteers was acceptable and 34% showed good response. Only two volunteers out of fifteen complained a mild bitter after taste. Mouth feel results show that the response of 60% of the volunteers was acceptable while 40% showed good response with no complain of numbness. These results indicate that the prepared ODTs have acceptable palatability.

4.5. Statistical Analysis

The differences in the release of the formulations were done by one way analysis of variance of means (ANOVA). All the formulations were found to be not significantly different ($p > 0.001$).Result was shown in Table 8.

5. Conclusion

Formulation of DCs-loaded EEPO microspheres slowed the drug release rate, especially in acidic medium, in which less than 4.5% was released within two hours. IN addition, formulation of DCS ODTs containing drug loaded EEPO microspheres improved drug taste. Thus, formulation DCS EEPO microspheres incorporated in ODTs could enhance patient palatability, control drug release rate and could be considered as enteric coated delivery ton protect stomach from the acidic drug

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