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RESEARCH ARTICLE

Formulation and Evaluation of Release-Retardant Matrix Tablets of Diclofenac Sodium

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Formulation and Evaluation of Release-Retardant Matrix Tablets of Diclofenac Sodium
Summary

The objective of the present study was to develop release-retardant matrix tablets of diclofenac sodium by wet granulation technique using hydroxypropylmethylcellulose, sodium carboxymethylcellulose, sodium alginate and cetostearyl alcohol. Before tablet preparation, the granules were evaluated for angle of repose, bulk density, compressibility index and drug content. All the granulations showed satisfactory flow properties, compressibility and drug content. The tablets were evaluated for thickness, diameter, diameter/height ratio, hardness, weight variation, drug content, and in vitro drug release. The dissolution data was further characterized by model-independent parameters such as time to release 25 and 90% drug (t25% and t90% respectively), dissolution efficiency at 720 min (DE_{720}), and mean dissolution time (MDT). The tablet formulations showed acceptable pharmacotechnical properties and complied with pharmacopeial specifications for tested parameters. All the formulations showed extended drug release up to 12 h. However, the formulation prepared with drug: hydroxypropylmethylcellulose (1:4) using ethanol as granulating agent (F10) extended the drug release up to 24 h with initial burst effect, and was further modified using hydrophobic granulating agent ethyl cellulose. F11 significantly reduced the burst release, extended the drug release up to 24 h followed by zero order kinetics ($r^2 = 0.9872$) and emerged as the most successful tablet formulation.

Key Words: *Diclofenac sodium, matrix tablet, sustained release, wet granulation, in vitro dissolution, model-dependent parameters, model-independent parameters.*
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Diklofenak Sodyumun Salım-Geciktirici Matriks Tabletletlerinin Formülasyonu ve Değerlendirilmesi
Özet

Bu çalışmanın amacı, setostearil alkol, sodyum aljinat, sodyum karboksimetilselüloz, ve hidroksipropilmetilselüloz kullanarak yaş granülasyon tekniği ile diklofenak sodyumun salım-geciktirici matriks tabletlerinin geliştirilmesidir. Tablet hazırlanmasından önce, granüleler, yığın açısı, yığın dansitesi, basılabilirlik indeksi, ve ilaç içeriği açısından değerlendirilmiştir. Bütün granüleler uygun ilaç içeriği , basılabilirlik ve akış özellikleri göstermiştir. Tabletler, kalınlık, çap, çap/kalınlık oranı, sertlik, ağırlık değişkenliği, ilaç içeriği ve in vitro salım açısından değerlendirilmiştir. Salım sonuçları ayrıca, ortalama salım zamanı (MDT), 720. dakikadaki salım etkinliği (DE_{720}), ilacın %25 ve %90'ının salımı için gerekli süre (t%25 ve t%90) gibi model-bağımsız parametreler açısından da karakterize edilmiştir. Tablet formülasyonları , test edilen parametreler yönünden Farmakope spesifikasyonları ile uyumlu ve kabul edilebilir teknolojik özellikler göstermiştir. Bütün formülasyonlar 12 saate kadar uzatılmış salım göstermiştir. Bununla birlikte, granülasyon maddesi olarak alkol kullanılan (F10) ve ilaç:hidroksipropilmetilselüloz (1:4) ile hazırlanan formülasyonda başlangıç patlama etkisi ile 24 saate kadar salım uzatılmış ve hidrofobik granülasyon maddesi olarak etil selüloz kullanılarak ayrıca değişim yapılmıştır. F11'in, önemli derecede patlama etkisini azalttığı , 0 derece kinetiği (r^2=0.9872) ile uyumlu olarak ilaç salımını 24 saate kadar uzattığı ve en başarılı tablet formülasyonu olduğu bulunmuştur.

Anahtar kelimeler: *Diklofenak sodyum, matriks tablet, sürekli salım, yaş granülasyon, in vitro çözünme, model-bağımlı parametreler, model- bağımsız parametreler*

INTRODUCTION

Diclofenac sodium (DS) is a nonsteroidal antiinflammatory drug (NSAID) frequently prescribed for rheumatoid arthritis and osteoarthritis. DS has a short half-life (1-2 h) with usual oral dosage regimen of 25 to 75 mg 2 to 4 times a day[1]. To reduce the frequency of administration and to improve patient compliance, development of a prolonged-release oral formulation of DS is desirable. The matrix system is the most

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common method of modulating the drug release, because of its flexibility. Hydrophilic polymer matrix systems are widely used in oral-controlled drug delivery to obtain a desirable release profile, cost-effectiveness and broad regulatory acceptance. Hence, in the present work, an attempt has been made to develop a release-retardant sustained-release matrix tablet of DS using hydrophilic matrix materials like hydroxypropylmethylcellulose (HPMC), sodium alginate (NaAlg) and sodium carboxymethylcellulose (NaCMC) along with hydrophobic material cetostearyl alcohol in different combinations.

MATERIALS and METHODS

Diclofenac sodium (DS) was a generous gift from Emcure Pharmaceutical Limited, Pune, India. NaCMC 1500 cp (mol. wt. 90000-700000) and cetostearyl alcohol were purchased from CDH, Delhi; HPMC E 15 LV 15000 mPa s (mol wt. 10000-150000) was from Titan Biotech, Bhiwadi; NaAlg 2000 cS and magnesium stearate were from SD Fine Chemicals, Mumbai; spray dried lactose was from Merck India Limited; and disodium hydrogen phosphate and sodium hydroxide were from Rankem Fine Chemicals, Delhi. Double distilled water was used throughout the studies.

Preparation of granules

Granules prepar ed by embedding the drug in cetostearyl alcohol with or without hydrophilic polymers

The granulations for tablet formulations were prepared by embedding the drug in cetostearyl alcohol with (F1 to F4) or without (F5) hydrophilic polymers. Compositions of formulations are shown in Table 1. Each batch was comprised of 25 g of granules. Spray dried lactose and DS (initially 100 mg in F1 and F3 and 25 mg in F2 and F4) were added to melted cetostearyl alcohol at 60 °C and stirred until drug was uniformly dispersed. HPMC or NaCMC was mixed with talc and 75 mg of DS (F2 and F4) and then partially hydrated using three parts of water for each part of polymer. The cetostearyl- embedded granules were mixed with the pastes of cellulose polymers (HPMC or NaCMC) and passed through sieve no. 22 (710 μ) and dried in hot air oven at 40 °C for 30 min. The granules were lubricated with magnesium stearate[2].

Granules prepared by aqueous wet granulation

The drug and the corresponding quantities of HPMC, Na Alg and NaCMC (F6 to F10) were mixed in a double cone mixer at 90 rpm for 15 min. A sufficient volume of water as granulating agent was added slowly. After sufficient cohesiveness was obtained, the mass was sieved through sieve no. 22. The granules were dried in hot air oven at 40 °C for 30 min, and lubricated with magnesium stearate[3].

Granules prepared by non-aqueous wet granulation

Formulation F11 was prepared by non-aqueous granulation technique. Required quantities of drug and

Table 1. Composition of tablet preparation

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Diclofenac sodium	100	100	100	100	100	100	100	100	100	100	100
Cetostearyl alcohol	90	90	90	90	90	---	---	---	---	---	---
HPMC	30	30	---	---	---	---	---	50	100	400	400
NaAlg	---	---	---	---	---	---	400	350	300	---	---
NaCMC	---	---	30	30	---	400	---	---	---	---	---
Ethyl cellulose (4% w / v)	---	---	---	---	---	---	---	---	---	---	8
Talc	90	90	90	90	90	---	---	---	---	---	---
Spray dried lactose	205	205	205	205	215	---	---	---	---	---	---
Magnesium stearate (% w / w)	2	2	2	2	2	2	2	2	2	2	2
Water (ml)	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.2	---
Ethanol (ml)	---	---	---	---	---	---	---	---	---	---	0.2

HPMC: Hydroxypropylmethylcellulose. NaAlg: Sodium alginate. NaCMC: Sodium carboxymethylcellulose.

HPMC were blended in a double cone mixer at 90 rpm for 15 min, and a sufficient volume of granulating agent (ethanolic solution of ethyl cellulose [EC] 4% w / v) was added slowly. After sufficient cohesiveness was obtained, the mass was sieved through sieve no. 22. The granules were dried in hot air oven at 40 °C for 12 h and thereafter kept in a desiccator for 12 h at room temperature. The granulation was lubricated with magnesium stearate[4].

Evaluation of granules

Determination of bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 20 g of powder from each formula, previously lightly shaken to break any agglomerates, was introduced into a 50 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 0.5-1.5 cm at 5 sec intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated[5].

Determination of angle of repose, compressibility index and Hausner's ratio

The angle of repose of granules was determined by the fixed height funnel method. The accurately weighed 20 g granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were then allowed to flow through the funnel freely onto the surface and the diameter of the powder cone was measured. The angle of repose, compressibility index and Hausner's ratio were determined using the formulas:

Angle of repose: $\tan \ominus = h / r$ where h = height of the pile, r = radius of the pile

Compressibility index (%) = (Tapped – Poured density) / Tapped density

Hausner's ratio = (Tapped density / Poured density) X 100

Determination of particle size

A sieve stack usually comprises six sieves with an aperture progression. Powder was loaded in the coarsest sieve of the assembled stack and nest was subjected to mechanical vibration. After 10 min, the particles were considered to be retained on the sieve mesh; the powder retained in each sieve was weighed and the respective parameters were calculated.

Preparation and evaluation of tablets

All the granulations were subjected to tablet preparation using a hand operated single punch tablet machine (HICON, INDIA).

Determination of diameter/height ratio (D/H ratio)

The height of tablets was determined using vernier calipers. From each batch, 20 tablets were used and average values were calculated. For each formulation, the hardness of six tablets was determined using the Monsanto hardness tester and average values were calculated.

Determination of uniformity of weight and assay

To determine uniformity of weight, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to official method [7]. For assay, 20 tablets were weighed and finely powdered. A quantity of powdered tablets equivalent to 50 mg of DS was shaken with 60 ml of methanol in a 200 ml volumetric flask and diluted to volume with the same solvent. From this, 5 ml of solution was filtered (Whatman No. 1 filter paper), diluted up to 100 ml with methanol and measured at 284.5 nm. The content of DS in each formulation was determined using a suitably constructed calibration curve.

In vitro dissolution study and analysis of dissolution data

In vitro dissolution tests were carried out using USP XXVII dissolution rate test apparatus Type I (basket type). The dissolution medium was 0.1 N HCl (pH 1.20 ± 0.02) for 2 h followed by phosphate buffer pH 6.80 ± 0.02 for 10 h (900 ml, 37 °C) at 75 rpm[8]. The dissolution medium from pH 1.2 HCl to pH 6.8 phosphate buffer during dissolution test was changed by adding 250 ml of 0.20 M disodium hydrogen phosphate previously equilibrated at 37 °C in to the dissolution vessel containing 750 ml of pH 1.2 HCl and

adjusted with 2 N hydrochloric acid or 2 N sodium hydroxide within 5 min of the completion of acid stage. Samples were withdrawn at predetermined time intervals and replaced with freshly prepared dissolution medium. The samples were filtered, suitably diluted and analyzed spectrophotometrically at 276 nm (Shimadzu 1700). Dissolution tests were performed in triplicate. To elucidate the mechanism of drug release from these formulations, the data were fitted to first order (log cumulative percentage drug remaining vs time), Higuchi matrix (cumulative percentage drug released vs square root of time), Korsmeyer-Peppas (log cumulative percentage drug released vs log time) and zero order (cumulative percentage drug released vs time) models[9]. The model-independent parameters such as time to release 25 and 90% drug ($t_{25\%}$, $t_{90\%}$), dissolution efficiency at 720 min (DE_{720},) and mean dissolution time (MDT) were also computed using PCP Disso v2.08 software. DE is defined as the area under the dissolution time curve up to a certain time, t, expressed as the percentage of the area of the rectangle described by 100% dissolution in the same time. The DE is a model-independent parameter that can have a range of values depending on the time interval chosen. In any case, a constant time interval should be chosen for the mathematical comparison of dissolution profiles. In the present study, DE_{720} values were calculated from the dissolution data and used for comparison.

$$DE = \frac{\text{Shaded area}}{\text{Rectangle area}} \times 100$$

MDT is the first statistical moment of the cumulative dissolution process and is estimated from the cumulative mass dissolved vs time profile using equation

$$MDT = \frac{\sum_{i=1}^{n} t_{mid}\, \Delta X_d}{\sum_{i=1}^{n} \Delta X_d}$$

where i is the sample number, n is the total number of sample times, tmid is the time at the midpoint between i and i–1, and ΔXd is the additional mass of drug dissolved between I and i–1.

RESULTS and DISCUSSION

Different formulations containing DS with NaAlg, HPMC, and NaCMC alone or in combinations were prepared. The combination of DS and HPMC (1:4) showed better results than other combinations and ratios of polymers. HPMC is mixed alkyl hydroalkylcellulose ether containing methoxyl and hydroxypropyl groups, and its hydration rate depends on the nature of these substituents. Specifically, the hydration rate of HPMC increases with an increase in the hydroxypropyl content. The solubility of HPMC is pH independent[10]. In the present study, HPMC was used in combination of 4% w / v ethanolic solution of EC as a granulating agent because it forms a strong viscous gel on contact with aqueous media, which is useful in controlled delivery of DS. Granulation is the key process in the production of tablet dosage form involving the controlled release of a drug from matrix-type particles. A granule is an aggregation of component particle that is held together by the presence of bonds of finite strength. Physical properties of granules such as shape, hardness, thickness, diameter and D / H ratio can significantly affect the rate of dissolution of a drug contained in a heterogeneous formulation. The granules of different formulations were evaluated for angle of repose, bulk density, compressibility index, Hausner's ratio, and surface mean diameter (Table 2). The results of angle of repose ranged from 16.29 ± 0.04 to 21.57 ± 0.04, indicating excellent flow property of the granules. The bulk density largely depends on particle shape. As the particle becomes more spherical in shape, bulk density is increased. In addition, as granule size increases, bulk density decreases. The smaller granules are able to form close, more intimate packing than larger granules. The results of bulk density (g / cc) ranged from 0.256 ± 0.06 to 0.689 ± 0.01. Compressibility index values between 11.29 ± 0.01 and 23.52 ± 0.003 and Hausner's ratio ranging from 1.16 ± 0.02 to 1.28 ± 0.03 suggested good to excellent flow properties. Arithmetic mean diameter (μ) of granules when determined by the method of sieving ranged from 65.83 ± 0.48 to 197.98 ± 0.54 for formulations F1 to F11.

All the formulations showed uniform thickness, di-

Table 2. Micrometric study of granules prepared for F1 to F11

Formulations	Angle of repose* (°) ± SD	Bulk density* (g/cc) ± SD	Hausner's ratio* ± SD	Carr's index* (%) ± SD	Arithmetic mean diameter* (μ) ± SD
F1	17.26 ± 0.02	0.476 ± 0.03	1.19 ± 0.04	16.00 ± 0.01	89.72 ± 0.47
F2	17.02 ± 0.0	0.477 ± 0.04	1.16 ± 0.02	14.28 ± 0.02	146.22 ± 0.64
F3	18.25 ± 0.04	0.479 ± 0.06	1.23 ± 0.02	19.23 ± 0.04	121.68 ± 0.50
F4	17.52 ± 0.06	0.487 ± 0.05	1.23 ± 0.06	19.60 ± 0.06	151.29 ± 0.39
F5	16.58 ± 0.03	0.526 ± 0.02	1.13 ± 0.02	18.75 ± 0.05	65.83 ± 0.48
F6	21.57 ± 0.04	0.512 ± 0.03	1.30 ± 0.02	23.52 ± 0.03	163.56 ± 0.52
F7	16.29 ± 0.04	0.256 ± 0.01	1.27 ± 0.06	21.62 ± 0.02	119.8 ± 0.72
F8	18.75 ± 0.05	0.625 ± 0.03	1.21 ± 0.05	11.29 ± 0.01	155.33 ± 0.54
F9	17.46 ± 0.06	0.571 ± 0.04	1.28 ± 0.04	22.22 ± 0.04	108.56 ± 0.68
F10	18.71 ± 0.07	0.277 ± 0.06	1.27 ± 0.03	21.73 ± 0.03	82.97 ± 0.48
F11	18.51 ± 0.01	0.689 ± 0.06	1.23 ± 0.03	11.62 ± 0.02	197.98 ± 0.54

* Study was performed on 3 replicates.

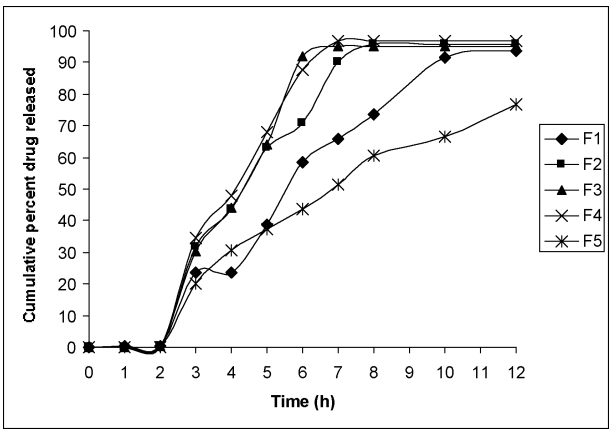

Figure 1. Comparative drug release profiles of tablet formulations. F1 and F3 are with 100 mg drug loaded in cetostearyl alcohol in combination with HPMC and NaCMC. F2 and F4 are with 25 mg drug loaded in cetostearyl alcohol and 75 mg drug loaded in HPMC and NaCMC, respectively. F5 is with 100 mg drug loaded in cetostearyl alcohol without hydrophilic polymer.

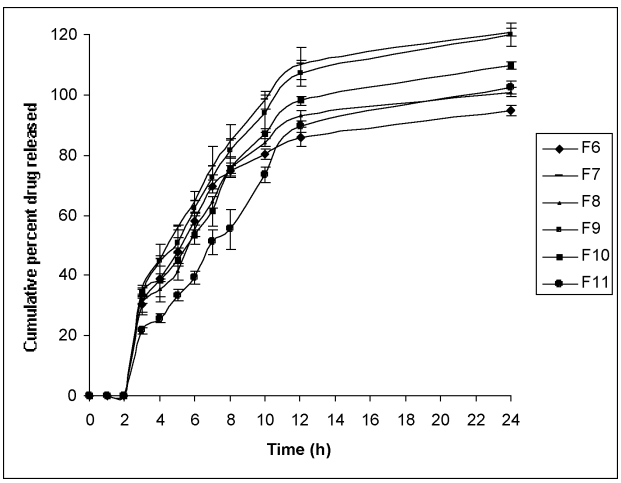

Figure 2. Comparative drug release profiles of tablet formulations F6 to F11.

from 7.12 ± 0.02 to 7.15 ± 0.05 mm and diameter and D / H ratio ranged from 10.04 ± 0.05 to 10.06 ± 0.04 mm and 1.40 to 1.41, respectively. F11 showed a comparatively higher hardness value of 7.5 ± 0.02 kg / sq.cm. This could be due to presence of EC, which is generally responsible for more hardness of the tablet, whereas low hardness value observed with formulation F6 may be due to presence of NaCMC, which generally has a disintegrating property. The hardness of all tablet formulations ranged from 3.00 ± 0.06 to 7.50 ± 0.02 kg / sq.cm (Table 3).

percentage deviation for the tablets of more than 250 mg is average weight ± 5%. The average percentage deviation of all tablet formulations was found to be within the official limit and hence all formulations complied with test for uniformity of weight as per Indian Pharmacopoeia. Good uniformity in drug content was found among different formulations of tablets and ranged from 96.4 ± 0.4 to 102.1 ± 0.3 (Table 4).

dissolution studies seemed to be influenced by very poor solubility of the drug in acidic solution as evi denced by almost negligible drug release within 2 h. However, the drug dissolution in buffer stage from all the formulations was relatively more rapid due to the acidic nature of DS. The results of dissolution studies indicated that F1, F2, F3 and F4 released 23.70%, 31.76%, 30.45% and 34.67% of DS at the end

Table 3. Nonofficial tests on formulated tablets

Formulation	Thickness* (mm) ± SD	Diameter* (mm) ± SD	Diameter/height ratio*	Hardness# (kg/cm2) ± SD
F1	7.12 ± 0.02	10.06 ± 0.03	1.40	4.5 ± 0.03
F2	7.14 ± 0.02	10.05 ± 0.02	1.40	3.5 ± 0.04
F3	7.15 ± 0.03	10.06 ± 0.04	1.41	4.0 ± 0.05
F4	7.13 ± 0.03	10.06 ± 0.03	1.40	4.0 ± 0.04
F5	7.14 ± 0.02	10.06 ± 0.02	1.40	4.5 ± 0.06
F6	7.15 ± 0.05	10.06 ± 0.03	1.41	3.0 ± 0.06
F7	7.13 ± 0.04	10.04 ± 0.05	1.40	3.4 ± 0.04
F8	7.14 ± 0.05	10.06 ± 0.04	1.40	3.8 ± 0.05
F9	7.14 ± 0.02	10.06 ± 0.03	1.41	4.9 ± 0.03
F10	7.15 ± 0.03	10.06 ± 0.05	1.40	5.5 ± 0.04
F11	7.15 ± 0.02	10.06 ± 0.02	1.41	7.5 ± 0.02

* Study was performed on 20 replicates. # Study was performed on 6 replicates.

Table 4. Official tests on formulated diclofenac sodium sustained release tablets

Formulation	Weight variation* ± SD	Drug content# (%) ± SD
F1	0.49 ± 0.04	98.5 ± 0.6
F2	0.51 ± 0.06	96.5 ± 0.6
F3	0.50 ± 0.03	98.1 ± 0.2
F4	0.50 ± 0.02	96.4 ± 0.4
F5	0.51 ± 0.03	101.5 ± 0.3
F6	0.49 ± 0.06	101.9 ± 0.6
F7	0.49 ± 0.04	100.8 ± 0.1
F8	0.51 ± 0.04	102.1 ± 0.3
F9	0.49 ± 0.05	100.6 ± 0.6
F10	0.51 ± 0.06	101.1 ± 0.5
F11	0.50 ± 0.02	101.1 ± 0.2

* Study was performed on 20 replicates.
# Study was performed on 3 replicates.

Table 5. Model-dependent and -independent parameters of formulated diclofenac sodium sustained release tablets

Formulations	Dissolution Efficiency at (%)			Mean Dissolution Time	Time (h)		
	180 min	480 min	720 min	480 min	$t_{25\%}$	$t_{50\%}$	$t_{90\%}$
F1	31.2	68.7	---	68.7	3:00	4:50	8:00
F2	33.2	62.2	---	62.2	2:30	4:18	7:12
F3	31.1	63.9	---	63.9	2:30	4:06	7:00
F4	33.9	56.2	---	56.2	2:48	4:06	6:12
F5	45.8	45.2	59.7	45.2	3:00	6:00	12:3
F6	33.3	46.4	63.9	46.4	3:30	7:00	24:0
F7	31.8	48.7	64.7	48.7	3:00	5:30	10:3
F8	28.9	49.6	64.3	49.6	3:00	4:30	9:00
F9	31.9	48.7	64.9	48.7	3:00	5:00	9:30
F10	33.3	49.6	66.9	49.6	3:30	5:12	11:0
F11	35	50.4	71.9	50.4	3:30	5:42	11:3

of 3 h; and 93.60%, 95.90%, 95.00% and 96.84% of the drug at the end of 12 h, respectively (Figs. 1 and 2). F1 and F3 showed initial burst release while F2 and F4 showed relatively controlled drug release because in F1 and F3 a total 100 mg drug was added to ceto stearyl alcohol while in F2 and F4 formulation 75 mg drug was loaded in polymers. These polymers are well known to retard the drug release by swelling in aqueous media. NaCMC released the drug at a faster rate than HPMC at the same drug and polymer ratio. A polymer's ability to retard the drug release rate was dependent on its viscosity grade. These results are in accordance with an earlier report[11]. The faster dissolution rate observed in NaCMC could be due to its swellability and disintegration property. F5 had only waxy material cetostearyl alcohol as release-retarding agent, and it released 76.61% ± 2.09 at 12 h and 86.11% at 24 h. F6, F7 and F10 possessed only NaCMC, NaAlg and HPMC, respectively. Among all these formulations, the release rate was increased in the rank order of: NaAlg > HPMC > NaCMC. The dissolution rate with NaAlg was higher than HPMC due to its low swellability, indicated by lower viscosity value. F7, F8 and F9 matrices were prepared with NaAlg and contained 0% (F7), 10% (F8), and 20% (F9) of HPMC, exhibiting different behaviors in the disso

Table 6. Summary of model fitting data of different formulations

Formulations	Zero order		First order		Higuchi matrix		Korsmeyer-Peppas	
	Slope	r^2	Slope	r^2	Slope	r^2	Slope	r^2
F1	9.2856	0.9558	–0.1121	0.9436	44.09	0.9624	2.2422	0.8639
F2	9.7372	0.8595	–0.2006	0.9549	47.18	0.9193	0.9841	0.9401
F3	10.0903	0.8223	–0.8990	0.8098	68.78	0.8897	0.8345	0.7968
F4	10.0535	0.8433	–0.8743	0.7645	37.95	0.7756	0.7429	0.8369
F5	4.0905	0.7708	–0.9453	0.8935	39.59	0.9196	0.9305	0.8660
F6	4.4515	0.6923	–0.0810	0.9595	39.85	0.9653	0.7731	0.9618
F7	5.7052	0.7496	–0.2080	0.8517	53.29	0.9790	2.2500	0.3872
F8	4.8354	0.7397	–0.0105	0.9523	42.65	0.9825	0.9188	0.9817
F9	5.6440	0.7703	–0.1528	0.8643	48.17	0.9815	0.8847	0.9899
F10	5.1698	0.7765	–0.0887	0.6332	39.45	0.9770	0.7920	0.6332
F11	4.9066	0.9872	–0.0665	0.9491	34.58	0.8763	0.4209	0.8346

lution medium due to different degrees of gelation occurring after 12 h of dissolution. F10 was prepared with drug-to-polymer ratio of 1:4 with HPMC. Only HPMC could retard the release up to 24 h with initial burst release, and hence it was selected for further formulation development. Formulation F1 to F10 showed burst release of DS in the simulated intestinal fluid probably due to faster dissolution of the drug from the core and its diffusion matrix forming the pores for entry of the solvent molecules. A suitable sustained release formulation should release the required amount of drug in the initial hours, followed by slow release. It can be concluded from the literature that more than 30% release of drug in the first hour of dissolution indicates a chance of dose dumping[12]. The results showed probability of dose dumping from the matrix tablets prepared without EC. The granulation prepared for F11 formulation (DS: HPMC 1:4, EC 4% w / v as granulating agent) showed excellent flow property over other formulations. Formulation F11 released 21.74% of the drug in the first hour in second dissolution fluid. As the F11 tablet sustained the drug release throughout the course of study with complete drug release at 24 h, F11 was considered as the most successful formulation of the study.

The results of model-independent dissolution parameters also suggested that the drug release could not be sustained at low level of hydrophilic and lipophilic polymers even in combination. However, lipophilic polymer alone (F5) showed sustained but low drug release up to 12 h. Furthermore, results of dissolution parameters of F6 to F10 showed that hydrophilic polymers could improve dissolution efficiency with sustained drug release but were associated with initial burst release. Among other formulations, F11 showed improved dissolution parameters with numerical values of 3.30 h, 11.3 h, 71.9% and 8.17 h for t25%, t90%, DE720, and MDT, respectively (Table 5). The dissolution data were subjected to model fitting using zero order, first order, Higuchi matrix and Korsmeyer-Peppas equations (Table 6). The goodness of fit for the formulations were found in the order of matrix > Korsmeyer-Peppas > zero order > first order. However, F11 was best fitted to zero order kinetics with value of correlation of determination (r^2) 0.9872. In the Peppas model, the values of release exponent n for all the formulations except F1 and F7 was between 0.5 to 1.0, indicating anomalous (non-Fickian) transport, whereas the value of n greater than 1.0 indicated super case II transport. The Higuchi model is used to study water soluble or low soluble drugs incorporated in matrices while the Peppas model is generally used to analyze the release of pharmaceutical polymeric dosage forms when the release mechanism is not well known or when more than one type of release phenomena could be involved. From a commercial point of view, EC is more economic because it was used in small quantity. Hence, F11 emerged as the successful release-retardant formulation, which utilized the approach of non-aqueous granulation using hydrophobic polymer EC, with respect to retardation

of the release and cost effectiveness.

CONCLUSION

It was evidenced from the results that the matrix tablet prepared with DS: HPMC in 1:4 ratio using EC 4% w / v in ethanol as the granulating agent was the most satisfactory in retarding the drug release up to 24 h and followed zero order release kinetics. This formulation approach offered an attractive alternative towards once a day tablet formulation of the drug.

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