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Polymethylmethacrylate Coated Alginate Matrix Microcapsules for Controlled Release of Diclofenac Sodium

Tapas Pal, Shubhajit Paul, Biswanath Sa

Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India.
Email: biswanathsa2003@yahoo.com

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ABSTRACT

Polymethylmethacrylate (*PMMA*) *coated microcapsules of diclofenac sodium* (*DFS*) *were prepared by a modified water-in-oil-in-water* ($W_1/O/W_2$) *emulsion solvent evaporation method using sodium alginate* (*SAL*) *as a matrix material in the internal aqueous phase* (W_1). *Their performance with respect to controlled release of the drug in simulated gastric fluid* (*SGF*) *and simulated intestinal fluid* (*SIF*) *were evaluated, and compared with non-matrix microcapsules prepared by the conventional* $W_1/O/W_2$ *emulsion solvent evaporation method. Scanning electron micrographs* (*SEM*) *revealed that all the microcapsules were discrete and spherical in shape; however, the surface porosity of the matrix microcapsules appeared to be less than that of the non-matrix microcapsules. In case of non-matrix microcapsules, an increase in the volume of water in* W_1 *phase resulted in decrease in the drug entrapment efficiency* (*DEE*) *along with increase in release of the drug in both SGF and SIF. While in case of matrix microcapsules increase in the amount of SAL in* W_1 *phase and concentration of the coating polymer in organic phase led to increase in DEE of the matrix microcapsules and considerable decrease in the drug release in both SGF and SIF. No interaction between the drug and any of the polymers used to prepare microcapsules was evident from Fourier transform infra-red* (*FTIR*) *analysis. The matrix microcapsules prepared using higher concentration of SAL and PMMA released the drug following zero order or Case-II transport model. The matrix microcapsules appeared to be suitable for releasing lesser amounts of DFS in SGF and providing extended release in SIF.*

Keywords*: *Polymethylmethacrylate*, *Sodium Alginate*, *Matrix Microcapsules*, *Diclofenac Sodium*, *Drug Release

1. Introduction

Diclofenac Sodium (DFS), a non steroidal anti-inflammatory drug, is widely used in rheumatoid arthritis, severe osteoarthritis and in ankylosing spondilities [1]. However, drug therapy with immediate release formulations like tablet, capsule of this agent is associated with several adverse effects like gastric irritation, bleeding, ulceration and eventually wall perforation especially in chronic dosing [2]. In addition, owing to its short biological half life (1 h - 2 h), DFS is administered 2 - 3 times a day [1]. A controlled release dosage form maintains adequate therapeutic plasma level of drug avoiding peak-and-valley effect and thereby, minimizes the emergence of adverse effects, prolongs the release of drug over extended period of time, reduces frequency of administration and hence improves patient compliance, provides therapeutic action during night time no-dosing period and thus, is suitable for better drug therapy [3,4].

When compared with single unit sustained release tablets, multiunit controlled release dosage forms such as microcapsules, microspheres pass through the gut as if a solution avoiding the vagaries of gastric emptying and different transit rates and thereby, release drugs more uniformly [5], and spread over a large area of absorbing mucosa decreasing dose dumping and preventing exposure to high drug concentration [6,7].

Among the various methods of preparing microcapsules, water-in-oil-in-water ($W_1/O/W_2$) emulsion solvent evaporation technique has been widely investigated. In this method, an aqueous solution or suspension of the drug (internal aqueous phase, W_1) is emulsified in a solution of polymer in organic solvent. The resulting primary emulsion (W_1/O) is then dispersed in a second aqueous phase (external aqueous phase, W_2) containing suitable emulsifiers to form multiple emulsion ($W_1/O/W_2$). Re-

moval of the volatile organic solvent leads to the formation of solid microcapsules. Drugs having different physical properties and diverse solubility have been microencapsulated by $W_1/O/W_2$ emulsion solvent evaporation technique using various polymers like polymethylmethacrylate [8], polylactide-co-glycolide [9,10], eudrajit RS [11], poly-Є-caprolactone [12]. Further modification of this method includes variation in the volume of internal aqueous phase [13], pH [14] and concentration of stabilizers [15] in W_2 phase, and addition of NaCl [16], glycerol [17], phosphate salt [18] in W_1 phase for achieving better physical properties of the microcapsules.

Recently, ranitidine-loaded matrix type microcapsules have been developed by $W_1/O/W_2$ emulsion solvent evaporation method incorporating chitosan as a matrix material in W_1 phase and cellulose acetate as encapsulating polymer in organic phase [19]. However, detailed study on PMMA coated SAL matrix microcapsules prepared by $W_1/O/W_2$ emulsion solvent evaporation method is not available. The objective of this study was to develop PMMA coated alginate matrix microcapsules by $W_1/O/W_2$ emulsion solvent evaporation method, and to study the effect of concentration of SAL in W_1 phase, and concentration of PMMA in organic phase on the release of DFS in SGF and SIF.

SAL, a hydrophilic biopolymer obtained from brown sea-weeds, has been widely used in drug delivery systems because of its high biological safety [20]. It has been used to encapsulate various drugs in alginate beads [21,22] and to prepare matrix tablets [23,24].

One of the rational advantages of using PMMA as a coating polymer is that it is widely used as a biostable polymer in biomedical field as bone cement in orthopaedics for local delivery of anti-inflammatory or antibiotic drugs [25]. PMMA beads have been used in Europe over the years for the management of total joint arthoplasty and soft tissue infection of abdomen, rectum and neck [26]. Therefore, an anti-inflammatory drug loaded in PMMA microcapsules with an inner aqueous phase containing SAL as a matrix material is expected to provide better control on drug release in both SGF and SIF.

2. Materials and Methods

2.1. Materials

Diclofenac sodium (Indian Pharmacopoeia) was obtained as gift sample from Plethico Pharmaceuticals Ltd, Indore, India; Sodium alginate (Mol. Wt. 240 KDa, S.D. Fine Chemicals, Ltd., Mumbai, India); Polymethyl methacrylate (low mol. wt., BDH Chemicals Ltd., Poole, England), Calcium chloride, Dichloromethane, Tween 80^R (Merck, India), Span 80^R (Fluka Chemie AG, Bucks, Switzerland) and all other analytical reagent grade chemicals were obtained commercially and used as received.

2.2. Preparation of Microcapsules

SAL (0.5% - 2.5% w/v) was dissolved in 3ml at 30˚C - 35˚C water by stirring with a magnetic stirrer for 20 min. 200 mg of DFS was added to the solution and stirred for further 20 min. The resulting mixture was added through a 16 gauge needle in 20 ml solution of PMMA (4% w/v) in dichloromethane containing 1% v/v Span 80 and emulsified at 4000 rpm for 2 min in a homogenizer (Eltek Motor, India). The resulting W_1/O primary emulsion was then added through a 16 gauge needle in 100 ml of water containing 1.25% v/v tween 80 and 2% w/v $CaCl_2$ and emulsified at 850 rpm to form $W_1/O/W_2$ emulsion. Stirring was continued for 1.5 h with a mechanical stirrer (Remi Motor, India) to evaporate off the organic solvent. Resultant microcapsules were separated by decantation, washed thrice with water and then, vacuum dried at 60˚C for 8 h. The microcapsules were stored in vacuum desiccator until used. Keeping the amount of SAL in W_1 phase fixed at 2% w/v, matrix microcapsules were also prepared varying the concentration (2% - 4% w/v) of PMMA solution. Non-matrix microcapsules (without containing SAL) were prepared in the same way using 3, 5 and 7 ml of water as internal aqueous phase.

Double distilled water was used throughout the preparation. The composition of the microcapsules has been shown in **Table 1**.

2.3. Fourier Transform Infrared Study (FTIR)

FTIR spectra of pure drug, blank (without containing drug) microcapsules and drug-loaded matrix microcapsules were recorded in a FTIR spectrometer (Jasco-FTIR, model 8300, Japan) in the range between 4000 and 400 cm^{-1} at a scanning speed 2 mm/sec. Each sample was mixed with KBr and converted into pellets by applying a pressure of 300 Kg/cm^2 with a hydraulic press.

2.4. Size of Microcapsules

Weighed amount of the microcapsules were placed on the top of a nest of British Standard Sieves (Gelological India) of 25 to 150 mesh with the coarsest sieve on the top, and shaken for 15 min on a mechanical shaker. The microcapsules retained on each sieve were collected and weighed. The average diameters of the microcapsules were determined following the method reported elsewhere [27]. The fraction having arithmetic mean diameter of 215 μm was used for further studies.

2.5. DEE of Microcapsules

Accurately weighed 30 mg of microcapsules were dissolved in 3 ml dichloromethane; 25 ml of USP phosphate

Table 1. Composition and characteristics of polymethylmethacrylate coated matrix and non-matrix microcapsules.

Rmulation code	Volume of internal aqueous phase (W1) (ml)	SAL concentration in internal aqueous phase (% w/v)	PMMA concentration in organic phase (% w/v)	Mean average diameter (μm)	DEE (%) mean ± SD
A1	3	0	4	213.45	35.12 ± 2.71
A2	5	0	4	221.46	32.56 ± 3.25
A3	7	0	4	226.91	28.71 ± 2.19
B1	3	0.5	4	234.11	58.62 ± 3.88
B2	3	1.0	4	236.80	64.16 ± 2.12
B3	3	1.5	4	270.05	67.46 ± 3.95
B4	3	2.0	4	291.72	72.16 ± 2.44
B5	3	2.5	4	308.60	71.98 ± 4.39
C1	3	2.0	2	213.88	47.25 ± 3.76
C2	3	2.0	3	239.39	62.21 ± 3.37
C3	3	2.0	4	291.72	72.16 ± 2.44

buffer (PB) solution (pH 6.8) was added and stirred for 30 min with a magnetic stirrer. The mixture was heated at 55˚C in a constant temperature bath with shaking to evaporate off the organic solvent. The solution was cooled and the volume was made up to 50 ml with PB solution. The solution was filtered through Whatmann filter paper (8 μm). An aliquot, following suitable dilution, was analyzed at 276 nm using a spectrophotometer (model UV2400PC series, Shimadzu, Japan) and the content of the microcapsules was determined using a calibration curve constructed using PB solution of pH 6.8. The reliability of the above method was judged by conducting recovery analysis at three levels of spiked drug solutions in the absence or presence of the polymers for three consecutive days. The average recovery was found to be 98.71 ± 3.06%. Drug entrapment efficiency (DEE) of the microcapsules was calculated using the following relationship:

$$\text{Drug entrapment efficiency } (\text{DEE}\%) = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100$$

2.6. Scanning Electron Microscopy (SEM)

Microcapsules were mounted on conducting stubs (made of brass) using double sided adhesive tape and vacuum coated with gold palladium film using a sputter coater (Edward S-150, UK). Images were taken using 15 kV electron beam intensity in a scanning electron microscope (Jeol, JSM-5200, Japan) to examine the surface morphology of the samples.

2.7. *In-vitro* Drug Release Study

In vitro drug release study was carried out in SGF (0.1 N HCl, pH 1.2) for an initial 2 h followed by in SIF (USP, Phosphate buffer, pH 6.8) for the rest of the period using USP II dissolution test apparatus (model TDP – 06P, Electro Lab, Mumbai, India). Microcapsules containing about 10mg DFS were placed in 400 ml SGF (37˚C ± 0.5˚C) and rotated with a paddle at 100 rpm. After 2 h, the acidic solution was removed carefully and replaced with 400 ml SIF. Aliquots were withdrawn at different times and replenished immediately with the same volume of fresh solution. The withdrawn samples were filtered through Whatman filter paper (8 μm), suitably diluted, and analyzed spectrophotometrically at 273 nm and 276 nm respectively for SGF and SIF. The amount of drug released in SGF and SIF were calculated from the calibration curves drawn respectively in 0.1 N HCl and PB (pH 6.8) solutions. Each release study was duplicated.

3. Results & Discussion

PMMA coated matrix and non-matrix microcapsules of DSF were prepared by $W_1/O/W_2$ emulsion solvent evaporation method. Initial experiments revealed that higher volume of organic phase and external aqueous phase as well as processing temperature considerably reduced DEE of the non-matrix microcapsules. Use of large volume of organic solvent required more time (about 5 h) for solvent evaporation and formation of microcapsules. This provided greater opportunity for the drug to partition from W_1 to W_2 phase. As a result DEE of the

microcapsules decreased. It has been reported that entrapment efficiency of vitamin B_{12} in poly (Є-caprolactone) microparticles decreased when the volume of external aqueous phase was increased and vice-versa [28]. Hence, 20ml of organic phase, 100ml of external aqueous phase and 30˚C to 35˚C processing temperature were used for the preparation of all microcapsules. Keeping the above conditions fixed the effect of the volume of internal aqueous phase of the non-matrix microcapsules and concentrations of SAL and PMMA of the matrix microcapsules on the properties of the microcapsules were studied.

3.1. Compatibility of Drug with Polymers

The compatibility of the drug with the polymers was studied by FTIR analysis. FTIR spectrum of pure DFS (**Figure 1(a)**) exhibited distinctive peaks at 3387.51 cm^{-1} due to N-H stretching of secondary amine, at 1575.63 cm^{-1} owing to –C═O stretching of carboxyl ion, and 746.86 cm^{-1} because of C–Cl stretching. As DFS contains aromatic rings, peaks were found just above 3000 cm^{-1} (at 3076.69 cm^{-1} and 3034.48 cm^{-1}). Generally 3 to 4 peaks in the range of 1400 cm^{-1} - 1550 cm^{-1} indicate the presence of aromatic ring. The spectrum of DFS showed peaks at 1401.72 cm^{-1}, 1453.62 cm^{-1} and 1504.70 cm^{-1} confirming the presence of aromatic rings. The FTIR spectrum of blank microcapsule (**Figure 1(b)**) which was composed of SAL and PMMA displayed a broad peak at 3449.97 cm^{-1} due to –OH group of SAL. The peak at 2927.75 cm^{-1} is due to C–H aliphatic stretching of PMMA (aliphatic stretching appears just below 3000 cm^{-1}). The peak at 1735.04 cm^{-1} represents –C═O stretching of carboxyl ion of both SAL and PMMA. The spectrum of blank microcapsule did not display any peak characteristics of NH stretching, aromatic C–H stretch and C–Cl stretch. FTIR spectrum of DFS loaded matrix microcapsule (**Figure 1(c)**) demonstrated a peak at 3450.98 cm^{-1} due to –OH stretching of SAL, 3388.38 cm^{-1} due to N–H of the drug, 2926.49 cm^{-1} due to CH aliphatic stretching of PMMA. The peaks between 1400 cm^{-1} - 1550 cm^{-1} are due to aromatic rings of the drug, a peak at 1736.03 cm^{-1} represent the –C═O stretching of carboxyl ions of SAL and PMMA, and a peak at 1576.50 cm^{-1} is due to –C═O stretching of carboxyl ion of the drug. In addition, the peak at 747.39 cm^{-1} indicates the presence of C–Cl of the drugs. The FTIR results thus confirmed the presence of the drug in the microcapsules that did not interact with any of the components of the matrix microcapsule.

3.2. Effect of Variables on Size of Microcapsules

Increase in the volume of the internal aqueous phase (W_1) tended to increase the size of the non-matrix microcapsules (**Table 1**). Increase in volume of W_1 phase increased the number of dispersed droplets in a fixed volume of organic phase, and the probability of coalescence between the dispersed droplets increases. This resulted increase in size of the non-matrix microcapsules. Similar results have been reported by various workers [29,30].

Incorporation of SAL as matrix material in the fixed volume (3 ml) of W_1 phase also affected the size of the matrix microcapsules. Increase in the concentration of SAL increased the size of the matrix microcapsules (**Table 1**). As the concentration of SAL was increased, the viscosity of the W_1 phase also increased. This hindered easy breakdown of W_1 phase into smaller droplets. In addition, increase in viscosity of W_1 phase made the primary W_1/O emulsion more viscous and formed larger $W_1/O/W_2$ emulsion droplets. As a result, matrix microcapsules of bigger size were formed.

Keeping the concentration of SAL in W_1 phase constant at 2% w/v, increase in the concentration of PMMA from 2% to 4% w/v increased the average diameter of the matrix microcapsules (**Table 1**). Increase in the concentration of PMMA increases the viscosity of organic phase that makes it difficult to form smaller $W_1/O/W_2$ emulsion droplets, and thus, leads to the formation of bigger microcapsules. Although the size of the microcapsules was confined within 36 - 120 mesh, 40% to 70% of the microcapsules were retained by 60 to 85 mesh screen. Hence, the microcapsules having an arithmetic mean diameter of 215 μm were used for evaluation.

3.3. Effect of Variables on DEE

Increase in the volume of W_1 phase decreased the DEE of non-matrix microcapsules significantly (**Table 1**). During the preparation of microcapsules by $W_1/O/W_2$ emulsion-solvent evaporation method, the organic polymer phase separates the internal and external aqueous phases and acts as a diffusion barrier for the drug between the two aqueous phases. Higher internal aqueous volume may increase the volume of W_1 droplets in the oil phase and consequently may decrease the thickness of the organic polymer phase. This promotes more partitioning/leaching of the drug from internal to external aqueous phase. As a result, the DEE of the microcapsules decreases. The observation is in agreement with the results of other researchers [31,32].

DEE of alginate matrix microcapsules was found higher than that of the non-matrix microcapsules (**Table 1**). Further, an increase in the concentration of SAL increased DEE upto a limiting value beyond which DEE decreased. Increase in the amount of SAL increases the viscosity of W_1 phase that minimizes the leaching of the drug into the external aqueous phase; and thus, increases DEE. However, when the concentration of SAL exceeded

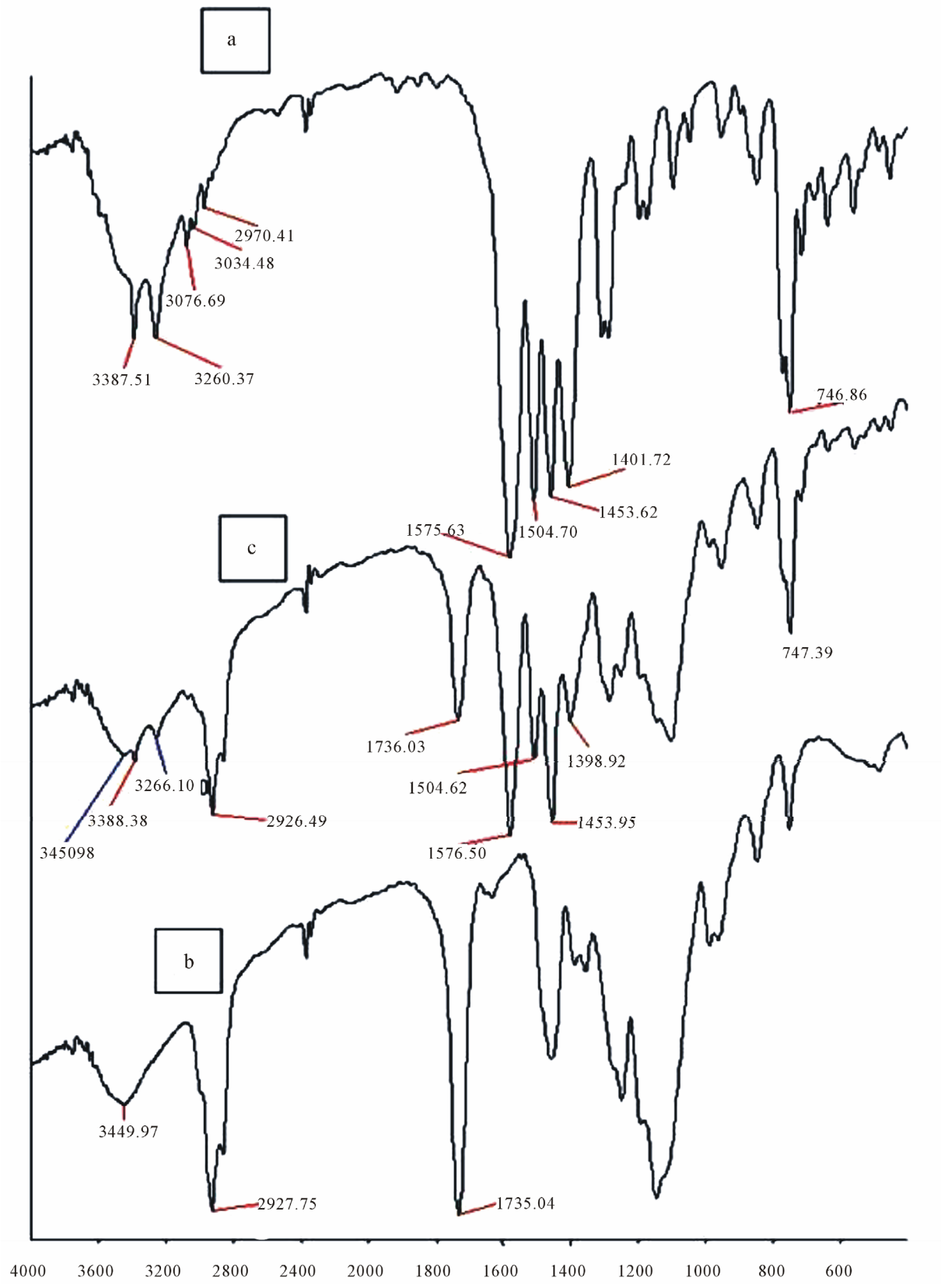

Figure 1. FTIR spectra of (a) diclofenac sodium, (b) blank microcapsules, (c) drug loaded microcapsules.

2% w/v, DEE of the microcapsules decreased. High viscosity of the internal aqueous phase results in the formation of inhomogeneous emulsion with numerous internal droplets in the W_1/O emulsion aggravating leakage of the inner core material to the external phase [33]. The loading efficiency of ranitidine in cellulose acetate microspheres containing chitosan as matrix material in the inner aqueous phase has been reported to decrease with increase in the concentration of chitosan in W_1 phase [19].

Using 2% w/v SAL in W_1 phase, matrix microcapsules were prepared with 2% to 4% w/v PMMA solution. Increase in the concentration of coating solution increased DEE of the matrix microcapsules (**Table 1**). Increase in the amount of PMMA increases the viscosity of the organic polymer phase which separates the internal aqueous phase from the external aqueous phase, and this is turn, decreases the leakage of the drug from W_1 to W_2 phase, and thus, DEE of the matrix microcapsules increases.

3.4. Effect of Variables on Drug Release

3.4.1. Effect of Volume of W_1 Phase

The results of *in vitro* drug release studies which were carried out initially for 2 h in SGF followed by in SIF have been represented in **Figure 2**. The release of drug in SGF from the non-matrix microcapsules which were prepared with different volume of inner aqueous phase was slow. Replacement of the dissolution medium after 2 h with SIF produced a sudden increase in release which extended for different periods of time depending on the volume of W_1 phase. Such difference in release in the two dissolution media may be attributed to pH dependent solubility of the drug which is poorly soluble in acidic solution and more soluble in aqueous solution of higher pH. In addition, as the volume of W_1 phase was increased, the release of drug in both the dissolution media increased. Time required for 50% ($t_{50\%}$) and 80% ($t_{80\%}$) drug release were determined from the cumulative percentage release versus time curves. $t_{50\%}$ were found to decrease from 3.72 h to 2.39 h and $t_{80\%}$ decreased from 7.87 h to 4.34 h as the volume of internal aqueous phase

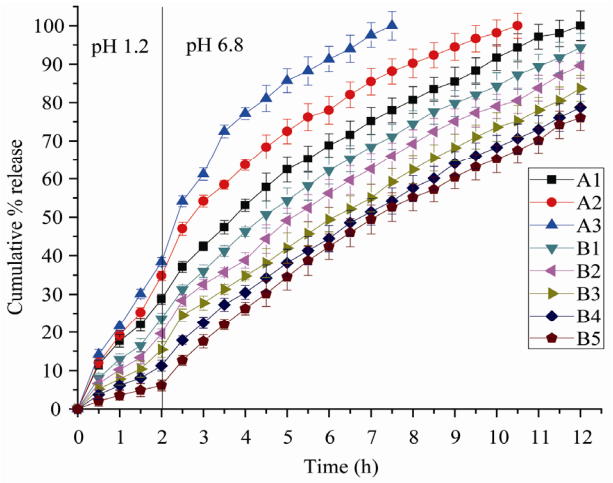

Figure 2. Release profile of diclofenac sodium from non-matrix microcapsules prepared with different volume of W_1 phase (3 ml - A1, 5ml - A2, 7ml - A3) and matrix microcapsules prepared with different concentration of SAL in W_1 phase (0.5% - B1, 1.0% - B2, 1.5% - B3, 2.0% - B4, 2.5% - B5).

Table 1. Composition and characteristics of polymethylmethacrylate coated matrix and non-matrix microcapsules.

Formulation code	Volume of internalaqueous phase (W1) (ml)	SAL concentration in internal aqueous phase (% w/v)	PMMA concentration in organic phase (% w/v)	Mean average diameter (μm)	DEE (%) mean ± SD
A1	3	0	4	213.45	35.12 ± 2.71
A2	5	0	4	221.46	32.56 ± 3.25
A3	7	0	4	226.91	28.71 ± 2.19
B1	3	0.5	4	234.11	58.62 ± 3.88
B2	3	1.0	4	236.80	64.16 ± 2.12
B3	3	1.5	4	270.05	67.46 ± 3.95
B4	3	2.0	4	291.72	72.16 ± 2.44
B5	3	2.5	4	308.60	71.98 ± 4.39
C1	3	2.0	2	213.88	47.25 ± 3.76
C2	3	2.0	3	239.39	62.21 ± 3.37
C3	3	2.0	4	291.72	72.16 ± 2.44

Table 2. Parameters of release and release kinetics of DFS from polymethylmethacrylate coated matrix and non-matrix microcapsules.

Formulation code	$t_{50\%}$ (h)	$t_{80\%}$ (h)	AUC (% mg·h/ml)	Parameters of release kinetics	
				n	R^2
A1	3.72	7.87	350.04[b]	0.702	0.992
A2	2.71	6.21	410.51[b]	0.707	0.975
A3	2.39	4.34	478.67[b]	0.767	0.978
B1	4.44	9.03	679.82	0.799	0.990
B2	5.17	10.26	622.37	0.857	0.989
B3	6.10	11.41	557.48	0.924	0.987
B4	6.75	—[a]	507.38	1.024	0.988
B5	7.15	—[a]	469.92	1.243	0.977
C1	3.30	5.68	399.62[b]	0.949	0.988
C2	4.78	8.31	291.07[b]	0.954	0.987
C3	6.75	—[a]	206.25[b]	1.024	0.988

a. Drug release was less than 80% in 12 h. b. AUC was calculated from 0 h to 7.5 h.

was increased from 3 ml to 7 ml (**Table 2**). For better comparison among the drug release from non-matrix microcapsules prepared with different volume of W_1 phase, area under curves (AUCs) were determined from the cumulative percentage release versus time curves using "Origin 8.0" software. Since the release of the drugs from the microcapsules prepared with 7 ml water in W_1 phase was complete in 7.5 h, AUCs of the formulations A1 to A3 were compared upto 7.5 h. Increase in the value of AUC means a faster release of a drug. The values of AUCs were found to increase from 350.04 μg/ml/h to 478.67 μg/ml/h as the volume of W_1 phase was increased for 3 ml to 7 ml. Higher volume of W_1 phase increases the porosity of the wall of the microcapsules and results in faster drug release [34]. SEM photographs (**Figures 3(a-c)**) showed the presence of pores on the surface of the microcapsules. The development of pores may be due to leakage of water through the organic phase. During $W_1/O/W_2$ emulsion solvent evaporation method, organic liquid diffuses from W_1/O droplets to external aqueous phase and simultaneously water from external aqueous phase back diffuses into the droplets. The back diffusion is related to the difference in the osmomolarity between the internal and external phases. The greater the back diffusion, the greater is the leakage of water [28] and hence, the wall of the microcapsules becomes more porous providing faster drug release.

3.4.2. Effect of SAL Concentration

The drug release from the matrix microcapsules followed the same trend as that found from the non-matrix microcapsules prepared without SAL. However, the release of drug from the matrix microcapsules was less than that from the non-matrix microcapsules. While the non-matrix microcapsule prepared with 3 ml water in W_1 phase released 100% drug in 12 h, the matrix microcapsules containing 3 ml water and 2.5% w/v SAL released only 76.06% drug in 12 h. For comparison, area under the curve (AUC) of release versus time curve was calculated. The value of AUC decreased from 679.82 μg/ml/h (for non-matrix microcapsules) to 469.92 μg/ml/h (for matrix microcapsules) containing 2.5% w/v SAL. It was further noted from the drug release profile that while non-matrix microcapsules prepared with 3 ml water in W_1 phase released 28.71% drug in 2 h in SGF, the matrix microcapsules containing 2% and 2.5% w/v SAL released respectively only 11.26% and 6.12% drug during the same period. In contact with acid solution, SAL is converted into insoluble alginic acid which provides resistance to drug diffusion. When the same microcapsules are brought in contact with aqueous solution of higher pH, alginic acid is reconverted into SAL which swells in water to from a viscous solution inside the matrix microcapsules. Thus, while the insoluble alginic acid formed inside the matrix microcapsules provides resistance to drug diffusion in SGF, formation of viscous SAL solution in the matrix microcapsules is responsible for slower drug release in SIF. The higher the amount of SAL in the matrix microcapsules, the higher will be the amount of alginic acid formed in acidic solution, and the higher will be the viscosity of SAL solution in SIF. Moreover, SEM photographs (**Figures 3(d-f)**) showed that although the gross

morphology of the matrix microcapsules did not change appreciably, increase in the concentration of SAL tended to decrease the porosity on the surface of the microcapsules. Thus increase in the concentration of SAL in the W_1 phase of the matrix microcapsules decreases the drug release in both SGF and SIF.

3.4.3. Effect of PMMA Concentration

The effect of PMMA, used as coating polymer, on the release of drug from the matrix microcapsules have been represented in **Figure 4**. The pattern of drug release in SGF and SIF was same as that found with other microcapsules. However, the matrix microcapsules prepared with lower polymer concentration released the drug faster than those prepared with higher polymer concentration. Comparison of the AUC upto 7.5 h indicated a decrease in AUC values with increase in concentration of PMMA. Increase in the amount of coating polymer leads around the matrix (**Figures 3(g-i)**), and thus, results in a decrease in drug release. This result is consistent with the report that release of protein from polylactide-co-glycolide microcapsules decreases as the concentration of the coating polymer is increased [35].

3.4.4. Kinetics of Drug Release

The release pattern of the drug from all the microcapsules appeared to be biphasic. The drug release was slow in SGF. When the microcapsules were placed in SIF after 2 h dissolution study in SGF, a sudden increase in drug release was observed following which the drug release increased steadily. To obtain an idea of the mechanism of drug release from various microcapsules, the release data were fitted in the classical power law expression [36].

$$\frac{M_t}{M_\alpha} = Kt^n$$

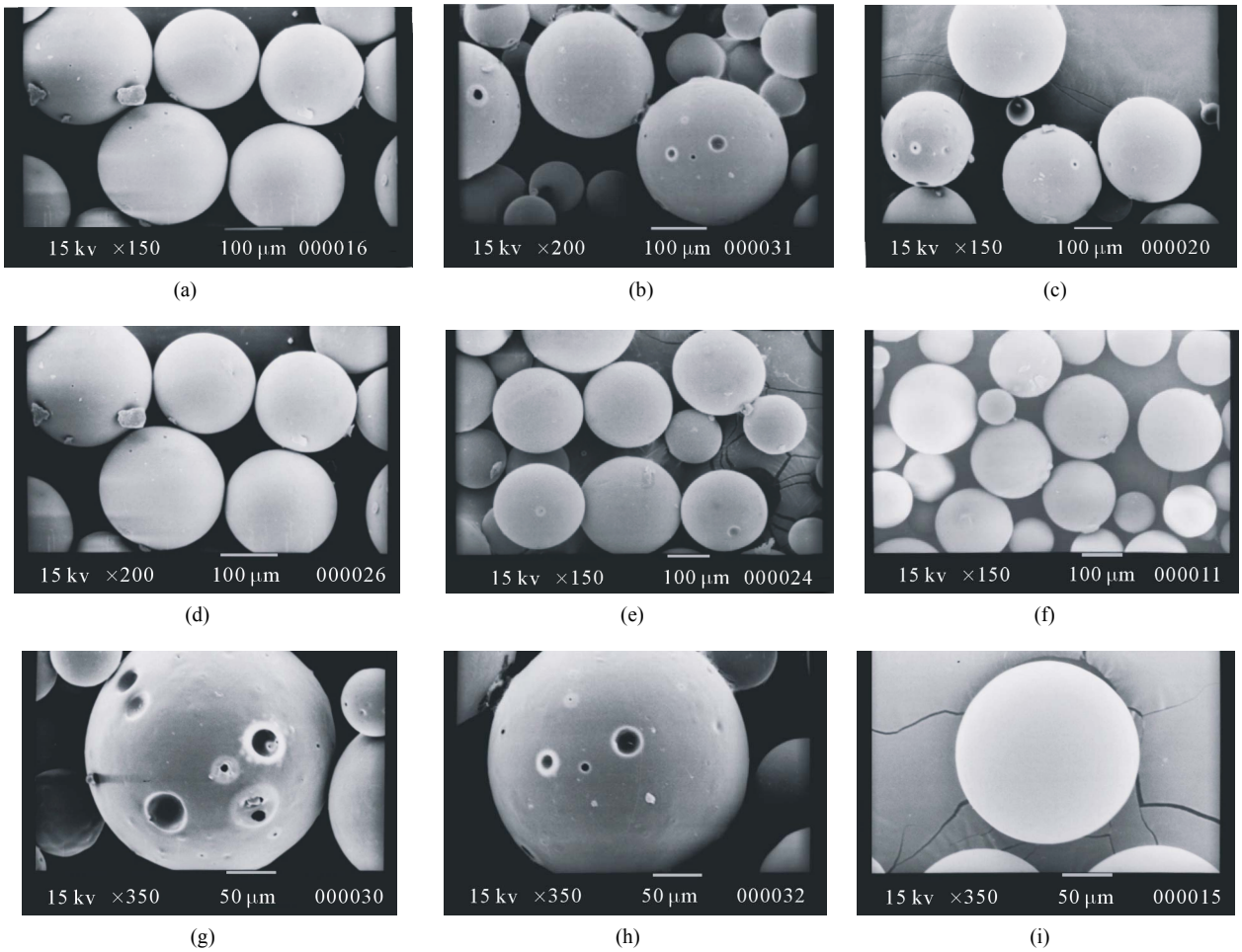

Figure 3. Scanning electron micrographs of: non-matrix microcapsules prepared with different volume of W_1 phase (3 ml - a, 5 ml - b, 7 ml - c); matrix microcapsules prepared with 4% w/v PMMA and different concentration of SAL (0.5% - d, 1.5% - e, 2.5% - f); matrix microcapsules prepared with 2% w/v SAL in W_1 phase and different concentration of PMMA (2% - g, 3% - h, 4% - i).

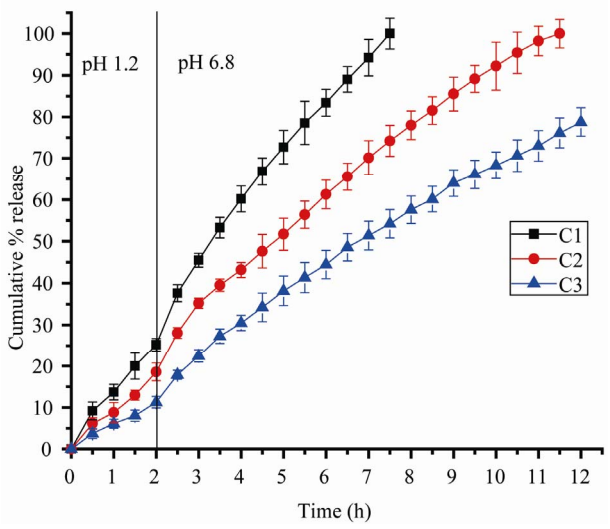

Figure 4. Release profiles of diclofenac sodium from matrix microcapsules prepared with 2% w/v SAL in W_1 phase and different concentration of PMMA (2% - C1, 3% - C2, 4% - C3).

Where M_t and M_α are respectively the amount of drug released at time 't' and at infinite time; 'K' represents a constant incorporating structural and geometrical characteristics of the dosage form, 'n' denotes the diffusion exponent indicative of the mechanism of drug release. Values of 'n' ranging from 0.45 to 0.5 indicate Fickian or diffusion controlled release; values of 'n' ranging from 0.5 to 0.89 indicate non-Fickian or anomalous release, and values of 'n' from 0.89 to 1 indicate Case-II transport or zero order release. **Table 2** shows that the release of drug from non-matrix microcapsules followed non-Fickian mechanism as the values of 'n' were confined within 0.70 to 0.77. The release of drug from matrix microcapsules containing lower concentration of SAL in W_1 phase also followed non-Fickian model. However, increase in the concentration of SAL shifted the drug release from the matrix microcapsules towards Case-II transport or zero order model. Similarly, the release of the drug from matrix microcapsules prepared with increasing concentration of coating polymer followed Case-II transport.

4. Conclusions

PMMA coated non-matrix and matrix microcapsules of DFS, a non steroidal anti-inflammatory drug, were prepared by $W_1/O/W_2$ emulsion solvent evaporation method. DEE of the matrix microcapsules were found to be considerably high than those of non-matrix microcapsules and increased with increase in the concentration of the matrix material. However, after a certain concentration of the matrix material, DEE tended to decrease probably due to the formation of inhomogeneous emulsion. Release of the drug from all the microcapsules appeared to be biphasic releasing less amount of drug in SGF and higher amount of drug in SIF. However, drug release from the matrix microcapsules in SGF was considerably less when compared with that from non-matrix microcapsules. In addition, the drug release from matrix microcapsules in SIF was more prolonged than that from non-matrix microcapsules and extended over a longer period of time depending on the concentration of SAL and PMMA. The release of the drug from most of the microcapsules appeared to follow non-Fickian model. Increase in the concentration of SAL in W_1 phase and PMMA in organic phase shifted the release kinetics towards zero-order model. The results of this study indicated that matrix microcapsules prepared with SAL as matrix material could be a suitable multiunit controlled release dosage form of DFS having high DEE that may release less amount of drug in stomach minimizing the emergence of gastric adverse effects and at the same time may provide prolonged release in the intestine to achieve better drug therapy.

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