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Multiple unite sustained released floating of sodium diclofenac: Formulation and evaluation using factorial design

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Abstract

The aim of this study was prepare and evaluate floating granules of sodium diclofenac with lipid excipient for prolonged gastric residence and reduced dose regimen. Floating granules prepared by extruder-spheronization technique. Compritol and gelucire as lipid excipient, HPMC as retardant and tween 80 as emulsifier were used. The effect of drug/lipid, drug/HPMC, drug amount, percentage of tween and type of lipid on floating ability, morphology and dissolution parameters were evaluated by factorial design. Results showed floating ability of granules was influenced by proportion of drug/lipid, drug/HPMC and percentage of tween. Floating property of Compritol was more than gelucire and provided good floating particles. Compritol granules provided suitable sustained release pattern in the manner that increase in D/L reduced D8 and MDT and increase in %T increased MDT. Higuchi model was the best fitted for dissolution data of granules prepared by Compritol and gelucire. In conclusion, Compritol provided more suitable floating ability and sustained release property.

Keywords: Sodium diclofenac; Floating granules; Gastric residence time; Extruder-spheronization

Introduction

The oral drug delivery has more attention among the different routs of drug administration. Regretfully, the variability of gastrointestinal physiology same as gastric emptying time, pH and agitation to cause an unpredictable bioavailability and lack of drug effectiveness. Prolongation of gastric time with sustained release systems leads to reduction the number of dosage regimen and improvement of drug bioavailability [1]. Different methods have been applied to keeping the dosage form in stomach including bioadhesive systems, swelling and floating systems [2]. Permanent retention is propounded for swelling system and irritation of the mucous layer for bioadhesive systems [3].

The use of high density solid dosage forms which remain in the down part of stomach have been applied. But bioavailability of them are unpredictable [4]. Floating systems to be more useful and protection against early and random gastric evacuation compare to other dosage forms that are used for this purpose. The effect of single-unit floating systems on gastric emptying time is non-reproducible and unpredictable. On the other hand, multiple-unit floating systems same as pellets and granules indicate lower dose-dumping and inter-subject variability [5].
Compritol 888 ATO and gelucire have been used for sustained release dosage form [6]. Compritol or glyceryl behenate has hydrophobic property with low

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HLB value of 2 [7]. Gelucire is composed of mono-di and tri glycerides with polyethylene glycol esters of fatty acids. Gelucire is a family of vehicles with a range of melting point (33-66) and HLB. Gelucire which compose of glycerides or PEG ester same as gelucire 50/13 are utilized in the preparation of sustained release formulations [8].

Sodium diclofenac is a non-steroidal anti-inflammatory drug that used to relieve the inflammation, stiffness, and joint pain associated with rheumatoid arthritis. The main side effects of the drug especially in case of the long-term use, may include: abdominal bleeding, pain or cramps, blood clotting problems, peptic ulcers, and vomiting. Solubility of Sodium diclofenac in the acidic environment such as the stomach (pH 1 to 3) is low and dependent to drug dose and gastric fluid volume [9, 10]. On the other hand, sodium diclofenac dissolves quickly in the intestinal alkaline condition so the effect of the long term drug uptake is impossible according to the short biological half life. Thus, total bioavailability of orally used sodium diclofenac has few important challenges.

So preparing formulations of diclofenac sodium with a floating controlled release property not only can increase competence and reduce the medication side effects [11]. Therefore, the efforts of many researchers have been concerned to design a controlled release system for sodium diclofenac and other NSAID compounds [11-14]. The purpose of this study was to prepare and evaluate the lipid floating granules as a controlled drug release system for sodium diclofenac.

Material and methods

Materials

Sodium diclofenac was gift from Hakim pharmaceutical Company (Tehran, Iran). Compritol 888 ATO and Gelucire 50/13 were gift from Gattefosse Company (France). Tween 80 and hydroxyl propyl methylcellulose (HPMC) were purchased from Merck (Germany) and sigma Aldrich respectively. Dialysis bag was purchased from Toba Azema Co, Tehran (Iran). Minitab14 software was used for experimental design and the evaluation of the effect of variables on responses.

Determination of sodium diclofenac

The amount of drug loading within lipid granules and release rate of the drug determined using UV spectroscopy at wavelengths of 276 nm. The validity of assay method including, linearity, repeatability, accuracy and limit of quantification (LOQ) were calculated.

Preparation of floating granules

In order to study the impact of independent variables on characteristics of granules, the full-factorial design with five variables and two levels were used. The drug-lipid proportion (d/l), amount of drug (d), drug-HPMC proportion (d/h), percentage of Tween (%T) and type of lipid (l) were selected as independent and drug content, the percentage of drug released after 8 hours (D_8) and mean dissolution time (MDT), granules precipitated after 2 (P_2) and 8 (P_8) hours as floatability parameters as dependent variables (table 1). 32 formulations were prepared based on full factorial design. Sustained release floating granules prepared with extruder- spheronization technique based on the method reported by Rahman et al [15]. Sodium diclofenac, HPMC and tween was added into melted lipid under stirring. The mass was stored at refrigerator and then forced through dies for providing cylindrical particles, with screw feed extruder equipped with 1 mm screen and operated at 25 rpm. Spheronization was performed with rotational speed at 800 rpm and 1 mm serrated plate of 38 cm diameter.

Table 1. Independent variable and their levels in factorial experimental design.

Independent variable	Levels	
	Low (-)	High(+)
Drug (mg)	50	100
Drug/lipid ratio (D/L)	1/6	1/3
Drug/ HPMC ratio	1/1	1/0.4
Tween 80 (%)	0%	1%
Lipid type	Gelucire 50/13	Compritol

Drug content determination

The drug content was calculated by extracting method. Defined amount of granules were accurately

weighed and added to 50 ml water. Mixture was heated to 70ºC until lipid melted. The solution was centrifuged, filtered and diluted. The drug content was measured at 276 nm [3].

Morphological characterization

Surface morphology and stability of microparticles were studied by SEM (VP-1455, LEO, Germany). Microparticles were dried and coated by gold palladium.

Floating ability

These experiments were performed using USP paddle dissolution apparatus (50 rpm, 37ºC, 200 ml) in HCL 0.1N. Floatability time was measured by visual observation and the floating ability was evaluated by percentage of precipitated granules after 2 (P_2) and 8 (P_8) hours [3].

Dissolution study

Dissolution studies for sustained release granules were performed in the HCL 0.1N. The release profile characterized using a six panel USP dissolution apparatus with 900 ml of medium with pH 1.2 and a temperature of 37°C. Furthermore, 5 ml of dissolution medium were withdrawn and replaced with fresh dissolution medium. Absorption of samples taken from centrifuge and separate clear supernatant solution and the appropriate dilution, by spectrophotometer at wavelength nm 276 against the control (dissolution test formulations were prepared without the drug) [16]. For dissolution kinetic evaluation, the dissolution data were plotted with first order, zero order and hiquchi square root equation and the best fit was found [17].

Statistical analysis

Minitab14 software was used for experimental design and the evaluation of the effect of variables on responses. Statistical significance of the difference between various treatments was performed using one-way ANOVA. Correlation analyses were performed by the least square linear regression method. Correlation coefficients were examined for significance by unpaired two tailed student's t- test. Significant level of choice in all stages of this investigation was less than 0.05.

Results and discussion

Validity of drug measurement method

The relationship between the light absorption and concentration was significant (R^2 = 0.994, P<0.001). Repeated surveys accountability in measurement methods within and between days for sodium diclofenac is represents the desired repeatability of measurement method on different days and caused nearly the same operation as well as error free results. The difference between real numbers and the estimated concentrations was about 5% that indicates the closeness of the estimated values to real results. The limit of quantification was 0.0005 mg/ml, but the only concentrations greater than 0.0006 mg / ml is reliable for such studies, because methods with concentrations higher than 0.0006 mg/ml have good accuracy and repeatability. Therefore in this study only the values greater than this cutoff were reported.

Profile formulations prepared according to the study design

Totally Profile of 32 floating granules formulation is presented in this study (Table 2).

Floating lipid granules containing sodium diclofenac

In order to compare the power produced by floating lipid granules, the number of granules to sediment after 2 and 8 hours and then the percentage of granules determined to sediment after 2 hours (P2) and 8 hours (P8) was calculated (Table 3).

All the formulations prepared with Gelucire showed completely precipitated the good effect on the floating property in less than 2 hours, but Tween 80 presence in the formulations could not put a specific effect on floating property. All formulations contain no Tween 80 were completely precipitated within less than 2 hours. However, formulations prepared with Compritol 888 ATO were effective on percentage of the floating granules after 2 and 8 hours. Sediment granules percentages were between zero to 35% and 8 to 70% after 2 and 8 hours, respectively.

The correlation between independent variables with P2 and P8 is expressed by the following equations:

$$P_8 = -8/8 + 81/1(D/L) + 0/021(D) + 10/1(D/H) + 24/8(T\%)$$

$$P_2 = -3/37 + 43/7(D/L) - 0/046(D) + 5/14(D/H) + 14/8(T\%)$$

Table 2. Profile based on 32 formulations of granules produced by factorial design.

Formulation No.	Factorial design condition	Drug (mg)	Lipid (mg)	HPMC (mg)	Tween 80 (mg)	Lipid type
1	- + + - -	50	150	20	0%	Gelucire50/13
2	+ - + - -	100	600	40	0%	Gelucire50/13
3	- - - + -	50	300	50	1%	Gelucire50/13
4	- - - + +	50	300	50	1%	Compritol
5	+ + + - -	100	300	40	0%	Gelucire50/13
6	+ + + + +	100	300	40	1%	Compritol
7	+ - + + -	100	600	40	1%	Gelucire50/13
8	- + + - +	50	150	20	0%	Compritol
9	- + - - -	50	150	50	0%	Gelucire50/13
10	- - - - +	50	300	50	0%	Compritol
11	- - - - -	50	300	50	0%	Gelucire50/13
12	- - + + -	50	300	20	1%	Gelucire50/13
13	- + + + +	50	150	20	1%	Compritol
14	+ - - - -	100	600	100	0%	Gelucire50/13
15	- + - + -	50	150	50	1%	Gelucire50/13
16	+ - - + -	100	600	100	1%	Gelucire50/13
17	- - + + +	50	300	20	1%	Compritol
18	- - + - -	50	150	50	0%	Gelucire50/13
19	+ + - - +	100	300	100	0%	Compritol
20	- + - + +	50	150	50	11%	Compritol
21	- - + - +	50	300	20	0%	Compritol
22	+ - - + +	100	600	100	1%	Compritol
23	+ - + + +	100	600	20	1%	Compritol
24	- + + + -	50	150	20	1%	Gelucire50/13
25	+ + + + -	100	300	40	1%	Gelucire50/13
26	+ + - + -	100	300	100	1%	Gelucire50/13
27	+ - - - +	100	600	100	0%	Compritol
28	+ + - + +	100	300	100	1%	Compritol
29	+ + - - -	100	300	100	0%	Gelucire50/13
30	- + - - +	50	150	50	0%	Compritol
31	+ + + - +	100	300	40	0%	Compritol
32	+ - + - +	100	600	40	0%	Compritol

The correlation between Tween 80 percentage, drug /HPMC ratio and drug/lipid ratio with P2 and P8 was significant in such a way that increases the independent variables leads to significantly increase in the granules sedimentation rate (Figure 1). It seems that in the presence of Tween 80 and HPMC with water absorption the floating property of the granules reduce. Of course the effect of Tween 80 is stronger than HPMC. Only interaction between the amount of drug and drug/HPMC ratio was thus important that 50 mg of the drug by increasing or reducing the amount of the HPMC, P2 has not major change. But 100 mg of the drug, increase in the amount of HPMC significantly increased P2. In other words, drug and HPMC have different synergic mechanisms on the P2. According to the significant correlation between HPMC and P2, it seems that the drug boosted the effect HPMC on P2.

Dissolution

Dissolution data of granules prepared with Compritol Percentage of drug dissolved after 8 hours (D8) and mean dissolution time (MDT) of different granules are shown in table 4.

The highest amount of D8 was 43.85% and achieved by formulation number 13. In the other hand highest value of MDT was 5.66 hr according to formulation number 14. The correlation between D/L with D8 and D/L and %T with MDT was significant in the manner that increase in D/L reduced D8 and MDT and increase in %T increased MDT.

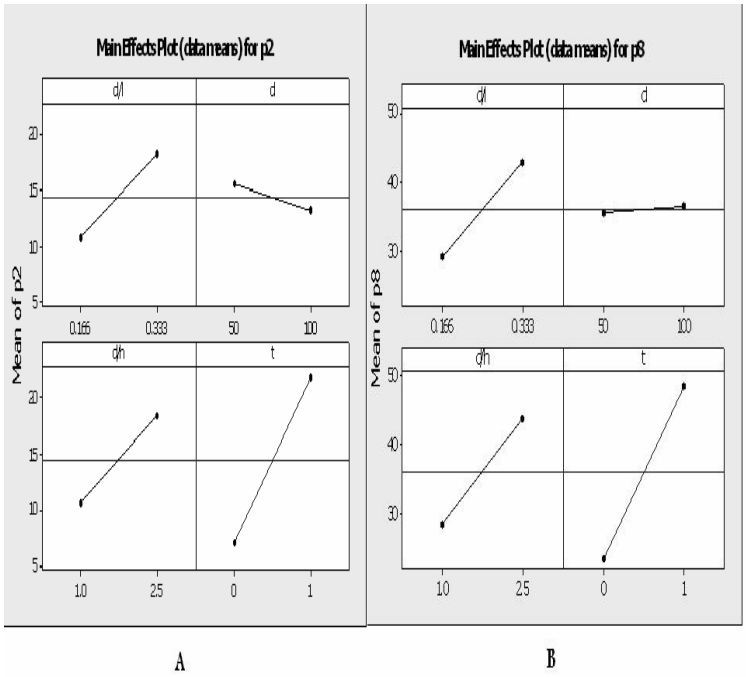

Figure 1. The correlation between independent variables with P2 (A) and P8 (B).

The retardant effect of drug/ Compritol ratio (1:3) for sodium diclofenac reported previously [16]. The effect of D/L on D8 and MDT was due to its effect on drug loading. It seams that, Tween improved drug affinity to Compritol that is lipid carrier with HLB=2. The drug dissolute amount was not affected by one and 1/0.4 weight ratio of drug/HPMC. Similar results reported for carbamazepin [18]. Although, the importance of HPMC concentration effect on drug release mechanism have been reported [19; 20] but in present study this effect was not found.

Analysis of dissolution kinetic was done with various equations such as zero order, first order and higuchi. r^2 values calculated were shown in table 5 and drug dissolution profile at zero order condition demonstrated in figure 2.

Results indicate that the best fit with higher correlation was found with higuchi equation and zero-order for all formulations. High value of r^2 for higuchi model indicates that diffusion is the main mechanism for drug release. In the other hand high value of r^2 in zero order model demonstrates that Compritol acts as reservoir for diclofenac. Low affinity of sodium diclofenac reinforces this hypothesis. No desirable burst release was found for sodium diclofenac.

Table 3. The percentage of granules have precipitated after 2 h (P2) and 8 h (P8) in the formulations prepared by the factorial design (mean ± SD, n=3).

Formulation No.	Factorial design condition	Sediment after 2 hours	Sediment after 8 hours
1	- + + - -	100	-
2	+ - + - -	100	-
3	- - - + -	100	-
4	- - - + +	23.23± 5.77	46.66± 7.63
5	+ + + - -	100	-
6	+ + + + +	35±5	70±8.66
7	+ - + + -	100	-
8	- + + - +	6.66±2.88	28.33±2.88
9	- + - - -	100	-
10	- - - - +	8.33±2.88	21.66±7.63
11	- - - - -	100	-
12	- - + + -	100	-
13	- + + + +	25±5	56.66±7.63
14	+ - - - -	100	-
15	- + - + -	100	-
16	+ - - + -	100	-
17	- - + + +	11.66±5.77	33.33±7.63
18	- - + - -	100	-
19	+ + - - +	0	11.66±2.88
20	- + - + +	11.66±5.77	33.33±7.16
21	- - + - +	0	8.33±2.88
22	+ - - + +	25±8.66	51.66±7.63
23	+ - + + +	30±0	58.33±7.63
24	- + + + -	100	-
25	+ + + + -	100	-
26	+ + - + -	5±0	18.33±7.64
27	+ - - - +	3.33±0	18.33±7.64
28	+ + - + +	13.33±7.63	38.33±16.07
29	+ + - - -	100	-
30	- + - - +	0	6.66±2.88
31	+ + + - +	15±5	48.33±7.63
32	+ - + - +	23.33±5.77	46.64±7.63

Dissolution data of granules prepared with gelucire 50/13

Amount 16 formulations based on factorial design only 10 formulations had suitable characters and were used for dissolution test. Dissolution parameters

according to different granules prepared with gelucire was shown in table 6. The highest amount of D8 was 78.36% belongs to formulation no.8 and for MDT was 5.37 according to formulation no. 9. Non significant correlation was found between variables and D8 and MDT.

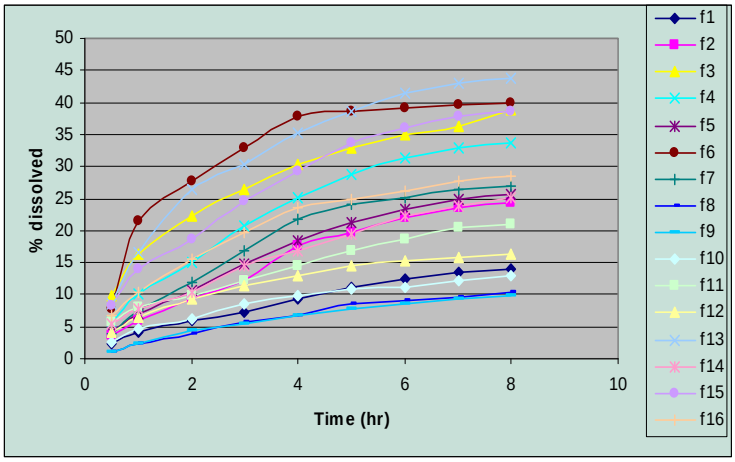

Fig 2. Dissolution profile of different granules prepared with Compritol.

Gelucire with HLB=13 indicates hydrophilic property more than Compritol. The results show that sodium diclofenac has good affinity to gelucire and so high loading capacity of gelucire neutralized effect of independent variables. Comparision between dissolution parameter for two lipids indicates more sustained release property for Compritol.

Table 4. D8 and MDT of different granules prepared with Compritol (mean ± SD, n=3)

Formulation No.	Factorial design condition	D8	MDT (hr)
1	+ + - +	14.01±1.05	0.37 ±5.44
2	+ + - +	1.33 ±24.44	0.24±5.37
3	- - + +	3.19±38.88	0.32 ±4.82
4	- - - +	2.25±33.68	0.39±4.88
5	+ - + +	25.59± 1.89	0.21±5.10
6	+ - - +	1.44±39.98	0.102 ±3.06
7	- + + -	0.98±27.02	0.17 ±4.63
8	+ - + -	0.33±10.28	0.24±5.21
9	- + - -	0/78±9.68	0.16±5.26
10	- - + -	0.98±12.88	0.26±4.90
11	- - - -	1.12±21.03	0.32 ±5.57
12	- + + +	1.48±16.29	0.38±4.53
13	+ - - -	2.24 ±43.85	0.2±4.27
14	- + - +	1.45 ±25.11	0.19±5.66
15	+ + + +	2.93 ±38.55	0.39±4.79
16	+ + - -	1.21±28.48	0.29 ±4.04

Table 5. r^2 values of granules prepared with Compritol in different kinetic models.

Formulation No.	Factorial design condition	Zero-order	First-order	Higuchi model
1	++ - +	0.976	0.862	0.94
2	+ + + -	0.963	0.859	0.94
3	- - + +	0.922	0.798	0.993
4	- - - +	0.943	0.820	0.97
5	+ - + +	0.958	0.844	0.96
6	+ - -+	0.735	0.574	0.957
7	- + + _	0.912	0.786	0.973
8	+ - + -	0.96	0.790	0.967
9	- + - -	0.959	0.790	0.974
10	- - + -	0.927	0.805	0.981
11	- - - -	0.983	0.90	0.963
12	- + + +	0.914	0.80	0.991
13	+ - - -	0.890	0.74	0.998
14	-+ - +	0.982	0.90	0.938
15	+ + + +	0.940	0.83	0.974
16	+ + - -	0.904	0.79	0.990

The results of dissolution kinetic analysis and drug dissolution profile at zero-order model are shown in table 7 and figure 3. r^2 values indicates best fit for higuchi model for dissolution data and so it seams that diffusion across the granules is rate limiting step for drug release.

Table 6. D8 and MDT of different granules prepared with gelucire (mean ± SD, n=3).

Formulation No.	Factorial design condition	D8	MDT (hr)
1	- + + +	51.35±2.84	0.28 ±4.53
2	- + + -	3.71 ±49.47	0.43 ±4.95
3	- + - +	3.92± 42.23	0.35 ±4.02
4	- + - -	3.11± 40.43	0.39±4.50
5	- - + +	40.52± 2.08	0.31±3.85
6	- - + -	1.95± 43.47	0.22 ±4.65
7	+ - - +	4.41± 76.83	0.19 ±4.03
8	+ - - -	6.33± 78.36	0.28±4.41
9	- - - +	2.96± 65.68	0.14±5.36
10	- - - -	5.83± 66.14	0.18±5.250

In comparison with Compritol, gelucire did not act as reservoir system because the lower value of r^2. higher hydrophilic property of gelucire tends to water absorption and improves drug release.

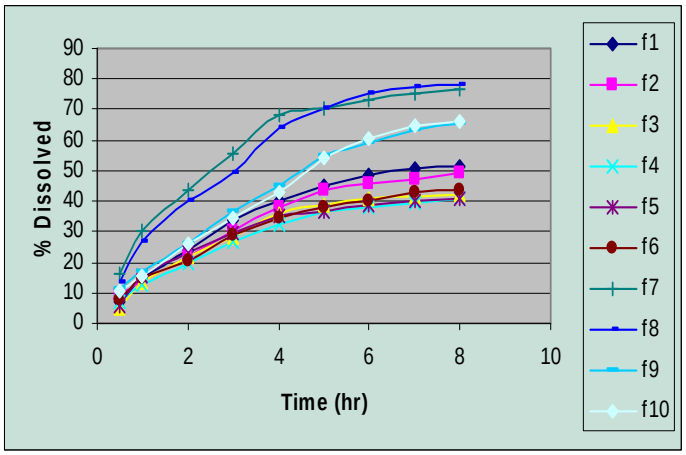

Figure 3. Dissolution profile of different granules prepared with gelucire.

Particles morphology

The SEM photomicrographs of granules prepared with Compritol are shown in figure 4. In these pictures effect of tween and dissolution condition on appearance and particle size were evaluated. Results suggested creation pores with tween at the surface of particles (B) after dissolution test.

Table 7. r^2 values of granules prepared with gelucire in different kinetic models.

Formulation No.	Factorial design condition	Zero-order	First-order	Higuchi model
1	+ + - +	0.914	0.764	0.984
2	+ + + -	0.934	0.826	0.965
3	- - + +	0.896	0.688	0.986
4	- - - +	0.908	0.780	0.979
5	+ - + +	0.843	0.650	0.993
6	+ - - +	0.924	0.8	0.980
7	- + + -	0.856	0.731	0.985
8	+ - + -	0.908	0.770	0.980
9	- + - -	0.965	0.870	0.970
10	- - + -	0.951	0.880	0.940

These pores were not seen in particles without tween (D). In the other hand, the particle size was not affected by dissolution test and in both condition particle size was in range of 5-10 µm. these results conforming calculated dissolution parameters.

Conclusion

The sodium diclofenac loaded floating granules were prepared by extruder-spheronization method with two type of lipid successfully. Floating ability of sustained release granules to be touched by Tween 80 percentage, drug /HPMC ratio and drug/lipid ratio.

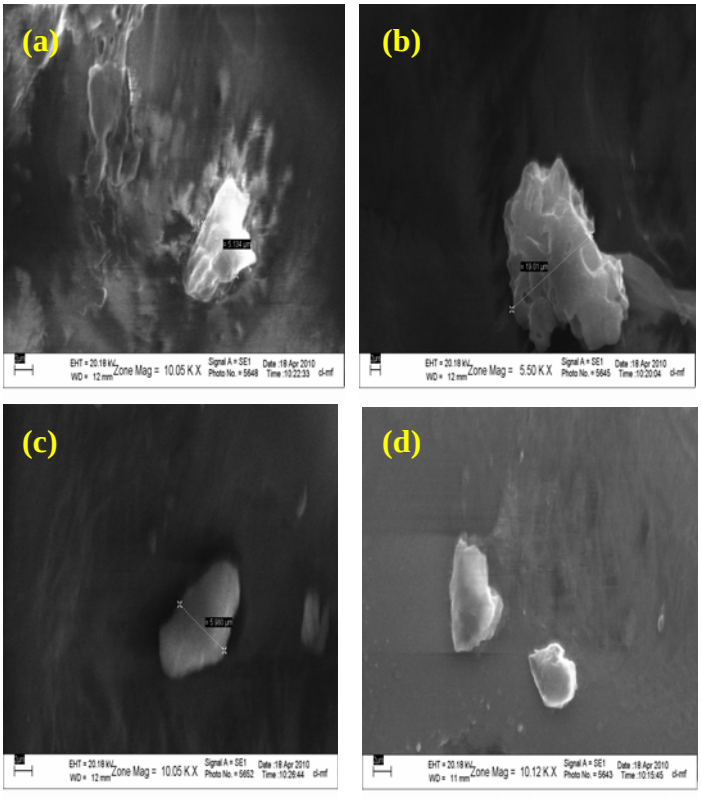

Figure 4. SEM photomicrographs of particle with tween before (a) and after (b) dissolution test and particles without tween before (c) and after (d) dissolution test.

All the formulations prepared with Gelucire showed completely precipitated less than 2 hrs and formulations prepared with Compritol 888 ATO were effective on percentage of the floating granules after 2 and 8 hours. Compritol granules provided suitable sustained release pattern in the manner that increase in D/L reduced D8 and MDT and increase in %T increased MDT. Higuchi model was the best fitted for dissolution data of granules prepared by Compritol and gelucire. In conclusion, Compritol provided more suitable floating ability and sustained release property.

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