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Preparation and Characterization of Sumatriptan Timed Delivery System Using Combination of Natural and Synthetic Polymers

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Abstract

BACKGROUND: Pulsatile drug delivery systems are time-controlled dosage forms that release active pharmaceutical component after a predefined period in order to synchronize circadian cycle of illness. Migraine has a diurnal cycle, with episodes peaking between 6 a.m. and 8 a.m. Sumatriptan acts as a selective agonist for 5-Hydroxytryptamine1 (serotonin) receptors. Thus, it is an effective therapy for acute migraine episodes.

AIM: The objective of the study is to create a time-controlled press-coated tablet containing two sumatriptan pulses. The first pulse demonstrated 100% active component release within 2 min, followed by the second sumatriptan pulse after just 5.5-h lag period.

MATERIALS AND METHODS: We prepared eleven formulations for rapid dissolving core tablets and thirty-three formulations for press-coated tablet that were manufactured by direct compression technique. The third layer was then squeezed onto press-coated tablet to create a two-pulse-time-controlled system. The qualities of core tablets and coatings were examined using a variety of criteria.

RESULTS: The formula F7 of core tablet was chosen because it had the lowest disintegration duration (8.8 s) with the quickest drug release within 2 min. In addition, formula C28 of the pectin-containing press-coated tablet: EC 100 mpa.s: HPMCK4M in concentrations of 20mg, 100 mg, and 80 mg were chosen as optimal coating layer.

CONCLUSIONS: Utilizing pulsatile delivery system for sumatriptan is an effective strategy in resolving migraine attacks.

Introduction

Pulsatile drug delivery systems are drug delivery systems that operate on a time-based schedule. These systems are intended to distribute medications on a time- and site-specific basis in accordance with the body's circadian cycle. Because continuous release techniques are not optimal, the pulsatile release pattern has become the most prevalent kind of controlled drug delivery system. The primary purpose for using pulsatile release is for medications that do not need a constant release rate, i.e., a zero-order release. After a lag period (an interval of no drug release), the drug must be released in a pulse that a quick and full drug release follows lag time. Chrono-pharmacotherapy (timed drug therapy) is the practice of synchronizing medication delivery with biological cycles in order to maximize therapeutic impact while minimizing adverse effects on the patient [1]. Pulsatile formulations are indicated for the treatment of migraine, hypercholesterolemia, cancer, diabetes, cardiovascular problems (e.g., hypertension, myocardial infarction), asthma, rheumatoid arthritis, duodenal ulcer, and colonic delivery [2].

The benefits of pulsatile medication delivery [3]

- Increased activity, decreased side effects, dosing frequency, and dosage size
- Increased patient compliance
- Drug adjusts to the circadian cycles of bodily functioning or disorders.

Sumatriptan

Sumatriptan is a serotonin 5-HT1 receptor selective agonist. It is an excellent therapy for migraine and cluster headaches that occur suddenly [4].

Aim of study

To prepare time-controlled tablet of sumatriptan that has 2-time release pulses and to obtain acceptable physical properties of tablet.

Materials and Methods

Included the following methods which are mentioned in detail in the supplementary file:

- Pre-compression parameters of core, coat, and outer layer powder blend: Include

1. Measurement of the angle of repose
2. Bulk density and tapped density
3. Hausner ratio and Carr's index (or % Compressibility) [5].

- Post-compression evaluation: Includes

1. Weight fluctuation, thickness, hardness, friability, and consistency [6]
2. *In vitro* disintegration time for core tablets
3. *In vitro* dissolution test
4. Evaluation of press-coated pulsatile tablet
5. *In vitro* release studies of press-coated pulsatile tablets.

The findings of the studies were presented as mean and standard deviation and analyzed using one-way analysis of variance, implementing p = 0.05 as significance level [7].

Results and Discussion

Pre-compression parameters of core powder blend

The results of bulk density, angle of repose, tapped density, Hausner ratio, and Carr's index for each designed core powder blend formula were presented in Table 1. These findings were calculated in accordance with USP [8]. The results show that prepared core formulas and coat powder blends exhibit adequate flow and compressibility parameters.

Post compression evaluation of core tablets

Weight variation, thickness, hardness, friability, and content uniformity

Results of weight variation test for the all prepared core tablet formulas were within acceptable average weight in agreement of requirements of USP pharmacopeia as shown in Table 2. Once tablets are compressed, a constant weight of tablets indicates proper powder flow and color filling [9].

Results of the thickness test for all prepared core formulas were in range of (5.381–5.731 mm) as shown in Table 2. A tablet's thickness may vary without affecting its weight. This is typically due to the variation in granule density; compression pressure applied, and the rate of compression [10].

Hardness testing is critical for solid oral dosage forms (i.e. tablets) because it offers an estimate of internal bonding strength of utilized powder-compact, which is what provides tablet with strength necessary to preserve internal structure when subjected to external forces. Thus, it is well established that changes in tablet hardness correspond with differences in dissolving or mechanical reaction during any post-compression processes such as tablet coating, packing, storage, or shipment [11].

Results of hardness test for all prepared core formulas were in the range of (4.1–4.86 Kg/cm^2) as shown in Table 2 which indicates that tablets had adequate strength property essential to resist handling, shipping, and tablet coating.

Formula 7 of core tablet which contains Avicel PH 102 as diluent shows higher hardness than formula11 which contains Spray-dried lactose as diluent which may be owing to smaller superficial area of spray-dried lactose would impair interactions between particles (adhesion and cohesion) due to less contact area for bonds during the compaction step, producing tablets less resistant to crumbling and crushing. Also, part of Avicel PH 102 popularity can be related to its excellent compatibility at low pressures, an excellent binder and tends to grow static charges in presence of excessive humidity [12], [13] and disintegrant. The mechanism of disintegrant action is anticipated to be a combination of disruption of wicking of particle-particle bonds [14].

Moreover, lactose is classified as a brittle material using the Wiederkehr - von Vincenz classification system, which is based on materials' compaction capacities. That is, lactose reduces mechanical strength of tablets and their resistance to fragmentation [15].

The results of friability test show that all prepared core tablets show acceptable friability, with

Table 1: Pre-compression physical parameter's for core powder blend

Formula	Angle of repose (degree) Mean ± SD, n = 3	Bulk density (g/cm^3) Mean ± SD, n = 3	Tapped density (g/cm^3) Mean ± SD, n = 3	Carr's index Mean ± SD, n = 3	Hausner ratio Mean ± SD, n = 3	Type of flow
F1	17.51 ± 0.03	0.546 ± 0.01	0.608 ± 0.02	10.21 ± 1.36	1.11 ± 0.019	Excellent
F2	18.4 ± 0.1	0.495 ± 0.08	0.57 ± 0.021	10.51 ± 1.0002	1.12 ± 0.02	Excellent
F3	25.7 ± 0.2	0.56 ± 0.56	0.632 ± 0.03	10.73 ± 0.37	1.119 ± 0.004	Excellent
F4	21.76 ± 0.25	0.468 ± 0.009	0.536 ± 0.015	12.73 ± 0.66	1.14 ± 0.007	Excellent
F5	26.26 ± 0.75	0.356 ± 0.017	0.393 ± 0.02	9.3 ± 0.62	1.1 ± 0.01	Excellent
F6	34.23 ± 0.68	0.336 ± 0.01	0.395 ± 0.013	14.86 ± 0.58	1.175 ± 0.007	Good
F7	21.36 ± 0.56	0.33 ± 0.02	0.371 ± 0.03	10.84 ± 0.39	1.122 ± 0.005	Excellent
F8	19.25 ± 0.75	± 0.3450.01	0.357 ± 0.015	3.41 ± 0.15	1.041 ± 0.007	Excellent
F9	20.5 ± 0.4	0.311 ± 0.026	0.334 ± 0.028	6.92 ± 0.2	1.07 ± 0.001	Excellent
F10	17.4 ± 0.5	0.354 ± 0.017	0.38 ± 0.019	7.72 ± 0.17	1.08 ± 0.002	Excellent
F11	27.9 ± 0.36	0.53 ± 0.03	0.566 ± 0.04	5.25 ± 0.09	1.06 ± 0.01	Excellent

Table 2: Post formulation results of press coated core tablet

Formula	Hardness (kg/cm^2)	Friability%	Weight variation (mg)	Thickness (mm)
C1	7.0 ± 0.15	0.41 ± 0.02	298 ± 0.05	5.38 ± 0.013
C2	6.8 ± 0.28	0.44 ± 0.06	300 ± 0.1	5.39 ± 0.005
C3	6.4 ± 0.14	0.46 ± 0.06	299 ± 0.06	5.40 ± 0.009
C4	6.4 ± 0.05	0.72 ± 0.07	301 ± 0.03	5.42 ± 0.008
C5	6.25 ± 0.3	0.63 ± 0.01	302 ± 0.02	5.44 ± 0.011
C6	7.25 ± 0.05	0.51 ± 0.02	300 ± 0.04	5.32 ± 0.012
C7	6.5 ± 0.03	0.61 ± 0.05	301 ± 0.05	5.33 ± 0.016
C8	6.7 ± 0.04	0.44 ± 0.02	303 ± 0.04	5.35 ± 0.007
C9	6.3 ± 0.09	0.79 ± 0.01	298 ± 0.1	5.36 ± 0.005
C10	6.25 ± 0.05	0.65 ± 0.04	300 ± 0.05	5.38 ± 0.006
C11	6 ± 0.07	0.69 ± 0.06	299 ± 0.03	5.28 ± 0.014
C12	6.5 ± 0.04	0.76 ± 0.03	300 ± 0.04	5.30 ± 0.008
C13	7.25 ± 0.1	0.64 ± 0.05	300 ± 0.04	5.31 ± 0.009
C14	7.5 ± 0.06	0.53 ± 0.07	303 ± 0.02	5.34 ± 0.006
C15	7.15 ± 0.02	0.62 ± 0.03	301 ± 0.04	5.35 ± 0.014
C16	6.5 ± 0.03	0.41 ± 0.04	300 ± 0.02	5.36 ± 0.034
C17	6.8 ± 0.14	0.57 ± 0.06	302 ± 0.03	5.37 ± 0.008
C18	6.5 ± 0.2	0.66 ± 0.03	299 ± 0.03	5.38 ± 0.012
C19	7 ± 0.25	0.35 ± 0.01	301 ± 0.02	5.42 ± 0.009
C20	6.5 ± 0.15	0.41 ± 0.05	301 ± 0.04	5.43 ± 0.008
C21	6.2 ± 0.75	0.49 ± 0.07	298 ± 0.02	5.40 ± 0.013
C22	6.25 ± 0.75	0.43 ± 0.02	302 ± 0.01	5.39 ± 0.005
C23	6 ± 0.06	0.7 ± 0.1	299 ± 0.05	5.38 ± 0.009
C24	6.2 ± 0.33	0.72 ± 0.03	301 ± 0.04	5.36 ± 0.008
C25	6.5 ± 0.05	0.68 ± 0.03	298 ± 0.04	5.44 ± 0.011
C26	6.75 ± 0.44	0.5 ± 0.04	301 ± 0.02	5.32 ± 0.012
C27	7.2 ± 0.12	0.44 ± 0.01	300 ± 0.03	5.31 ± 0.016
C28	7.5 ± 0.09	0.32 ± 0.06	302 ± 0.01	5.35 ± 0.007
C29	6.4 ± 0.02	0.67 ± 0.02	302 ± 0.01	5.40 ± 0.005
C30	6.5 ± 0.22	0.52 ± 0.04	301 ± 0.02	5.35 ± 0.006
C31	6.25 ± 0.4	0.6 ± 0.01	299 ± 0.04	5.28 ± 0.014
C32	6.75 ± 0.06	0.5 ± 0.02	298 ± 0.07	5.30 ± 0.008
C33	6.25 ± 0.04	0.6533 ± 0.015	300 ± 0.03	5.33 ± 0.009

weight loss of <1% as illustrated in Table 3. Since all the prepared formulas met the standard friability criteria, so they are predictable to show acceptable stability and withstand abrasion in handling, packaging, and shipment [16].

In vitro disintegration study of core tablets

The results of disintegration test of all prepared core formulas are presented in Table 2. In this study, three types of superdisintegrants were used, CCS and CP had three different concentrations (1%, 3%, and 5%) w/w while the SSG had four diverse concentrations (1%, 3%, 5%, and 7%) w/w.

As shown in Table 2, F1, F4, and F7 that contained 5% (w/w) croscarmellose sodium, 5% (w/w) sodium starch glycolate and 5% (w/w) crospovidone. F7 had shortest disintegration time and this may be due to the remarkable fast water penetration and extensive swelling capacity of SSG. SSG was reported to possess the capability to absorb water and expand up to 300 times its volume and being unaffected by an increase in compression pressure [17].

The results showed that F2 which contains 3% croscarmellose sodium had shorter disintegration time than F1 that contains higher concentration of this superdisintegrant which may be due to partial gelling that potentially could form a viscous barrier delaying entry of water into tablet leading to this delay in the disintegration of tablets of F2 [17].

In case of the superdisintegrant sodium starch glycolate was used in formulas F7, F8, F9, and F10 in concentrations 5%, 3%, 1%, and 7% (w/w), respectively. Here, we can see as we increase concentration of the superdisintegrant the disintegration time decreases (from 1% to 5%) until we reach the concentration 7% the disintegration time increases obviously and this also may be due to partial gelling [18].

Furthermore, the results of disintegration test for formulas F4, F5, and F6 had shown that as we increased in the concentration of crospovidone superdisintegrant, there was a decrease in disintegration time until we reached to concentration 5% (w/w), this formula had longer disintegration time partly due to rapid liquid penetration of largest capillaries isolates other areas of finer pore structure that air cannot escape. These areas make no contribution to the overall uptake of liquid. Hence, F5 gave the shortest disintegration time in formulas containing crospovidone as superdisintegrant [19].

At last, F11 contains the superdisintegrant sodium starch glycolate in the same concentration as F7 but here we use spray-dried lactose as diluent instead of avicel PH-102. The result showed an increase in the disintegration time might be because spray-dried lactose tends to dissolve rather than disintegrate regardless of the presence of superdisintegrant added to the formulation [20], [21].

In vitro dissolution test

Effect of superdisintegrant type

Formulas F1, F4, and F7 contain different types of superdisintegrant, i.e., croscarmellose sodium, crospovidone, and sodium starch glycolate of concentration 5% w/w, respectively. F7 has faster dissolution rate where 100% release of Sumatriptan from core tablet obtained in 2 min this significant difference ($p \leq 0.05$ This was explained by the fact that sodium starch glycolate has the added benefit of being soluble and dispersible in water.

Table 3: Physical evaluation of core tablets of sumatriptan

Formula	Weight variation (mg) Mean ± SD, n = 20	Thickness (mm) Mean ± SD, n = 10	Hardness (kg) Mean ± SD, n = 5	Friability %	Content uniformity % Mean ± SD, n = 3	Disintegration time seconds Mean ± SD, n = 6
F1	98.03 ± 2.1	5.71 ± 0.02	4.1 ± 0.13	0.58	97.31 ± 0.77	14.25 ± 0.95
F2	98.8 ± 0.97	5.731 ± 0.02	4.22 ± 0.17	0.48	96.17 ± 0.47	11 ± 4.89
F3	99.18 ± 0.6	5.731 ± 0.01	4.52 ± 0.32	0.33	98.07 ± 0.45	17.5 ± 2.5
F4	98.3 ± 1.05	5.55 ± 0.014	4.81 ± 0.2	0.283	99.6 ± 0.96	43.1 ± 7.02
F5	97.3 ± 1.4	5.5 ± 0.01	4.4 ± 0.28	0.38	100.06 ± 1.2	18 ± 2.2
F6	98.1 ± 1.15	5.65 ± 0.009	4.16 ± 0.1	0.572	96.866 ± 0.4	20.5 ± 7.3
F7	96.4 ± 1.6	5.5 ± 0.02	4.43 ± 0.3	0.38	98.48 ± 2.6	8.8 ± 1.4
F8	98.3 ± 0.63	5.381 ± 0.04	4.7 ± 0.2	0.31	95.15 ± 1.08	11.67 ± 1.6
F9	98.3 ± 0.5	5.5 ± 0.02	4.78 ± 0.2	0.315	96.712 ± 0.95	21.5 ± 2.25
F10	98.1 ± 0.85	5.4 ± 0.03	4.86 ± 0.15	0.306	98.4 ± 0.95	30 ± 3
F11	99.5 ± 0.96	5.6 ± 0.02	4.33 ± 0.35	0.300	101.82 ± 2.2	120.5 ± 4.79

Its spherical particles, spread in a tablet system, provide a greater surface area, enabling water to penetrate the tablet interior rapidly. The primary reasons for this disintegrant's effectiveness are presumably its high rate of water absorption and significant swelling capabilities; these qualities result in pressure being applied inside the tablet, therefore dissolving interparticle bonds.

This is followed by the dissolving of sodium starch glycolate particles, which causes the whole tablet structure to crumble and disintegrate [22]. In water, SSG may expand up to 300 times its initial volume [23].

Effect of sodium starch glycolate concentration

Formulas F7, F8, and F9 contain different concentrations of sodium starch glycolate used to study the effect of superdisintegrant concentration on the release of Sumatriptan from core tablets as shown in Figures 1 and 2 which contains 5% w/w sodium starch glycolate shows higher percent of drug release. There was a significantly different ($p \leq 0.05$) in dissolution rate between the formulas because as we increase in the concentration of superdisintegrant, the disintegration time will decrease [24].

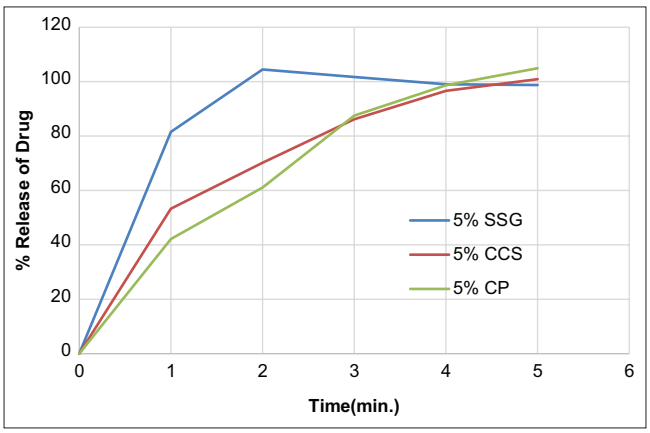

Figure 1: Effect of superdisintegrant type on drug release from core tablet (phosphate buffer pH 6.8, temp. 37°C)

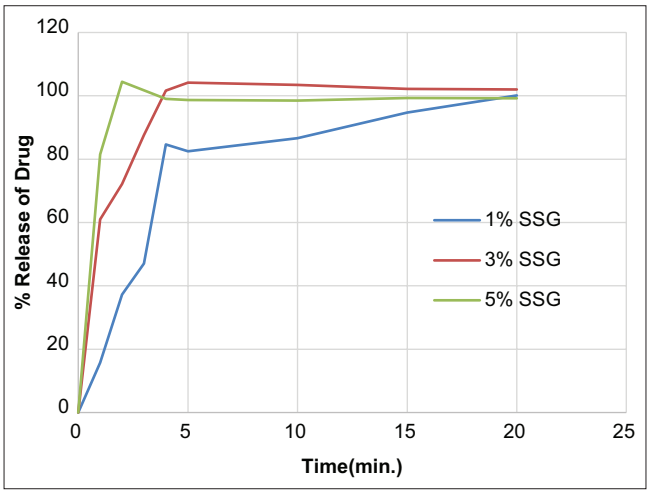

Figure 2: Effect of sodium starch glycolate concentration on drug release from core tablet (phosphate buffer pH 6.8, temp. 37°C)

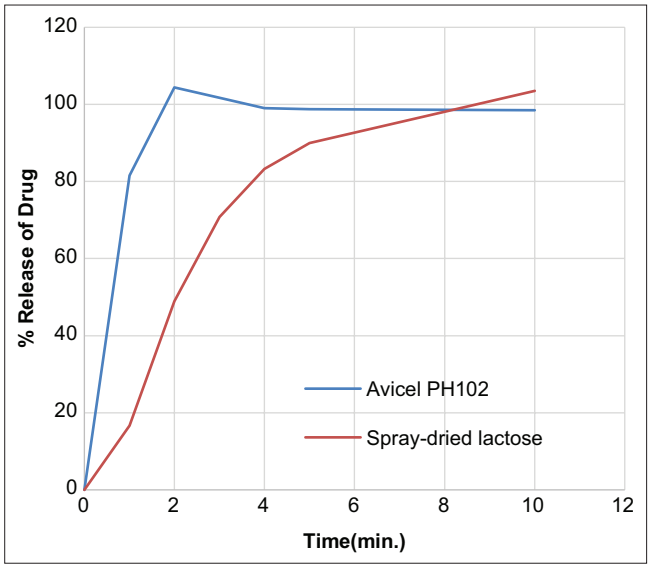

Figure 3: Effect of diluent type on drug release from core tablet (phosphate buffer pH 6.8, temp. 37°C)

Effect of diluent type

Formulas F7 and F11 were used to study the effect of diluent type on drug release as shown in Figure 3. Water-soluble fillers such as spray-dried lactose tend to dissolve rather than disintegrate, while insoluble fillers such as Avicel PH 102 produce rapid disintegration. It has been shown that superdisintegrants have a greater effect on disintegration time in an insoluble system than in a soluble or partially soluble system. As disintegration time of formula increases, it leads to slow down of the drug release from the core tablet [25], [26].

From the above results, it was found that F7 was the best one to give the faster release of the active ingredient and was selected as the best core tablet.

Evaluation of press-coated pulsatile tablet

The best-selected core tablet formula F7 was used to prepare the press-coated tablets.

The results of weight variation, thickness, hardness, and friability of all the press-coated tablets were shown in Table 2. These results show that all the prepared press-coated tablets formula agrees with the requirements of USP. The hardness of the press-coated tablets was kept constant in the range 6-7 kg/cm^2 by mounting the compression force of the machine to eliminate the variability in hardness. The hardness of the press-coated tablets slightly increased as ethyl cellulose concentration was increased due to the high compressibility of ethyl cellulose [27].

In vitro release studies of press-coated pulsatile tablets

Different natural polymers as chitosan, gellan gum, karaya gum, and pectin either alone or in combination at different ratios tried to compress

Table 4: Lag time of dissolution for different coating formula

Formula	Composition	Lag time in h: min
N1	K.G 100	Failed in compression
N2	Gellan gum 100	Failed in compression
N3	Chitosan 100	Failed in compression
N4	K.G: EC100mpa.s 90:10	Failed in compression
N5	Chitosan: EC100mpa.s 90:10	More than 6
N6	Gellan gum: EC100mpa.s 90:10	10 min. in 0.1N HCL
N7	K.G: Gellan gum: EC100mpa.s 10:80:10	13 min. in 0.1N HCl
N8	K.G: Gellan gum: EC100mpa.s 10:65:25	1 min. in 0.1N HCl
N9	Chitosan: Gellan gum: EC100mpa.s 45:45:10	More than 6
N10	Chitosan: Gellan gum: EC100mpa.s 15:60:25	1 min. in 0.1N HCl
N11	Chitosan: Gellan gum: EC100mpa.s 25:50:25	1 min. in 0.1N HCl
N12	Chitosan: Gellan gum: EC100mpa.s 30:45:25	1 min. in 0.1N HCl
N13	Gellan gum: EC100 mpa.s 50:50	0.5 hr. in 0.1N HCl
N14	Gellan gum: EC100 mpa.s 40:60	0.5 hr. in 0.1N HCl
N15	Gellan gum: EC10 mpa.s 30:70	2:30
N16	Gellan gum: EC10 mpa.s 20:80	2:30
N17	Pectin: EC100 mpa.s 75:25	Failed in compression
C1	K.G: EC10 mpa.s 20:80	More than 6
C2	K.G: EC 10 mpa.s 30:70	More than 6
C3	K.G: EC 100: HPMCK100M 20:60:20	More than 6
C4	K.G: EC100:HPMCK100M 20:40:40	More than 6
C5	K.G: EC100:HPMCK100M 20:20:60	More than 6
C6	K.G: EC100:HPMCK15M 10:5:85	More than 6
C7	K.G: EC100:HPMCK15M 10:10:80	More than 6
C8	Chitosan: EC10 20:80	More than 6
C9	Chitosan: EC10 30:70	More than 6
C10	Chitosan: EC10 40:60	More than 6
C11	Chitosan: EC10 50:50	More than 6
C12	Chitosan: EC100:HPMCK15M 10:5:85	More than 6
C13	Chitosan: EC100:HPMCK15 10:10:80	More than 6
C14	Pectin: EC10 20:80	8:00
C15	Pectin: EC10 30:70	7:30
C16	Pectin: EC10:HPMCK100M 20:60:20	More than 6
C17	Pectin: EC10:HPMCK100M 20:40:40	More than 6
C18	Pectin: EC10:HPMCK100M 20:20:60	More than 6
C19	Pectin: EC10:HPMCE3 20:20:60	10:15
C20	Pectin: EC10:HPMC90Sh-100SR 20:20:60	More than 6
C21	Pectin: EC10:HPMC90Sh-100SR 20:30:50	More than 6
C22	Pectin: EC10:HPMCE15 20:20:60	20
C23	Pectin: EC10:HPMCE15 30:20:50	Less than 1 hr. in 0.1N HCl
C24	Pectin: EC10:HPMCE15 40:20:40	Less than 0.5 hr. in 0.1N HCl
C25	Pectin: EC100:HPMCK4M 10:20:70	2:45
C26	Pectin: EC100:HPMCK4M 10:40:50	3
C27	Pectin: EC100:HPMCK4M 10:45:45	3:45
C28	Pectin: EC100:HPMCK4M 10:50:40	4:30
C29	Pectin: EC100:HPMCK4M 10:60:30	More than 6
C30	Pectin: EC100:HPMCK4M 10:70:20	More than 6
C31	Pectin: EC100:HPMCK15M 10:5:85	6:20
C32	Pectin: EC100:HPMCK15M 10:10:80	7
C33	Pectin: EC100:HPMCK15M 15:5:80	5:45

as coating material but without any success, so the mixture of these natural polymers with other synthetic polymers was successfully compressed and gave good results.

The coat formula C1-C33 (Table 4) was designed to optimize a suitable combination of two and sometimes three polymers. Some of them are hydrophilic in nature such as HPMC, karaya gum (K.G.), and pectin, others have hydrophobic properties such as (EC) and chitosan to be used as a coating layer providing around 5 h lag time and 100% release of the drug. The results of in vitro release studies of press-coated pulsatile tablets were shown in Table 4.

Conclusion

Based on the results of this study, the following was concluded:

1. Sodium starch glycolate was assigned as the best superdisintegrant as compared to croscarmellose sodium and crospovidone
2. Avicel PH 102 was selected the best diluent used in core formulation as compared to spray-dried lactose
3. Formula (F7) of the core tablet, was assigned as the selected formula of core tablet as it has shortest disintegration time (8.8 s) and fastest drug release from the core tablet (within 2 min)
4. Formula (C28) of the press-coated tablet was determined as the selected formula
5. The outermost layer of the pulsatile tablet contained the selected core tablet formula (F7)
6. The release profile of the two-pulse system showed the first pulse of sumatriptan release within 2 min of dissolution of the final tablet and the second pulse released after a lag time of 5.5 h
7. Using sumatriptan as pulsatile delivery system is promising method for controlling migraine as it follows the circadian rhythm.

Recommendation for Future Study

Bioavailability and bioequivalence studies of the prepared two-pulse pulsatile tablets of sumatriptan were recommended for future study.

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Supplementary Data

1. Materials

Materials utilized in this study were recorded in Table S1.

Table S1: Materials used in the study

No.	Material	Supplier company
1	Sumatriptan	Avril company, China
2	Croscarmellose sodium	Hyperchem-China
3	Crospovidone	Hyperchem-China
4	Di-sodium hydrogen orthophosphate	Samara drug industry-Iraq
5	Ethylcellulose 10 mpa·s	Hyperchem-China
6	Ethylcellulose 100 mpa·s	Hyperchem-China
7	karaya gum	Hyperchem-China
8	Hypromellose (Hydroxypropyl methylcellulose K4M)	Indian fine chem-India
9	Hypromellose (Hydroxypropyl methylcellulose K15M)	Hyperchem-China
10	Hypromellose (Hydroxypropyl methylcellulose K100M)	Hyperchem-China
11	Hypromellose (Hydroxypropyl methylcellulose E3)	Hyperchem-China
12	Hypromellose (Hydroxypropyl methylcellulose E15)	Hyperchem-China
13	Hypromellose (Hydroxypropyl methylcellulose 90SH-100SR)	Hyperchem-China
14	Gellan gum	Hyperchem-China
15	Chitosan	Samara drug industry-Iraq
16	Spray-dried Lactose	Hyperchem-china
17	Magnesium stearate	Samara drug industry-Iraq
18	Pectin	Hyperchem-china
19	Methanol	Samara drug industry-Iraq
20	Microcrystalline cellulose (Avicel PH 102)	Hyperchem-China
21	Potassium di-hydrogen orthophosphate	Samara drug industry-Iraq
22	Polyvinyl pyrrolidone K30	Samara drug industry-Iraq
23	Sodium starch glycolate	Hyperchem-China
24	Bromothymol Blue	Samara drug industry-Iraq
25	Talc	Samara drug industry-Iraq

2. Instruments

Instruments used in as a part of this study were listed in Table S2.

Table S2: Instruments used in this study

No.	Instrument	Manufacturer
1	Differential scanning calorimeter	Shimadzu 60Plus- Japan
2	Disintegration apparatus	Copley- UK
3	Dissolution apparatus	Copley- UK
4	Electronic balance	Kern-Germany
5	Electronic digital caliper	Powefix- Germany
6	Friability test apparatus	Tianjan gouming material- Guoming-India
7	Fourier transform infra-red spectrometer	Biotech engineering Management-UK
8	Hardness tests apparatus	Monsanto- USA
9	Hot air oven	Astell Hearson-UK
10	Hot air oven	Memmert-Germany
11	Magnetic stirrer	Stuart-England
12	Melting point apparatus	Stuart-England
13	pH meter	Hanna-Italy
14	Ultrasonic cleaner	Copley-Malaysia
15	U.V. spectrophotometer	EMC LAB-Germany
16	Tablet machine	Erweka- Germany
17	Water bath	Memmert-Germany
18	Water bath shaker	Karl Kolb- Germany
19	Water distillater	Boeco- Germany

3. Methods

A. Characterization of Sumatriptan

- Measurement of melting point

The melting point was determined by using open capillary tube technique as submitted by the United States Pharmacopeia (USP). A capillary glass tube sealed from one side was used, and a compact powder of sumatriptan was organized by putting a small quantity of drug material into the capillary tube which was then smoothly clicked on a solid surface to produce a column of the drug at the closed end. Then, the capillary tube was placed in electrical melting point device and observed till the drug was melted where the temperature at which the complete melting occurs was recorded [1]. The measured melting point of sumatriptan by using capillary method was found 169 ℃, which is consistent with the reported melting point range 169-171 ℃, which indicates the purity of drug powder [2].

The differential scanning calorimetry (DSC) of pure Sumatriptan powder is shown in Figure S1 and complied with reference. The DSC thermogram of the pure drug showed an endothermic peak of 170 0C, corresponding to the melting point of the crystalline form of the drug [3].

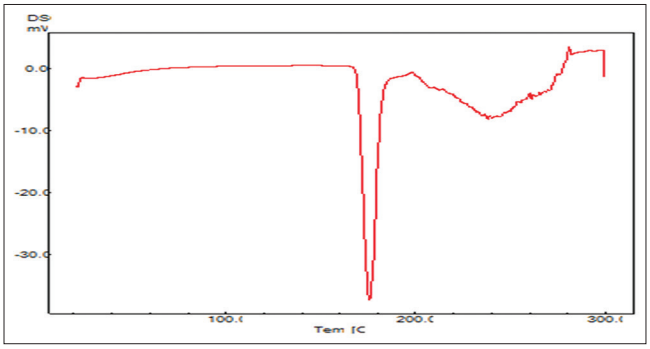

Figure S1: DSC thermogram of pure sumatriptan

- DSC

Differential scanning calorimetry is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a reference and sample is measured as a function of temperature at a heating rate of 10°C/min. Both the sample and reference are maintained at nearly the same temperature throughout the study. Mainly, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time [4].

- Fourier transform infrared spectroscopy (FTIR)

The FTIR spectrum of sumatriptan was recorded using FTIR spectrometer in a spectral region between 4000 and 400 and analyzed by transmittance technique. The drug sample was mixed in a mortar with potassium bromide KBr (1:100) and pressed in a hydraulic press (14 tons) to small disc [5]. The FTIR spectrum of pure sumatriptan powder is shown in Figure S2 and was compared with reference FTIR spectrum [6].

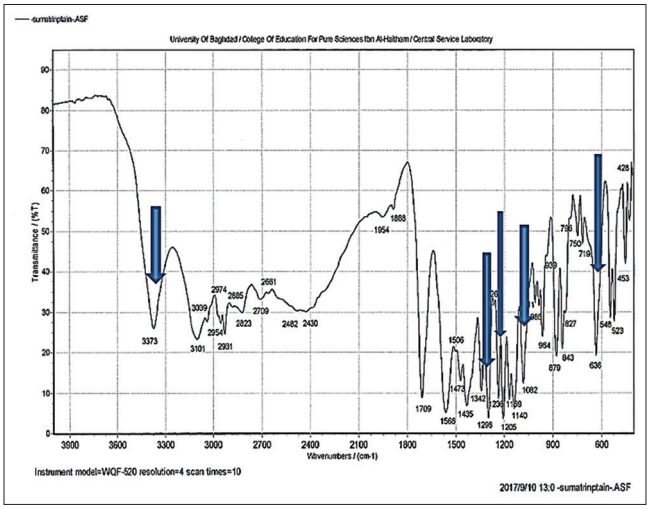

Figure S2: Fourier transform infrared spectrum of Sumatriptan

It was found that the characteristic peaks of sumatriptan at 3373 cm^{-1}, 1298 cm^{-1}, 1236 cm^{-1}, 1082 cm^{-1} and 636 cm^{-1} which were explained in Table S3.

Table S3: Characteristic absorption bands of pure Sumatriptan [6]

Frequency (cm^{-1})	Explanation
3373	N-H Stretching vibration
1298,1236	C-N stretching vibration
1082	S = O stretching vibration
636	C-S stretching vibration

• Determination of λ max of Sumatriptan

A stock solution of sumatriptan (100 μg/ml) in 0.1N HCl and phosphate buffer pH 6.8 were prepared separately then after a suitable dilution scanned by UV-spectrophotometer from 200 o 400 nm then λ max of sumatriptan was determined [Figures S3 and S4] [2].

• Calibration curves of Sumatriptan

The calibration curves of sumatriptan in 0.1N HCl and phosphate buffer preparing a serial dilution with different concentrations in the range of (5–75) μg/ml from the stock solution. The absorbance of each sample was measured at λ max of the drug. The measured absorbance was plotted against the respective concentration [7]. Figures S5 and S6 shows the calibration curves of sumatriptan in 0.1 N HCl pH 1.2 and phosphate buffer pH 6.8 respectively. Straight lines were obtained by plotting the absorbance versus concentration with regression coefficient. This indicates that calibration curves obey Beer's law within the range of concentration used.

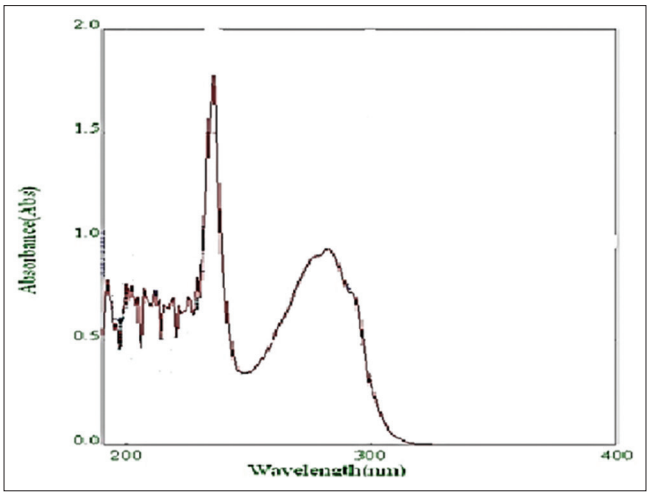

Figure S3: UV Spectrum of Sumatriptan in 0.1 N HCl

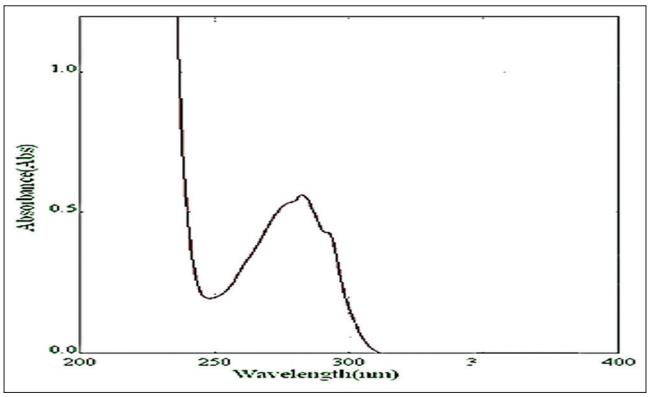

Figure S4: UV spectrum of sumatriptan in phosphate buffer pH 6.8

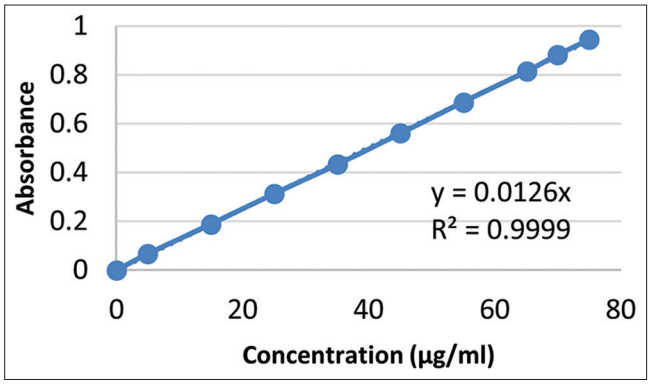

Figure S5: Calibration curve of sumatriptan in 0.1 N HCl using UV spectrophotometer at λmax 282 nm

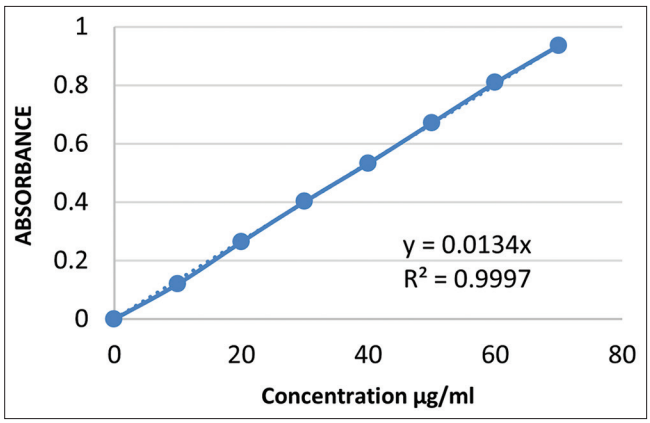

Figure S6: Calibration curve of Sumatriptan in phosphate buffer pH 6.8 using UV spectrophotometer at λmax 282 nm

• Determination of Sumatriptan Saturated Solubility

The solubility of Sumatriptan was determined in different media. An excess amount of drug was added separately to 10 ml of 0.1 N HCl, and phosphate buffer 6.8 in small glass test tubes. The test tubes were tightly stoppered and continuously stirred on isothermal water bath shaker for 48 h at 37.0 ± 1.0°C to get equilibrium, and then samples were centrifuged at 3000 rpm for 15 min. The supernatants were separated and filtered using filter paper 0.45 μm, and after appropriate dilution, solubility was determined by UV spectrophotometer [8], [9].

The solubility of Sumatriptan in different media was shown in Table S4. Sumatriptan is freely soluble in both buffers (0.1 N HCl and pH 6.8 phosphate buffer).The solubility of the active ingredient is the most significant features in the selection of the possible dissolution media. USP favors media which are related to the physiological conditions.

Table S4: Saturated solubility of sumatriptan in different media

Medium	Saturated solubility (mg/ml) Mean ± SD, n = 3
0.1 N HCl	274.0437 ± 0.0055
Phosphate buffer (pH 6.8)	237.096 ± 0.0059

The obtained solubility results indicate that these buffers provided sink condition in the dissolution media.

B. Preparation of Two-Pulse Drug Release System

Two-pulse drug release tablets were prepared by using direct compression method for the three layers.

- Preparation of Inner layer (core tablet)

Different powder blends of core tablet which contain Sumatriptan as an active ingredient with different types of superdisintegrants and different types of diluents were prepared to be evaluated for their flow properties and compressibility before compressing into a tablet using direct compression method as shown in Table S5.

Powder mixtures of Sumatriptan with PVP K30 as binder and microcrystalline cellulose (MCC, Avicel PH-102) or spray-dried lactose as diluent and cross-carmellose sodium (Ac-Di-Sol) or SSG or crosspovidone as superdisintegrant ingredients were dry blended for 20 min. Followed by addition of talc and Magnesium Stearate. The mixtures were then further blended for 5 min., 100mg of resultant powder blend was manually compressed using single biconcave punch machine, with a 6mm punch and die to obtain the round core tablet [10], [11].

- Formulation of coating mixed blend for press – Coated tablet

Different natural polymers (chitosan, gellan gum, karaya gum and pectin) either alone or in combination at different ratios formulas N1-N17 were tried to be compressed as coating material but without any success, so a mixture of these natural polymers with other synthetic polymers was successfully compressed and had given a good result.

Various coating formula containing different compositions and grades of Ethylcellulose and/or HPMC with natural polymers chitosan or gellan gum or karaya gum or pectin were weighed, dry blended at about 10 min and used as a press-coating material for coating the core tablet to prepare press-coated pulsatile tablets by direct compression method [10]. The composition of the coat was shown in Table S6. The core tablets were press-coated with coat blend where 40% of the coating material was weighed and placed in 9-mm die of the tablet machine, the core tablet was placed centrally in the die cavity, and the remaining quantity 60% of coating material was poured into the die cavity over the core tablet and finally compressed using single punch machine [11].

- Formulation of the outer layer

The outer layer of tablets (third layer) has the same formulation of the selected formula for the core tablet (F7) without dye, it was prepared by direct compression method similar to core tablet formulations. Powder blend was manually compressed using single biconcave punch machine, with an 11mm punch and die to obtain the round three-layer press coated tablet.

- Pre-compression parameters of core, coat and outer layer powder blend

Micromeritic properties of core, coat and outer layer powder blends were recorded. These properties include [12].

- Angle of repose measurement

The angle of repose was determined by taking accurately weighed the quantity of powder blend into the funnel. The funnel height was adjusted such that the funnel tip should touch the apex of the blend. This blend was then allowed to freely flow through the funnel onto the surface. From the formed powder cone, radius and height were measured, and their angle of repose was calculated using the following equation [13].

$$\tan\theta = h/r \quad (1)$$

where h and r are the height and radius of the formed powder cone respectively, and θ is an angle of repose.

The type of flow according to angle of repose values are shown in Table S7.

- Apparent bulk density and tapped density

The bulk density, as a measure used to designate packing materials was determined by transporting the precisely weighed amount of blend (2 g) to the graduated cylinder (10 ml) with the help of a funnel. The volume was noted. The proportion of the weight of the sample to the volume was calculated.

To measure tapped density, the same quantity of blend (2 g) was transported to a 10 ml graduated cylinder and tapped by hand at a specific height for a fixed number of taps (100). Average of three determinations was taken. The tapped density was defined as the ratio of the sample weight to tapped volume [14].

- Carr's Index (or % Compressibility) and Hausner Ratio [15]

Table S5: Composition of Sumatriptan core tablet

Ingredients (mg)	Sumatriptan	Croscarmellose Sodium	Crospovidone	Sodium starch glycolate	Avicel PH 102	Spray-dried lactose	PVP K30	Bromothymol Blue	Magnesium stearate	Talc	Total weight
F1	25	5	-	-	64	-	2	1	1	2	100
F2	25	3	-	-	66	-	2	1	1	2	100
F3	25	1	-	-	68	-	2	1	1	2	100
F4	25	-	5	-	64	-	2	1	1	2	100
F5	25	-	3	-	66	-	2	1	1	2	100
F6	25	-	1	-	68	-	2	1	1	2	100
F7	25	-	-	5	64	-	2	1	1	2	100
F8	25	-	-	3	66	-	2	1	1	2	100
F9	25	-	-	1	68	-	2	1	1	2	100
F10	25	-	-	7	62	-	2	1	1	2	100
F11	25	-	-	5	-	64	2	1	1	2	100

Table S6: Composition of coat mixture formula for sumatriptan

Formula	Karaya gum (mg)	Gellan gum	Chitosan (mg)	Pectin (mg)	EC10 mpa.s (mg) Mpa	EC100 mpa.s (mg)	HPMC K100M (mg)	HPMC K15M (mg)	HPMC K4M (mg)	HPMC E3 (mg)	HPMC E15 (mg)	HP5MC90Sh-100SR (mg)	Total weight (mg)
N1	200												200
N2		200											200
N3			200										200
N4	180					20							200
N5			180			20							200
N6		180				20							200
N7	20	160				20							200
N8	20	130				50							200
N9		90	90			20							200
N10		120	30			50							200
N11		100	50			50							200
N12		90	60			50							200
N13		100				100							200
N14		80				120							200
N15		60			140								200
N16		40			160								200
N17				150		50							200
C1	40				160								200
C2	60				140								200
Formula	Karaya gum (mg)	Gellan gum	Chitosan (mg)	Pectin (mg)	EC10 mpa.s (mg)	EC100 mpa.s (mg)	HPMC K100M (mg)	HPMC K15M (mg)	HPMC K4M (mg)	HPMC E3 (mg)	HPMC E15 (mg)	HP5MC90Sh-100SR (mg)	Total weight (mg)
C3	40				120		40						200
C4	40					80	80						200
C5	40					40	120						200
C6	20					10		170					200
C7	20					20		160					200
C8			40		160								200
C9			60		140								200
C10			80		120								200
C11			100		100								200
C12			20			10		170					200
C13			20			20		160					200
C14				40	160								200
C15				60	140								200
C16				40	120		40						200
C17				40	80		80						200
C18				40	40		120						200
C19				40	40					120			200
C20				40	40							120	200
C21				40	60							100	200
C22				40	40						120		200
Formula	Karaya gum (mg)	Gellan gum	Chitosan (mg)	Pectin (mg)	EC10 mpa.s (mg) Mpa	EC100 mpa.s (mg)	HPMC K100M (mg)	HPMC K15M (mg)	HPMC K4M (mg)	HPMC E3 (mg)	HPMC E15 (mg)	HP5MC90Sh-100SR (mg)	Total weight (mg)
C23				60	40						100		200
C24				80	40						80		200
C25				20		40			140				200
C26				20		80			100				200
C27				20		90			90				200
C28				20		100			80				200
C29				20		120			60				200
C30				20		140			40				200
C31				20		10		170					200
C32				20		20		160					200
C33				30		10		160					200

Table S7: Flow properties and corresponding angles of repose [1]

Flow property	Angle of Repose (degrees)
Excellent	25-30
Good	31-35
Fair –aid not need	36-40
Passable –may hang up	41-45

They show a measurement of the propensity of a powder to be compressed. It is represented in percentage and is give

Carr's index = (Tapped density–Bulk density)/Tapped density×100 (2)

Hausner ratio:

It is an indirect index of ease of powder flow. It is measured by the following formula.

Hausner's ratio = Tapped density/Bulk density (3)

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25) [16].

The relationship between compressibility index and Hausner's ratio as shown in Table S8.

Post-Compression Evaluation

- Weight variation test [18].

This test was done by weighing 20 tablets individually, the calculating the average weight and comparing the weight of each tablet to the average weight. The tablets meet the USP requirements if no more than two tablets are outside the percentage limit and if no tablet differs by double percentage limit, as shown in the Table S9:

- Thickness

The thickness of tablets for each layer (core, press coated core, and the final tablet)was determined

Table S8: Flowability and its corresponding values of compressibility index and Hausner's ratio [17]

Compressibility index	Flow character	Hausner ratio
10<	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
38>	Very very poor	1.60>

Table S9: Weight variation according to USP [1]

Average weight of tablets (mg)	Maximum % difference allowed
130 or less	10
130–324	7.5
More than 324	5

by using vernier caliper. Ten tablets were chosen randomly for this test from each formula, and the average value was reported [19].

- Hardness test

The crushing strength of the tablets (core, coated core, the final tablet) was measured using a Monsanto hardness tester. Five tablets from each formulation batch were tested randomly, and the average reading was noted. The hardness is measured in kg/cm^2 [20].

- Friability test

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed and revolved at 25 rpm for 4 min. The tablets were then reweighed after removal of fines, and the percentage of weight loss was calculated. The % friability was then calculated by

$$F = W\ initial – W\ final \times 100 / W\ initial \quad (4)$$

Acceptance criteria for % friability that is the percentage of weight loss should be less than 1% [21].

- Content uniformity

This test applied to core tablet and final tablet. Ten tablets were weighed and powdered by using mortar and pestle. The powder which is equivalent to 50 mg of sumatriptan in case of coated tablet and 25 mg of sumatriptan in case of core tablet was weighed and dissolved in 0.1 N HCl solution (pH 1.2).

The solution gained was filtered, and one mL of the filtrate was appropriately diluted and analyzed for Sumatriptan spectrophotometrically at its λ max [12], [22].

- *In vitro* disintegration time for core tablets

The disintegration test was done for all core tablet formulas at 37°C using phosphate buffer (pH 6.8) as disintegration media. Disintegration apparatus of a 1 L cylinder with a basket rack assembly containing six open-ended tubes and 10-mesh screen on the bottom was used. A tablet was placed in every tube of the basket and the time required for complete disintegration of the tablets with no palpable mass remaining in the apparatus was noticed [1].

- *In vitro* dissolution test

In vitro dissolution test is applied for (core, coated core, and final tablet) using USP apparatus Type II (paddle) at 37 ± 0.5°C in 900 mL of dissolution medium (0.1 N HCl buffer pH 1.2 and phosphate buffer pH 6.8) at 50 rpm. Five mL samples were withdrawn periodically at predetermined time intervals, and each sample was substituted with an equal volume of fresh dissolution medium. Then, the samples were filtered and analyzed spectrophotometrically at its λ max. Each test was done in triplicate. For optimization many variables evaluated to test its effect on the dissolution of the core, press coated core and final tablet from different formulas [23].

- Variables affecting release of sumatriptan from the core tablet
- Effect of superdisintegrants type

Three different types of superdisintegrants (croscarmellose, crospovidone, and sodium starch glycolate) at 5% concentrations were used in (F1, F4and F7) to study the effect of superdisintegrant types on the drug release properties from sumatriptan core tablet.

- Effect of concentration of superdisintegrant

Different percentages of sodium starch glycolate (superdisintegrant) were utilized in the formulation of core tablet formula (F9, F8, F7) containing 1,3 and 5% to analyze the effect of using different concentrations of sodium starch glycolate on sumatriptan release from the core tablet.

- Effect of diluent types

Formulas 7 and 11 were used to study the effect of types of diluents on drug release properties of core tablet in which Avicel PH 102 in formula seven was replaced by spray dried lactose in formula 11.

- Variables affecting the release of sumatriptan from the press coated core tablet (Effect of various types of polymers and their combination)

Thirty-three formulas of coated core tablet were made using different polymers (either alone or in combination) in different ratios as recorded in Table S4 to study their effect on sumatriptan release from press coated core tablet and also their effect on the lag time required for release of the drug.

- Drug – excipients compatibility studies

Physicochemical compatibility between sumatriptan and different excipients was studied using FTIR and DSC.

- FTIR

The pure drug powder and the optimum formula of core tablet (F7) were analyzed individually by using (Shimadzu 8300, Japan) according to KBr disk method. About 2–3 mg sample was mixed with dried IR grade potassium bromide powder to form a uniform blend of about 200 mg, and analyzed by FTIR spectroscopy at 4000–400 cm^{-1} [24].

1. DSC

It was carried out by the same way for the pure

drug powder, and the physical mixture of the optimum formula of core tablet (F7), and the optimum formula of core tablet (F7), and final three layer press coated tablet using Differential Scanning Calorimeter (Shimadzu DSC- 60). Samples were heated in an aluminum sample pans at a rate of 10°C/min over a temperature up to 350 °C under a nitrogen flow of 50 ml/min [25].

2. Accelerated stability studies

The stability of the selected press coated tablets was studied at three different temperatures: 40, 50 and 60°C for 12 weeks. Samples were taken at 14 days interval, and sumatriptan was determined by the same method mentioned previously in content uniformity test section [26].

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