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A – koncepcja i projekt badania, B – gromadzenie i/lub zestawianie danych, C – analiza i interpretacja danych,
D – napisanie artykułu, E – krytyczne zrecenzowanie artykułu, F – zatwierdzenie ostatecznej wersji artykułu

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Streszczenie

Wprowadzenie. Matryce hydrofilowe użyte jako doustne postacie leków o przedłużonym uwalnianiu są aplikacyjnie odpowiednim podłożem dla krótko działających NLPZ – ketoprofenu. Odpowiednio dobrana matryca hydrofilowa w doustnych preparatach może znacząco poprawić skuteczność działania i bezpieczeństwo stosowania ketoprofenu.

Cel pracy. Zbadanie przydatności polimerów (syntetycznego Kollidonu K25 i K90 oraz półsyntetycznego – hydroksyetylocelulozy) i dwuwodnego wodorofosforanu wapnia (jako nieorganicznego wypełniacza) w technologii matrycowych stałych doustnych postaci leku z ketoprofenem. Zbadanie wpływu niejonowych surfaktantów (Tween 80, Rofam 70) na kinetykę uwalniania.

Materiał i metody. Ketoprofen, HEC, Kollidon K25 i K90, wapniowy wodorofosforan, stearynian magnezu. Inkorporacja. Badania mas tabletkowych. Tabletkowanie bezpośrednie. Badanie parametrów farmakopealnych i dostępności farmaceutycznej. Aproksymacja otrzymanych wyników.

Wyniki. Wyniki przeprowadzonych badań granulometrycznych mas tabletkowych były zgodne z normami farmakopealnymi. Rezultaty badań morfologicznych i biofarmaceutycznych otrzymanych matryc (tabletek) były zgodne z normami farmakopealnymi dla formulacji z HEC, K25 i K90. Wyniki uwalniania najbardziej zbliżone do kinetyki zerowego rzędu otrzymano dla matrycy zawierającej HEC i K25. Tween 80 dodany do 0,1N HCl przyspieszał uwalnianie ketoprofenu, natomiast Rofam 70 spowalniał. Tween 80 i Rofam 70 dodany do buforu pH 7,4 przyspieszał uwalnianie ketoprofenu.

Wnioski. W przedstawionym modelowym układzie badań preformulacyjnych wykazano przydatność HEC i Kollidonu K25 w technologii matryc hydrofilowych z ketoprofenem. Tenzydy dodane do medium nie wpływają na szybkość uwalniania ketoprofenu.

Słowa kluczowe: ketoprofen, hydroksyetyloceluloza, Kollidon K25, Tween 80, Rofam 70

Abstract

Background. Hydrophilic matrices used as oral forms of sustained release drugs are a suitable application medium for short-acting nonsteroidal anti-inflammatory drugs (NSAID) – ketoprofen. A properly selected hydrophilic matrix in oral preparations may significantly increase efficacy and application safety of ketoprofen.

Objectives. The aim of the research was to analyze the usefulness of polymers (synthetic Kollidon K25 and K90, semi-synthetic hydroxyethylcellulose) and calcium hydrogen phosphate dihydrate (as an inorganic filler) in manufacturing solid oral matrix forms of ketoprofen and to study of the effect of non-ionic surfactants (Tween 80, Rofam 70) on release kinetics.

Material and methods. Ketoprofen, HEC, Kollidon K25, and K90, calcium hydrogen phosphate, magnesium stearate. Incorporation. Studies on the tablet mass. Direct tableting. Studies on the pharmacopoeial parameters and pharmaceutical availability. Approximation of the results.

Results. The results of the granulometric studies on tablet mass were in accordance with pharmacopoeial standards. The results of morphological and biopharmaceutical studies of the obtained matrices (tablets) were consistent with the pharmacopoeial standards for formulations with HEC, K25 and K90. The release results most closely related to row 0 kinetics were obtained for the matrix containing HEC and K25. Tween 80 added to 0.1N HCl accelerated the release of ketoprofen, while Rofam 70 decelerated it. Tween 80 and Rofam 70 added to the pH 7.4 buffer accelerated the release of ketoprofen.

Conclusions. The presented model system of preformulation studies showed the usefulness of HEC and Kolidon K25 in the technology of hydrophilic matrices with ketoprofen. Surfactants added to the medium do not affect the release rate of ketoprofen.

Key words: Tween 80, ketoprofen, hydroxyethylcellulose, Kollidon K25, Rofam 70

Wprowadzenie

Odpowiedni skład matrycy hydrofilowej zwiększa skuteczność działania ketoprofenu, zmniejsza działania niepożądane oraz poprawia komfort i wygodę stosowania leku.[1] Jednym z najczęściej występujących skutków ubocznych stosowania ketoprofenu jest działanie wrzodotwórcze na śluzówkę żołądka przewodu pokarmowego.[2] Odpowiednia matryca hydrofilowa mogłaby znacząco zmniejszyć to negatywne działanie.[3–5]

Aby uwalnianie z matrycy było jak najbardziej zbliżone do kinetyki zerowego rzędu, należy w badaniach preformulacyjnych empirycznie określić jakościowy i ilościowy udział składowych matrycy.[6]

Celem pracy było zbadanie przydatności polimerów (syntetycznych Kollidonów K25 i K90; półsyntetycznych – hydroksyetylocelulozy) i dwuwodnego wodorofosforanu wapnia (jako nieorganicznego, nierozpuszczalnego wypełniacza) w konstruowaniu matrycowych stałych doustnych postaci leku z ketoprofenem (ang. *active pharmaceutical ingredient* – API).

Specyfika uwalniania API zależy od wzajemnych relacji ilościowo-lepkościowych składowych matrycy oraz od rodzaju i składu płynu akceptorowego (medium).[7] Ze względu na przynależność ketoprofenu do II grupy systemu klasyfikacji biofarmaceutycznej (ang. *biopharmaceutics classification system* – BCS) zaproponowane zostały modyfikacje do testu uwalniania przez wprowadzenie niejonowych surfaktantów (innowacyjnego Rofamu 70 oraz referencyjnego Tweenu 80) do płynu akceptorowego.[8,9]

Materiał i metody

Odczynniki, materiały i aparatura

Substancja lecznicza:
- ketoprofen (S.I.M.S srl, Società Italiana Medicinali Scandicci, Florencja, Włochy).

Substancje pomocnicze:
- hydroksyetyloceluloza (HEC; 2-Hydroxyethyl cellulose, average M_w ~250,000; Sigma-Aldrich, Polska);
- wapniowy wodorofosforan dwuwodny (POCH S.A., Gliwice, Polska);
- Kollidon K25 (Sigma-Aldrich, Polska);
- Kollidon K90 (Sigma-Aldrich, Polska);
- stearynian magnezu (POCH S.A., Gliwice, Polska);
- Tween 80 (Sigma-Aldrich, Polska);
- Rofam 70 (Instytut Ciężkiej Syntezy Organicznej „Blachownia", Kędzierzyn-Koźle, Polska);
- kwas solny 0,1M, odważka analityczna (Chempur, Piekary Śląskie, Polska);
- diwodorofosforan potasu (POCH S.A., Gliwice, Polska);
- wodorofosforan disodu (POCH S.A., Gliwice, Polska);
- chlorek sodu (Eurochem BGD Sp. z o.o., Tarnów, Polska).

Aparatura użyta do badań:
- tabletkarka uderzeniowa Korsch typu EKO (Erweka GmbH, Heusenstamm, Niemcy);
- aparat do przeprowadzania uwalniania substancji czynnej z tabletek typu DT600 (Erweka GmgH);
- twardościomierz typu TBH 125 (Erweka GmbH);
- friabilator typu uTar 220 (Erweka GmbH);
- wolumetr ZD Polfa W2 (Polfa, Warszawa, Polska);

– analizator sitowy (Haver & Boecker, Oelde, Niemcy);
– spektofotometr UV-VIS Nicolet Evolution 300 z programem operacyjnym Vision Pro-Thermo Electron Corporation (Thermo Fisher Scientific, Waltham, Stany Zjednoczone);
– waga analityczna typu WPS 60/C (Radwag, Radom, Polska);
– suwmiarka – model CD-15CP (Mitutoyo, Kawasaki, Japonia).

Metodyka badań

Przygotowanie mas tabletkowych

Opierając się na dostępnym piśmiennictwie, otrzymano 4 wariantowe formulacje mas tabletkowych różniące się składem substancji stanowiących matryce. Wybrano 4 warianty, tj. wykonano 4 formulacje zawierające różne elementy budujące matrycę w ilości 245 mg: formulacja I zawierała HEC jako element budujący matrycę, formulacja II – fosforan dwuwapniowy, formulacja III – Kollidon K90, formulacja IV – HEC. Fosforan wapnia stanowił obojętny nieorganiczny składnik budujący matrycę (występujący w największej ilości). W każdej formulacji do elementu budującego matrycę dodano składnik uzupełniający w ilości 150 mg: formulacja I – Kollidon K25, formulacja II – Kollidon K90, formulacja III – Kollidon K25, formulacja IV – Kollidon K90.[10–14] We wszystkich formulacjach substancą poślizgową i smarującą był stearynian magnezu. Jako modelową substancję leczniczą zastosowano ketoprofen. Masy tabletkowe przygotowano w ilości 1000 g na każdy skład formulacyjny (tabela 1). Składowe formulacyjne i ketoprofen rozdrobniono w moździerzu i ujednolicono, przesiewając przez sito 0,1 mm. Wymieszano w dużym moździerzu w kolejności od składników występujących w największej ilości do ilości najmniejszej, na końcu dodając stearynian magnezu. Masy tabletkowe poddano tabletkowaniu bezpośredniemu z użyciem tabletkarki ekscentrycznej (uderzeniowej). Zastosowano stemple płaskie o średnicy 11 mm.

Badania przeprowadzone na masach tabletkowych

Przed procesem tabletkowania wykonano podstawowe badania mas tabletkowych zaleconych przez Farmakopeę Polską XI (FP XI) – analiza sitowa, badanie gęstości nasypowej swobodnej, gęstości nasypowej po ubiciu, pomiar kąta usypu.[15] Do badań użyto po 30 g mas tabletkowych. Analizę sitową wykonano z zastosowaniem zestawu sit: 0,315 mm; 0,16 mm; 0,09 mm; 0,08 mm i 0,063 mm (tabela 2).

Badanie gęstości nasypowej i gęstości po ubiciu wykonano przy użyciu cylindra miarowego. Odmierzono 50 mL masy

Tabela 2. Zestawienie wyników analizy sitowej dla masy tabletkowej (30,0 g) formulacji

Table 2. Results of sieve analysis (30.0 g) of the formulations

Rozmiar oczek sita [mm]	Masa mieszaniny na sicie [g]	Masa początkowa [%]
Formulacja I		
0,315	1,817	9,39
0,15	4,082	27,27
0,09	13,161	47,20
0,08	3,51	12,70
0,063	1,456	5,85
Ilość odzyskanej masy początkowej: 80,16%; straty: 19,92%		
Formulacja II		
0,315	9,514	33,38
0,15	2,731	15,77
0,09	12,179	44,26
0,08	0,569	1,90
0,063	0,665	2,22
Ilość odzyskanej masy początkowej: 97,52%; straty: 2,47%		
Formulacja III		
0,315	14,431	46,43
0,15	5,369	21,90
0,09	7,579	26,93
0,08	0,463	1,21
0,063	0,00	0,33
Ilość odzyskanej masy początkowej: 96,80%; straty: 3,20%		
Formulacja IV		
0,315	9,878	35,59
0,15	10,292	38,97
0,09	6,314	22,71
0,08	0,594	1,31
0,063	0,00	0,00
Ilość odzyskanej masy początkowej: 98,58%; straty: 1,41%		

Tabela 1. Skład recepturowy tabletek

Table 1. Formula of the tablets

Substancje lecznicze oraz pomocnicze	Formulacja I	Formulacja II	Formulacja III	Formulacja IV
Ketoprofen	100	100	100	100
Fosforan dwuwapniowy	0	245	0	0
Kollidon K25	150	0	150	0
Kollidon K90	0	150	245	150
Hydroksyetyloceluloza	245	0	0	245
Stearynian magnezu	5	5	5	5

Tabela 3. Parametry granulometryczne mas tabletkowych

Table 3. Granulometric parameters of tablet formulations

Skład formulacyjny	Objętość po ubiciu [mL]	Masa mieszaniny [g]	Gęstość nasypowa swobodna [g/mL]	Gęstość nasypowa po ubiciu [g/mL]	Współczynnik Carra [%]	Współczynnik Hausnera	Kąt usypu
Formulacja I	39,00 ±0,0000	20,689 ±0,0899	0,41378	0,52377	0,21	1,2658	56,00° ±1,0000
Formulacja II	37,5 ±0,2887	26,803 ±0,3192	0,53606	0,7244	0,26	1,3513	41,67° ±0,5774
Formulacja III	40,00 ±0,2887	25,474 ±0,1273	0,5094	0,63685	0,2	1,25	21,00° ±1,000
Formulacja IV	39 ±0,5774	23,582 ±0,2271	0,47164	0,60466	0,22	1,282	37,67° ±0,5774

tabletkowej poszczególnych formulacji do naczynia pomiarowego. Naczynie umieszczono w wolumetrze wykonującym drgania w celu ubicia mieszaniny. Po procesie ubijania zawartość cylindra zważono na wadze. Otrzymane wyniki pozwoliły na obliczenie gęstości nasypowej, gęstości (swobodnej) po ubiciu, współczynnika Carra oraz Hausnera (tabela 3).

Gęstość nasypową wyliczono, posługując się wzorem:

$$\text{gęstość nasypowa} = \frac{\text{masa mieszaniny [mg]}}{\text{objętość przed ubiciem [mL]}}$$

Gęstość po ubiciu wyliczono ze wzoru:

$$\text{gęstość po ubiciu} = \frac{\text{masa mieszaniny [mg]}}{\text{objętość po ubiciu [mL]}}$$

Współczynnik Carra (C) wyliczono ze wzoru:

$$C = \frac{\text{objętość przed ubiciem} - \text{objętość po ubiciu}}{\text{objętość przed ubiciem}} \times 100$$

Współczynnik Hausnera (H) wyliczono ze wzoru:

$$H = \frac{\text{objętość przed ubiciem}}{\text{objętość po ubiciu}}$$

Pomiar kąta usypu wykonano z użyciem szklanego lejka zgodnie z wytycznymi FP XI, mierzono wysokość i średnicę podstawy powstałego stożka. Badania powtarzano trzykrotnie dla każdej masy tabletkowej. Wartości kąta usypu wyliczono wg wzoru:

$$tg(\alpha) = \frac{\text{wysokość}}{0{,}5} \times \text{podstawa}$$

Badania przeprowadzone na tabletkach

Analizę otrzymanych postaci leku przeprowadzono wg zaleceń FP XI.[15] Otrzymane tabletki oceniono pod względem morfologicznym (wielkość, kształt i kolor) oraz zbadano ich parametry technologiczne, takie jak: jednolitość masy pojedynczych tabletek, odporność mechaniczną na ścieranie (badanie przeprowadzono z użyciem friabilatora) i zgniatanie (badanie przeprowadzono twardościomierzem), jednolitość zawartości substancji czynnej w tabletach. Ze względu na charakter otrzymanych tabletek (tabletki o przedłużonym uwalnianiu) nie badano czasu ich rozpadu. Dane uzyskane dla tych parametrów zostały opracowane statystycznie za pomocą programu Microsoft Office Excel 2016 MSO (16.0.4266.1001; 64-bitowa), tabela 4. Na ich podstawie (średnica, grubość, siła potrzebna do zgniecenia tabletki) obliczono współczynnik twardości (tabela 5).

Tabela 4. Wartości podstawowych parametrów statystycznych opisujących masę i wymiary tabletek

Table 4. Values of basic statistical parameters describing the mass and dimensions of tablets

Formulacja I			
Parametr	masa [g]	grubość [mm]	średnica [mm]
M (*n* = 20)	0,4986	5,422	11,022
SD	0,009516744	0,08612109	0,026277867
Me	0,498	5,415	11,03
Mo	0,494	5,34	11,01
Kurt	–0,126209327	–0,70654155	7,633611966
Formulacja II			
Parametr	masa [g]	grubość [mm]	średnica [mm]
M (*n* = 20)	0,4905	4,3180	11,0515
SD	0,0075	0,0574	0,033446737
Me	0,49	4,31	11,05
Mo	0,49	4,31	11,05
Kurt	0,0314	1,2968	2,485087572
Formulacja III			
Parametr	masa [g]	grubość [mm]	średnica [mm]
M (*n* = 20)	0,4968	5,5016	11,109
SD	0,0095	0,0914	0,18856522
Me	0,4983	5,5117	11,07
Mo	0,501	5,4921	11,07
Kurt	–0,4809	–0,7468	18,86129639
Formulacja IV			
Parametr	masa [g]	grubość [mm]	średnica [mm]
M (*n* = 20)	0,4993	5,392	11,0265
SD	0,00732	0,0764	0,125918729
Me	0,4980	5,38	11,06
Mo	0,4972	5,38	11,09
Kurt	0,2286	1,8324	15,41815085

Tabela 5. Parametry statystyczne opisujące twardość otrzymanych tabletek

Table 5. Statistical parameters describing the hardness of the tablets prepared

Parametr	Formulacja I	Formulacja II	Formulacja III	Formulacja IV
M siły potrzebnej do zgniecenia tabletki [N] ($n = 10$)	111,9	42,6	36,5	62,6
SD	6,315	3,684	2,206	2,697
Me	112	42	36	62
Kurt	–0,549	–1,567	2,268	0,593
Współczynnik twardości *T* [kg/mm^2]	0,191	0,092	0,061	0,107
Ścieralność [%]	0,48	2,37	3,47	0,93

Współczynnik twardości (T) obliczono na podstawie wzoru:

$$T = \frac{P_{\max}}{2r}$$

gdzie:
P_{max} – siła potrzebna do zgniecenia tabletki [kg],
r – średni promień tabletki [mm],
h – średnia grubość tabletki [mm].

Badanie jednolitości zawartości substancji czynnej w tabletkach

Badanie B dla 10 tabletek formulacji I i IV przeprowadzono zgodnie z wytycznymi FP XI. Oznaczenie zawartości wykonano metodą potencjometryczną (FP XI).

Badanie uwalniania substancji czynnej z tabletek

Badanie uwalniania substancji czynnej przeprowadzono dla formulacji I i IV. Formulacje II i III zostały odrzucone, ponieważ nie spełniały norm farmakopealnych dotyczących ścieralności (uzyskano wartości ścieralności powyżej 1%).

W celu oceny możliwości wykorzystania przedstawionych formulacji jako matryc dla niesteroidowych leków przeciwzapalnych (NLPZ) w tabletkach o przedłużonym działaniu zbadano dostępność farmaceutyczną ketoprofenu. Dostępność farmaceutyczną ketoprofenu z otrzymanych tabletek przeprowadzono metodą łopatkową na podstawie wytycznych FP XI. Ze względu na charakter substancji biologicznie czynnej (drażniące działanie na śluzówki żołądka; docelowo tabletka powinna być pokryta otoczką enteralną nierozpuszczalną w środowisku 0,1N HCl) odstąpiono od uwalniania w fazie kwasu i buforu. Natomiast preformulacyjny charakter badań sprawił, że użyto kolejno 7 rodzajów płynów akceptorowych w ilości 500 mL o temperaturze 37 ±0,5°C (tabela 6). Ze względu na przynależność ketoprofenu do II grupy BCS czynnikiem ograniczającym dostępność farmaceutyczną jest jego słaba rozpuszczalność (51 mg/L). W celu poprawy rozpuszczalności ketoprofenu zmodyfikowano skład płynów biorczych przez dodatek niejonowych surfaktantów – Tween 80 i Rofam 70. Surfaktanty dodano w ilościach przekraczających (ok. 56%) krytyczne stężenie micelarne (ang. *critical micelle concentration* – CMC). Według piśmiennictwa CMC w 0,1N HCl dla Tween 80 wynosi 13–15 mg/L, a dla Rofam 70–510 mg/L.[9] W badaniach zastosowano 500 mL objętości medium (w stosunku do dawki 100 mg ketoprofenu), żeby w płynie biorczym, który został zmodyfikowany obecnością surfaktanta, uzyskać jego stężenie powyżej CMC (jak najmniejsza ilość tenzydu w stosunku do dawki ketoprofenu). Do badań użyto po jednej tabletce z każdej formulacji, wykonując po 6 powtórzeń ($n = 6$). Łopatka obracała się 50 razy na min. Uwalnianie prowadzono przez 475 min. Próbki pobierano w następujących interwałach czasowych: co 5 min (do 40. min uwalniania), co 15 min (do 115. min uwalniania) i 60 min (do 475. min uwalniania). Na podstawie pomiarów absorbancji (λ = 230 350 nm) próbek (w odpowiednim medium) obliczono z wyznaczonych równań kalibracyjnych:

– dla wody (λ = 257 nm): $R^2 = 0{,}9962$; $p < 0{,}05$,
– dla 0,1N HCl (λ = 260 nm): $R^2 = 0{,}9943$; $p < 0{,}05$,
– dla buforu pH 7,4 (λ = 262 nm): $A = 0{,}5935c + 0{,}0586$; $R^2 = 0{,}9976$; $p < 0{,}05$,
– dla 0,1N HCl + Tween 80 (λ = 260 nm): $A = 0{,}7253c + 0{,}6437$; $R^2 = 0{,}9936$; $p < 0{,}05$,
– dla 0,1N HCl + Rofam 70 (λ = 260 nm): $A = 0{,}5494c + 0{,}3746$; $R^2 = 0{,}9874$; $p < 0{,}05$,
– dla buforu pH 7,4 + Tween 80 (λ = 262 nm): $A = 0{,}6469c + 0{,}0853$; $R^2 = 0{,}9947$; $p < 0{,}05$,

Tabela 6. Płyny akceptorowe użyte do uwalniania

Table 6. Acceptor fluids used for release

Medium (na 1 tabletkę)	Formulacja I	Formulacja IV
Woda	500 mL	500 mL
0,1N HCl	500 mL	500 mL
Bufor fosforanowy pH 7,4	500 mL	500 mL
Tween 80 + 0,1N HCl	11,76 mg + ad 500 mL	11,76 mg + ad 500 mL
Rofam 70 + 0,1N HCl	400 mg + ad 500 mL	400 mg + ad 500 mL
Tween 80 + bufor fosforanowy pH 7,4	11,76 mg + ad 500 mL	11,76 mg + ad 500 mL
Rofam 70 + bufor fosforanowy pH 7,4	400 mg + ad 500 mL	400 mg + ad 500 mL

– dla buforu pH 7,4 + Rofam 70 (λ = 262 nm): A = 0,7593c + + 0,4258; R^2 = 0,9953; p < 0,05 stężenia ketoprofenu. Pozwoliło to obliczyć procentową ilość uwolnionej substancji czynnej (współczynnik uwalniania – Q).

Na podstawie otrzymanych wyników wykonano wykresy Q [%] w funkcji czasu [min] (ryc. 1–14) i opisano je równaniami korelacyjnymi (tabela 7).[16]

Tabela 7. Równania korelacyjne

Table 7. Correlation equations

Regresja liniowa	Regresja potęgowa	Regresja logarytmiczna	Regresja wykładnicza
Typy równań korelacyjnych dla formulacji I w wodzie			
$y = 0{,}0813x + 28{,}83$	$y = 8{,}439\ln(x) + 5{,}3337$	$y = 14{,}938x^{0{,}2275}$	$y = 25{,}057e^{0{,}0026x}$
$R^2 = 0{,}6583$	$R^2 = 0{,}98025$	$R^2 = 0{,}96194$	$R^2 = 0{,}3919$
Typy równań korelacyjnych dla formulacji IV w wodzie			
$y = 0{,}043x + 45{,}384$	$y = 9{,}5281x^{0{,}3658}$	$y = 6{,}9564\ln(x) + 23{,}569$	$y = 32{,}781e^{0{,}0018x}$
$R^2 = 0{,}2574$	$R^2 = 0{,}675$	$R^2 = 0{,}8694$	$R^2 = 0{,}122$
Typy równań korelacyjnych dla formulacji I w 0,1N HCl			
$y = 0{,}3384x - 0{,}4454$	$y = 5{,}0849x^{0{,}2958}$	$y = 5{,}8851\ln(x) - 5{,}5115$	$y = 0{,}1743e^{0{,}2435x}$
$R^2 = 0{,}9784$	$R^2 = 0{,}93042$	$R^2 = 0{,}86599$	$R^2 = 0{,}7194$
Typy równań korelacyjnych dla formulacji IV w 0,1N HCl			
$y = 0{,}0109x + 29{,}863$	$y = 24{,}54x^{0{,}0565}$	$y = 1{,}7211\ln(x) + 24{,}003$	$y = 29{,}799e^{0{,}0003x}$
$R^2 = 0{,}625$	$R^2 = 0{,}9292$	$R^2 = 0{,}952$	$R^2 = 0{,}5785$
Typy równań korelacyjnych dla formulacji I w 0,1N HCl + Tween 80			
$y = 0{,}3384x - 0{,}4454$	$y = 5{,}4939x^{0{,}2912}$	$y = 5{,}9087\ln(x) - 4{,}5274$	$y = 0{,}1743e^{0{,}2435x}$
$R^2 = 0{,}9784$	$R^2 = 0{,}96556$	$R^2 = 0{,}91155$	$R^2 = 0{,}7194$
Typy równań korelacyjnych dla formulacji IV w 0,1N HCl + Tween 80			
$y = 0{,}0116x + 30{,}771$	$y = 25{,}894x^{0{,}0518}$	$y = 1{,}6527\ln(x) + 25{,}347$	$y = 30{,}757e^{0{,}0004x}$
$R^2 = 0{,}694$	$R^2 = 0{,}8738$	$R^2 = 0{,}8713$	$R^2 = 0{,}6537$
Typy równań korelacyjnych dla formulacji I w 0,1N HCl + Rofam 70			
$y = 0{,}0486x + 11{,}916$	$y = 6{,}3076x^{0{,}2549}$	$y = 5{,}2144\ln(x) - 2{,}2628$	$y = 13{,}707e^{0{,}0021x}$
$R^2 = 0{,}873$	$R^2 = 0{,}90708$	$R^2 = 0{,}85911$	$R^2 = 0{,}91494$
Typy równań korelacyjnych dla formulacji IV w 0,1N HCl + Rofam 70			
$y = 0{,}0042x + 30{,}031$	$y = 27{,}686x^{0{,}0233}$	$y = 0{,}7033\ln(x) + 27{,}594$	$y = 30{,}018e^{0{,}0001x}$
$R^2 = 0{,}5527$	$R^2 = 0{,}9267$	$R^2 = 0{,}934$	$R^2 = 0{,}5386$
Typy równań korelacyjnych dla formulacji I w buforze fosforanowym pH 7,4			
$y = 0{,}0576x + 21{,}151$	$y = 9{,}7187x^{0{,}2476}$	$y = 7{,}2643\ln(x) - 1{,}3946$	$y = 21{,}578e^{0{,}0018x}$
$R^2 = 0{,}9479$	$R^2 = 0{,}9823$	$R^2 = 0{,}9266$	$R^2 = 0{,}8544$
Typy równań korelacyjnych dla formulacji IV w buforze fosforanowym pH 7,4			
$y = 0{,}0168x + 40{,}07$	$y = 31{,}959x^{0{,}0648}$	$y = 2{,}6475\ln(x) + 31{,}058$	$y = 39{,}95e^{0{,}0004x}$
$R^2 = 0{,}6188$	$R^2 = 0{,}9101$	$R^2 = 0{,}9415$	$R^2 = 0{,}5612$
Typy równań korelacyjnych dla formulacji I w buforze fosforanowym pH 7,4 + Tween 80			
$y = 0{,}0574x + 24{,}003$	$y = 11{,}711x^{0{,}2272}$	$y = 7{,}2878\ln(x) + 1{,}3052$	$y = 24{,}371e^{0{,}0017x}$
$R^2 = 0{,}9411$	$R^2 = 0{,}9819$	$R^2 = 0{,}9334$	$R^2 = 0{,}848$
Typy równań korelacyjnych dla formulacji I w buforze fosforanowym pH 7,4 + Rofam 70			
$y = 0{,}053x + 26{,}659$	$y = 13{,}61x^{0{,}2074}$	$y = 6{,}9501\ln(x) + 4{,}689$	$y = 26{,}808e^{0{,}0015x}$
$R^2 = 0{,}9104$	$R^2 = 0{,}9919$	$R^2 = 0{,}9618$	$R^2 = 0{,}8056$
Typy równań korelacyjnych dla formulacji IV w buforze fosforanowym pH 7,4 + Tween 80			
$y = 0{,}0167x + 43{,}03$	$y = 34{,}801x^{0{,}0607}$	$y = 2{,}648\ln(x) + 33{,}983$	$y = 42{,}91e^{0{,}0004x}$
$R^2 = 0{,}5988$	$R^2 = 0{,}8996$	$R^2 = 0{,}9307$	$R^2 = 0{,}5444$
Typy równań korelacyjnych dla formulacji IV w buforze fosforanowym pH 7,4 + Rofam 70			
$y = 0{,}0155x + 44{,}317$	$y = 36{,}523x^{0{,}0552}$	$y = 2{,}4614\ln(x) + 35{,}904$	$y = 44{,}199e^{0{,}0003x}$
$R^2 = 0{,}5685$	$R^2 = 0{,}8492$	$R^2 = 0{,}8849$	$R^2 = 0{,}5117$

Omówienie

Omówienie wyników badań przeprowadzonych na masach tabletkowych

Dane uzyskane po przeprowadzeniu analizy sitowej wykazały różnice w rozkładzie wielkości cząstek poszczególnych mas tabletkowych. W przypadku formulacji I i II największa frakcja mieszaniny proszkowej zatrzymała się na sicie 0,09. Podczas formulacji III najwięcej mieszaniny osadziło się na sicie 0,315, a w formulacji IV na sicie 0,15. Najmniejszą stratę oraz najmniejszą część masy tabletkowej na sicie o najmniejszej wielkości oczek (0,063 mm) zaobserwowano dla formulacji IV, natomiast największą stratę mieszaniny proszkowej opisano w formulacji I.

Po przeprowadzeniu badań gęstości nasypowej luźnej, po ubiciu oraz po wyliczeniu odpowiednich współczynników okazało się, że wszystkie formulacje wykazują podobne do siebie wartości. Współczynnik Hausnera jest wskaźnikiem sypkości materiałów w masie proszkowej oraz jest bezpośrednio związany z gęstością nasypową luźną i ubitą (podatność proszku na zagęszczanie). Dość dobrą sypkością charakteryzowały się formulacja I oraz formulacja III, natomiast formulacje II i IV odznaczały się dostateczną sypkością. Współczynnik Carra przedstawia zmiany objętości mieszaniny tabletkowej po poddaniu jej procesowi ubijania. Najniższe wartości tego współczynnika, a tym samym najmniejsze zmiany objętości masy tabletkowej są najkorzystniejsze i występowały w formulacji III oraz formulacji I.

Dla proszków o dobrej sypkości (formulacje I i II) wartości gęstości nasypowej swobodnej oraz gęstości nasypowej po ubiciu są zbliżone.

Wyliczone wartości kątów usypu klasyfikują wg norm farmakopealnych zdolności płynięcia mas tabletkowych: bardzo dobre i dość dobre zdolności płynięcia mają masy tabletkowe formulacji III oraz IV, natomiast słabe wartości płynięcia wykazują masy proszkowe z formulacji I i II.[15]

Omówienie wyników badań przeprowadzonych na tabletkach

Otrzymano tabletki o gładkiej białej powierzchni, bez plam i uszkodzeń. Analizując parametry statystyczne morfologii otrzymanych tabletek, można zauważyć, że w każdej formulacji uzyskano stosunkowo niskie wartości odchyleń standardowych ze średniej arytmetycznej, co może świadczyć o niewielkiej różnicy pomiędzy masą, grubością i średnicą poszczególnych tabletek z serii a wartością średnią tych parametrów. Wartości mediany (*Me*) i modalnej (*Mo*), czyli odpowiednio wartości środkowej i najczęściej występującej, w większości przypadków są bardzo zbliżone lub wręcz pokrywają się z otrzymaną średnią arytmetyczną (*M*). Kurtoza (*Kurt*) z kolei informuje, jaki jest udział wartości skrajnych w wynikach pomiarów. Wartość kurtozy >0 świadczy o tym, że wyniki są zbliżone do średniej arytmetycznej, a <0 o tym, że są bardziej rozrzucone. Na tej podstawie można stwierdzić, że najmniej wyników skrajnych dotyczących pomiarów masy tabletek wystąpiło w przypadku formulacji IV, dotyczących pomiarów grubości – w formulacjach IV oraz II, a średnicy w przypadku tabletek formulacji III i IV (tabela 4).

Badanie ścieralności

Normę farmakopealną spełniały formulacje: I (zawierająca w składzie Kollidon K25 i hydroksyetylocelulozę) i IV (zawierająca w składzie Kollidon K90 i hydroksyetylocelulozę). Ponieważ ścieralność pozostałych 2 formulacji (II oraz III) znacznie przekraczała normy farmakopealne (ścieralność powyżej 1%), zostały one wykluczone z dalszych badań (tabela 5).

Badanie twardości – współczynnik twardości

Wartości siły potrzebnej do zgniecenia tabletki przedstawiały się następująco: tabletki z formulacji I (zawierające w składzie Kollidon K25 oraz hydroksyetylocelulozę) – 111,9 N, tabletki z formulacji IV (zawierające Kollidon K90 i HEC) – 62 N, z formulacji II (zawierające w składzie Kollidon K90) – 42 N i tabletki z formulacji III (zawierające w składzie Kollidon K25 i K90) – 36 N.

Analiza wartości wyliczonych współczynników twardości T [kg/mm^2] wskazuje, że najwyższą twardość mają tabletki z formulacji I (T = 0,191 kg/mm^2), następnie z formulacji IV (T = 0,107 kg/mm^2), a formulacje II i III posiadają odpowiednio: T = 0,092 kg/mm^2 i T = 0,061 kg/mm^2 (tabela 5).

Wartości T dla wersji II, a zwłaszcza wersji III są niższe od oczekiwanych.

Badanie jednolitości zawartości substancji czynnej w tabletkach

Wyznaczona zawartość w każdej z 10 tabletek formulacji I i IV była zgodna z normą – zawierała się w zakresie 85–115% średniej zawartości.

Badanie uwalniania substancji aktywnej

Uwalnianie w wodzie

Analiza profilów uwalniania oraz opisujących je równań korelacyjnych wskazuje, że w przypadku formulacji I do 200. min uwalnianie przebiega z kinetyką I rzędu, współczynnik Q osiąga wartość ok. 51%. Proces uwalniania przebiega z kinetyką zerowego rzędu 200.–505. min, współczynnik uwalniania Q osiąga wartość ok. 54%.

W formulacji IV uwalnianie do 110. min przebiega z kinetyką I rzędu, współczynnik uwalniania *Q* osiąga wartość ok. 59% (proces uwalniania przebiega z większą dynamiką). Proces uwalniania przebiega z kinetyką zerowego rzędu 110.–505. min, współczynnik uwalniania osiąga wartość ok. 62%.

W obu formulacjach ponad 50% dawki ketoprofenu uwalnia się z kinetyką I rzędu – dotyczy to początkowych 2–3 h procesu. Dalsza część procesu przebiega z kinetyką zerowego rzędu, ale do końca procesu uwalnia się niewielka ilość ketoprofenu (2% w formulacji IV i 6% w formulacji I). W formulacji IV uzyskano większą maksymalną wartość *Q*, która wynosiła ok. 62%, w przypadku formulacji I maksymalna wartość *Q* była niższa i wynosiła ok. 56%.

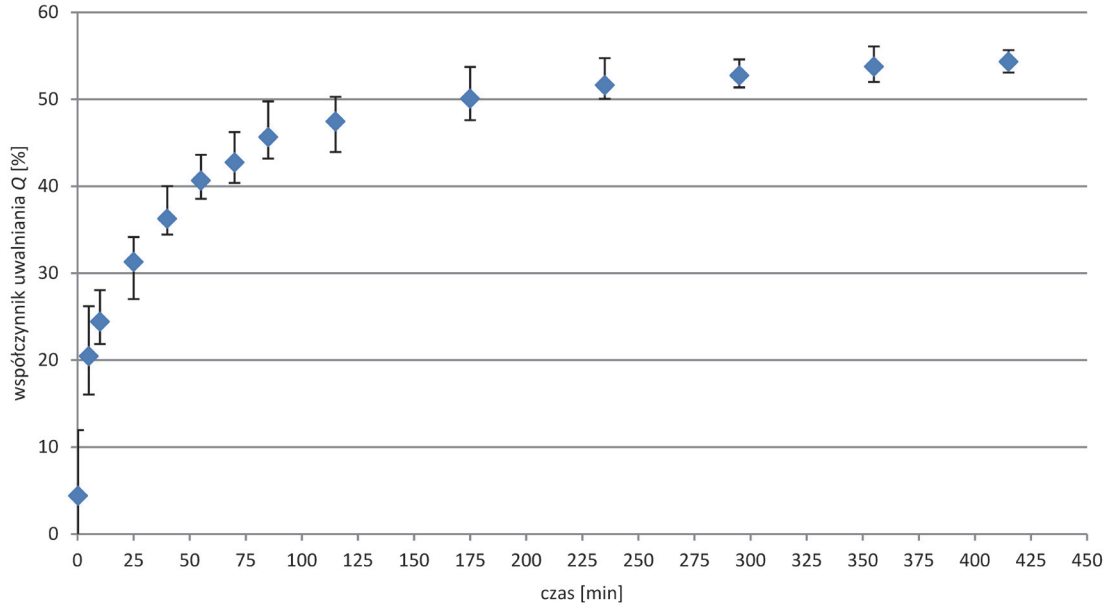
Proces uwalniania dla formulacji IV charakteryzuje się większą dynamiką – współczynnik *Q* osiąga wartość 50% już po ok. 25 min, natomiast w przypadku formulacji I dopiero po ok. 140 min (ryc. 1, 2, tabela 7).

Uwalnianie w 0,1N HCl

Analiza profilów uwalniania oraz opisujących równań korelacyjnych wskazuje, że najkorzystniejsza kinetyka uwalniania (charakterystyczna dla form o przedłużonym uwalnianiu) występuje w przypadku formulacji I. W zakresie czasowym 1.–25. min i 225.–375. min daje się zaobserwować fragmenty krzywej uwalniania charakterystyczne dla kinetyki I rzędu. Może to świadczyć o częściowej sorpcji substancji leczniczej w podłożu (HEC, Kollidon K25).

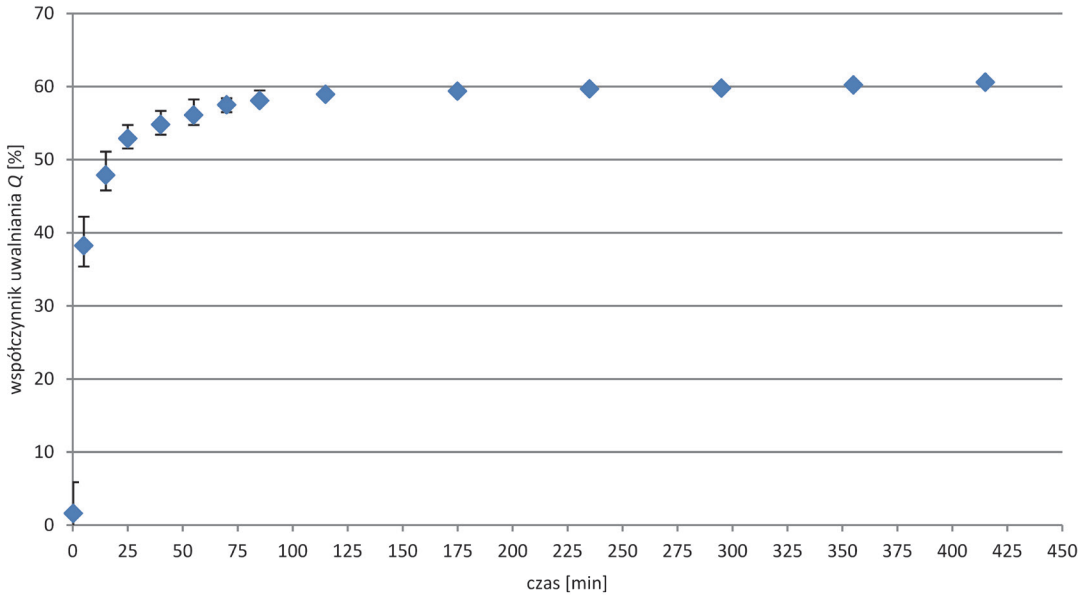
Współczynnik uwalniania *Q* po 8 h wynosił ok. 34%.

W formulacji IV kształt krzywej uwalniania był symetryczny z krzywą uwalniania w wodzie, współczynnik *Q* osiągał tu jednak mniejsze wartości. Do 110. min uwalnianie przebiega z kinetyką I rzędu, współczynnik uwalniania osiąga wartość ok. 32%. Od 110. min do końca procesu (505. min) uwalnianie przebiega z kinetyką zbli-



Ryc. 1. Krzywa uwalniania ketoprofenu z tabletek formulacji I w 500 mL wody

Fig. 1. Curve of ketoprofen release from tablets – formulation I in 500 mL of water



Ryc. 2. Krzywa uwalniania ketoprofenu z tabletek formulacji IV w 500 mL wody

Fig. 2. Curve of ketoprofen release from tablets – formulation IV in 500 mL of water

żoną do zerowego rzędu, współczynnik uwalniania osiąga wartość niespełna ok. 34%.

W przypadku obu formulacji uzyskano podobne maksymalne wartości współczynnika Q, które wynosiły odpowiednio: formulacja I – 33% i formulacja IV – ok. 34%. Wartości te były znacząco niższe od maksymalnych wartości *Q* uzyskanych w uwalnianiu w wodzie (ryc. 3, 4, tabela 7).

Uwalnianie w 0,1N HCl z dodatkiem surfaktantów

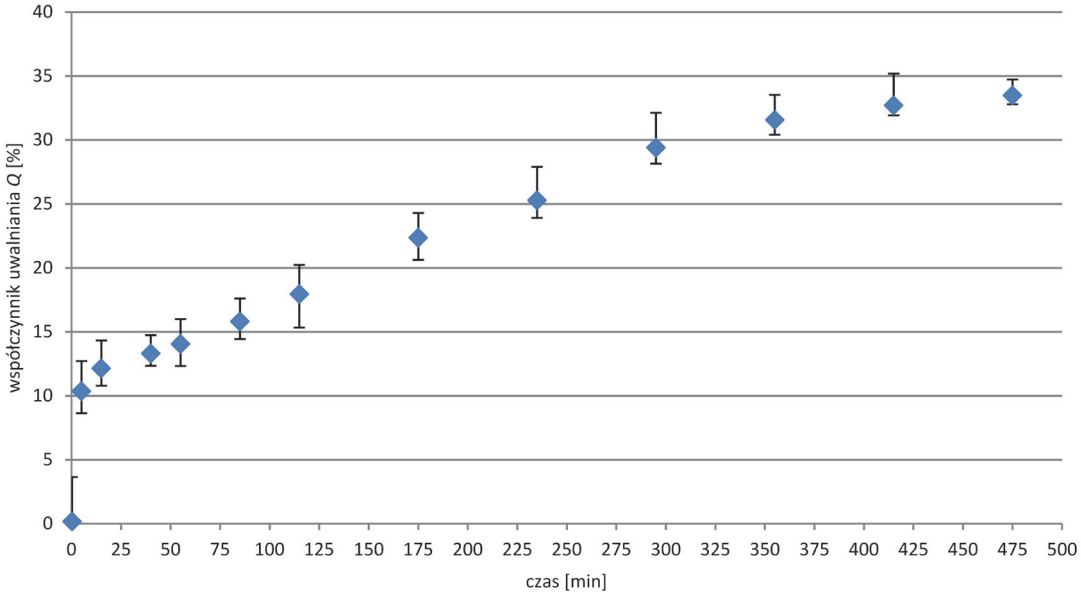
Dodatek surfaktantów (Tween 80, Rofam 70) do medium 0,1N HCl nie wpłynął w znaczący sposób na kształt krzywych uwalniania ketoprofenu w obu formulacjach. Zaobserwowano natomiast niewielki wpływ surfaktantów na dynamikę uwalniania. Dodatek Tweenu 80 do medium uwalniającego w obu formulacjach zwiększał wartości współczynnika *Q* o ok. 1–2%.

Dodatek Rofamu do medium uwalniającego w obu formulacjach zmniejszał wartości współczynnika *Q* o ok. 1–2% (ryc. 5–8, tabela 7).

Uwalnianie w buforze fosforanowym pH 7,4

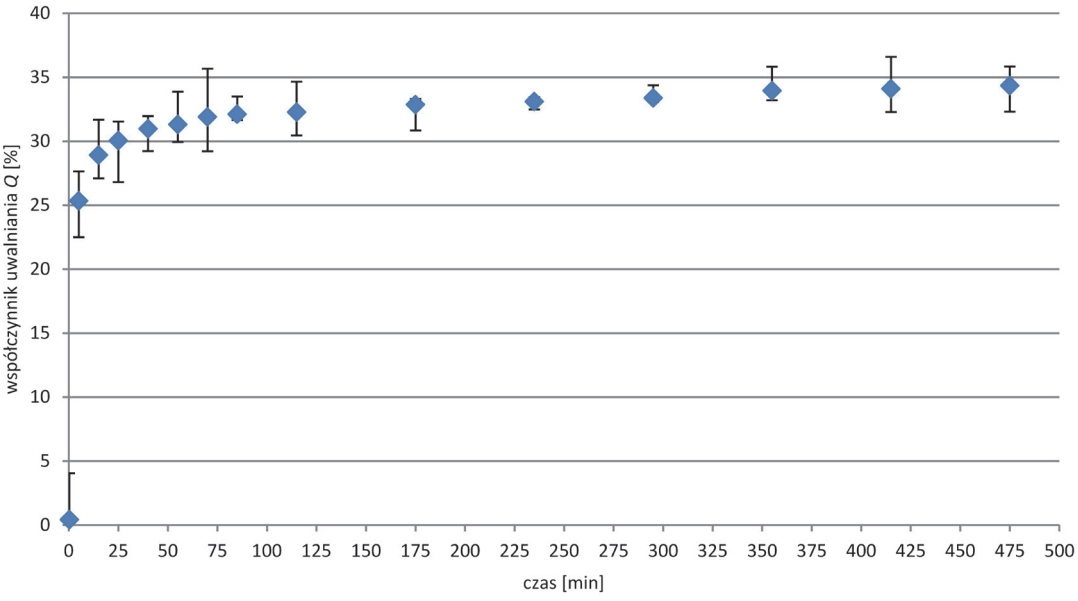
Analiza profilów uwalniania oraz opisujących je równań korelacyjnych wskazuje, że w przypadku formulacji I do 55. min uwalnianie przebiega z kinetyką I rzędu, współczynnik *Q* osiąga wartość ok. 28%. Proces uwalniania przebiega z kinetyką zerowego rzędu 55.–505. min, współczynnik uwalniania Q osiąga wartość ok. 50%.

W formulacji IV uwalnianie do 55. min przebiega z kinetyką I rzędu, współczynnik uwalniania *Q* osiąga wartość ok. 47% (proces uwalniania przebiega z większą dynamiką). Proces uwalniania przebiega z kinetyką zerowego rzędu 55.–505. min, współczynnik uwalniania osiąga wartość ok. 47%.



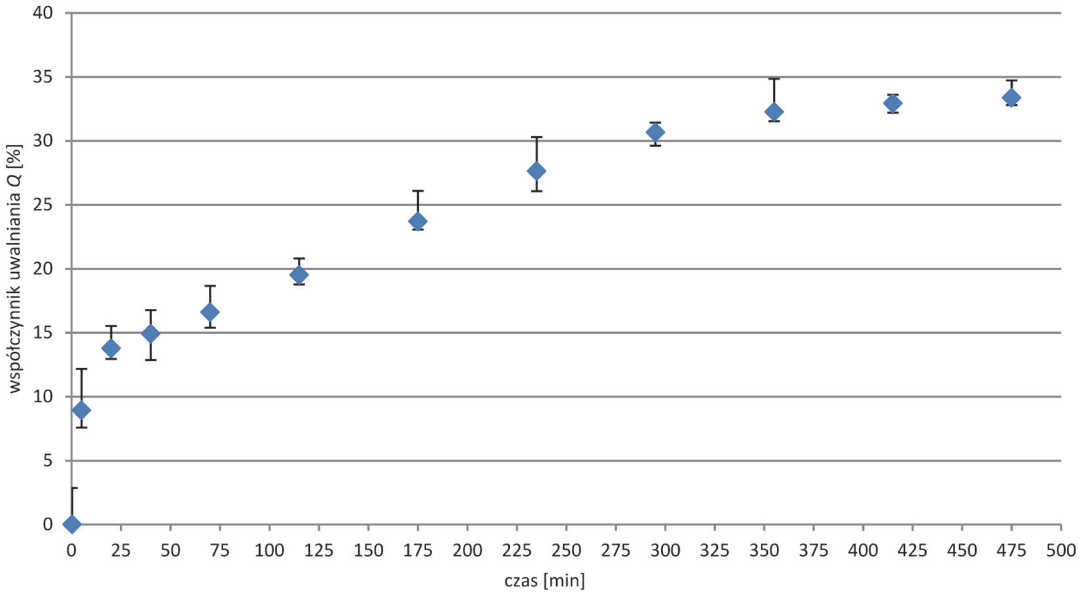
Ryc. 3. Krzywa uwalniania ketoprofenu z tabletek formulacji I w 500 mL 0,1N HCl

Fig. 3. Curve of ketoprofen release from tablets – formulation I in 500 mL of 0.1N HCl



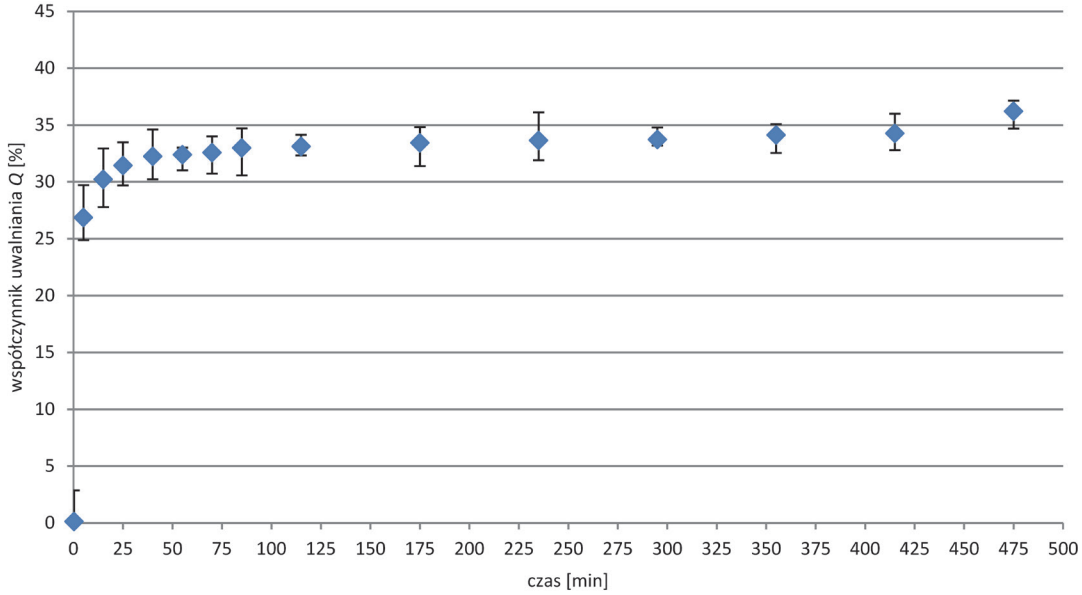
Ryc. 4. Krzywa uwalniania ketoprofenu z tabletek formulacji IV w 500 mL 0,1N HCl

Fig. 4. Curve of ketoprofen release from tablets – formulation IV in 500 mL of 0.1N HCl



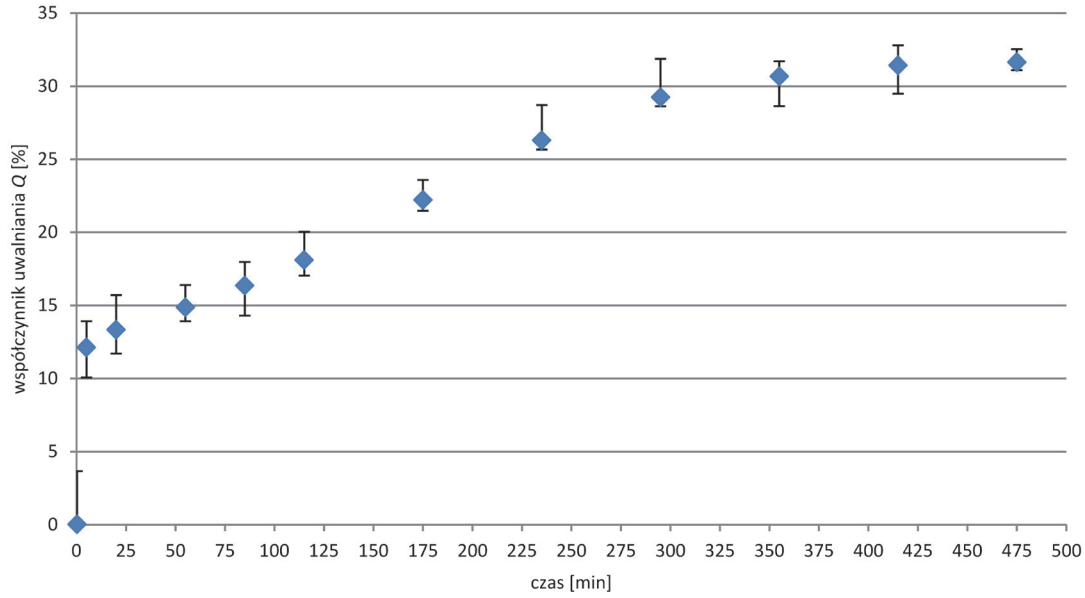
Ryc. 5. Krzywa uwalniania ketoprofenu z tabletek formulacji I w 500 mL 0,1N HCl + + Tween 80

Fig. 5. Curve of ketoprofen release from tablets – formulation I in 500 mL of 0.1N HCl + + Tween 80



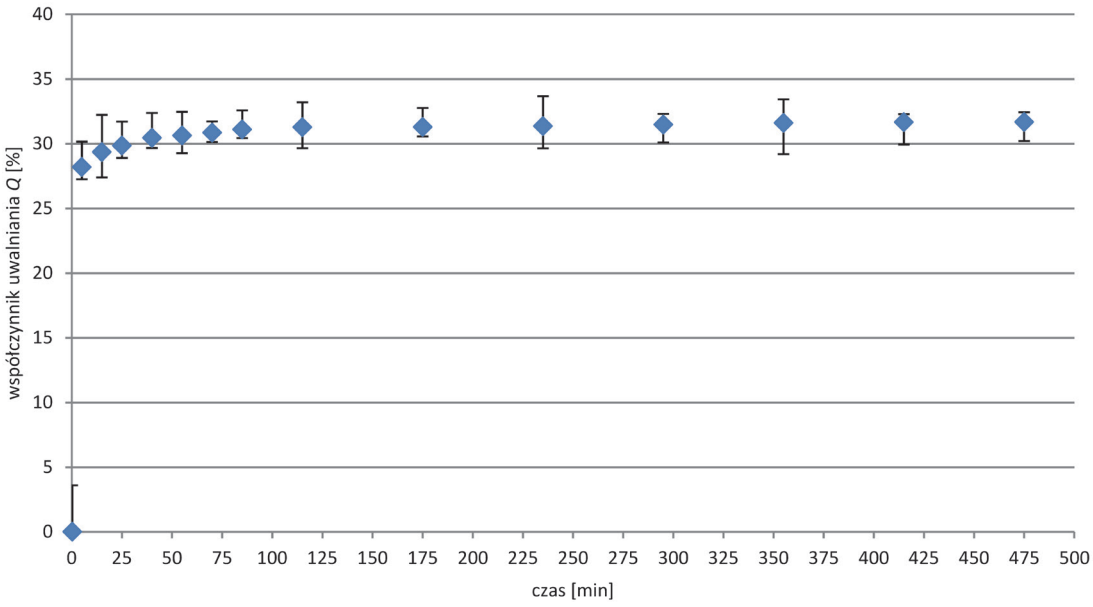
Ryc. 6. Krzywa uwalniania ketoprofenu z tabletek formulacji IV w 500 mL 0,1N HCl + + Tween 80

Fig. 6. Curve of ketoprofen release from tablets – formulation IV in 500 mL of 0.1N HCl + + Tween 80



Ryc. 7. Krzywa uwalniania ketoprofenu z tabletek formulacji I w 500 mL 0,1N HCl + + Rofam 70

Fig. 7. Curve of ketoprofen release from tablets – formulation I in 500 mL of 0.1N HCl + + Rofam 70



Ryc. 8. Krzywa uwalniania ketoprofenu z tabletek formulacji IV w 500 mL 0,1N HCl + Rofam 70

Fig. 8. Curve of ketoprofen release from tablets – formulation IV in 500 mL of 0.1N HCl + + Rofam 70

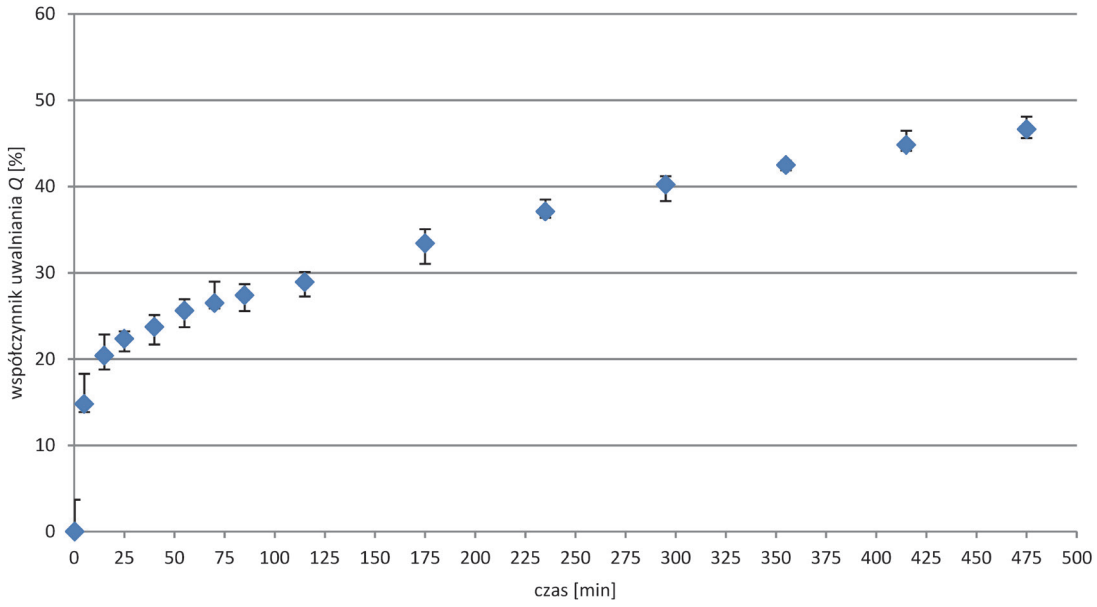
Formulacja I wykazuje (podobnie jak uwalnianie w wodzie i 0,1N HCl) uwalnianie najbardziej zbliżone do form o przedłużonym uwalnianiu. W formulacji IV do 55. min uwalnianie zachodzi z większą dynamiką, wartość *Q* osiąga wartość ok. dwukrotnie wyższą niż w 55. min formulacji I. Maksymalne wartości *Q* uzyskane w 505. min są takie same. Są niższe od maksymalnych wartości Q dla uwalniania w wodzie, ale posiadają wyższe wartości od maksymalnych wartości *Q* dla uwalniania w 0,1N HCl (ryc. 9, 10, tabela 7).

Uwalnianie w buforze fosforanowym pH 7,4 z dodatkiem surfaktantów

Dodatek surfaktantów (Tween 80, Rofam 70) do medium buforu fosforanowego pH 7,4 (podobnienie jak w przypadku 0,1N HCl) nie wpłynął w znaczący sposób na kształt krzywych uwalniania ketoprofenu w obu formulacjach. Zaobserwowano natomiast niewielki wpływ surfaktantów na dynamikę uwalniania. Dodatek Tweenu 80 do medium uwalniającego w obu formulacjach zwiększał wartości współczynnika *Q* o ok. 1–2%. Na zwiększenie wartości *Q* miało także wpływ dodanie Rofamu 70 do medium uwalniającego. Wartości *Q* zwiększyły się o ok. 2% (ryc. 11–14, tabela 7).

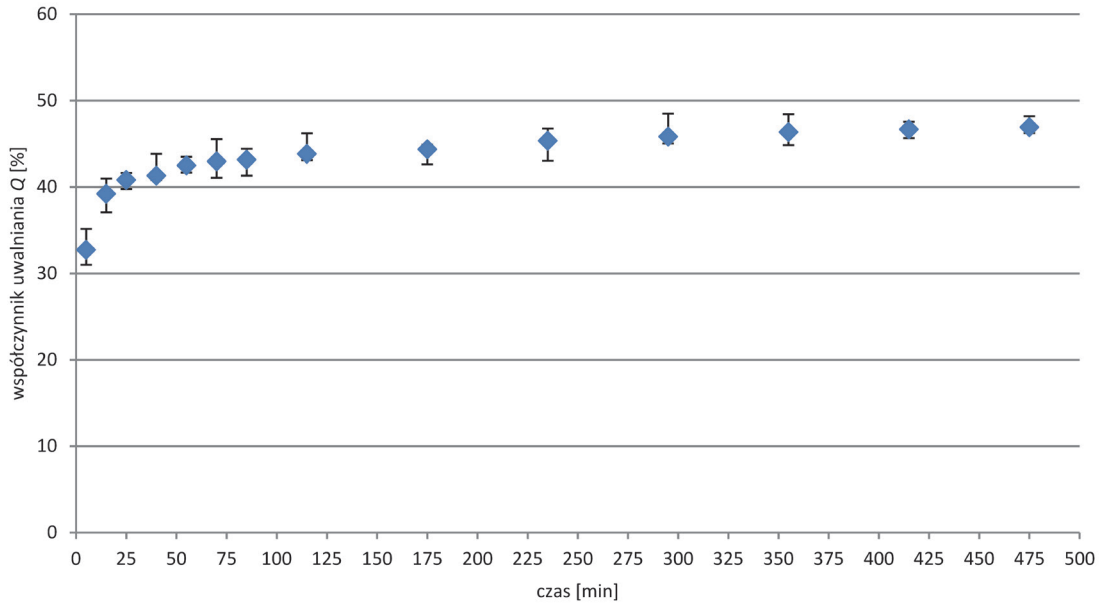
Wnioski

W przedstawionym modelowym układzie badań preformulacyjnych i biofarmaceutycznych wykazano przydatność HEC i Kollidonu K25 (formulacja I) w technologii matryc hydrofilowych. W opisanych składach formulacyjnych nie otrzymano prawidłowych technologicznie matryc



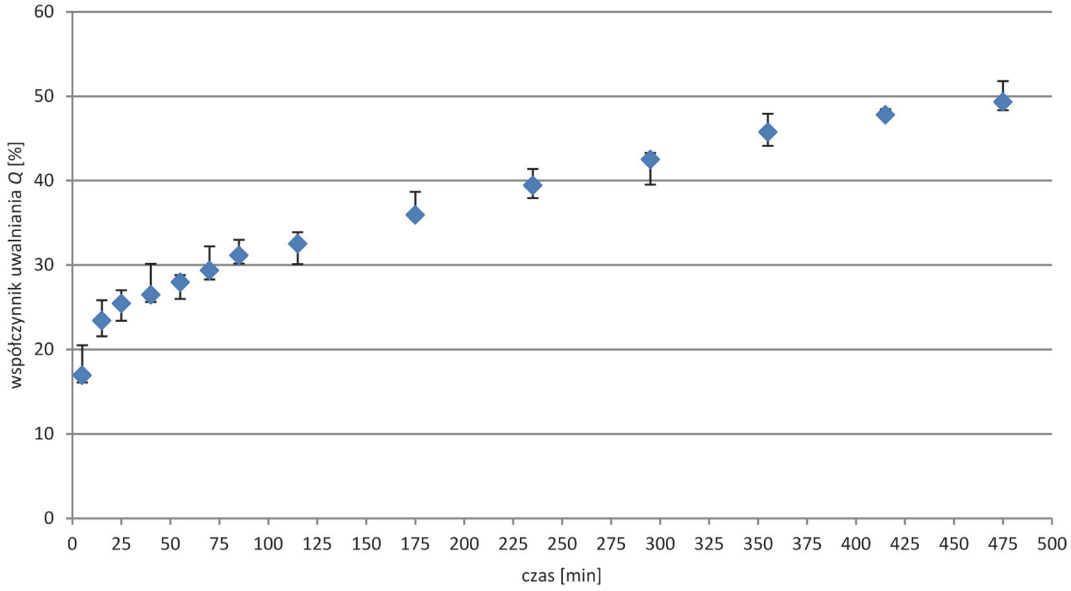
Ryc. 9. Krzywa uwalniania ketoprofenu z tabletek formulacji I w 500 mL buforu fosforanowego pH 7,4

Fig. 9. Curve of ketoprofen release from tablets – formulation I in 500 mL of phosphoric buffer pH 7.4



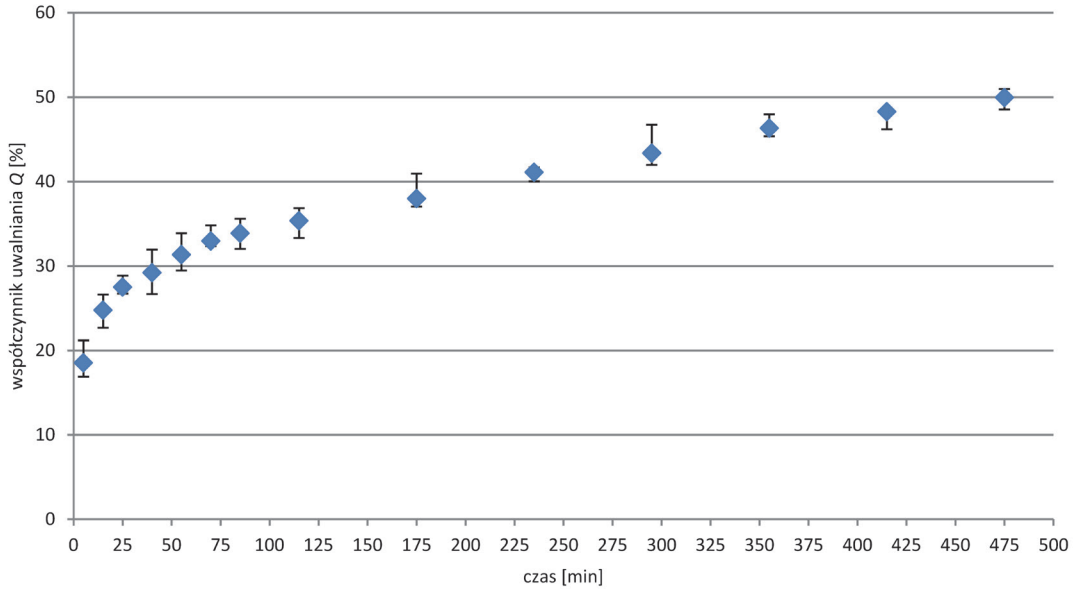
Ryc. 10. Krzywa uwalniania ketoprofenu z tabletek formulacji IV w 500 mL buforu fosforanowego pH 7,4

Fig. 10. Curve of ketoprofen release from tablets – formulation IV in 500 mL ofphosphoric buffer pH 7.4



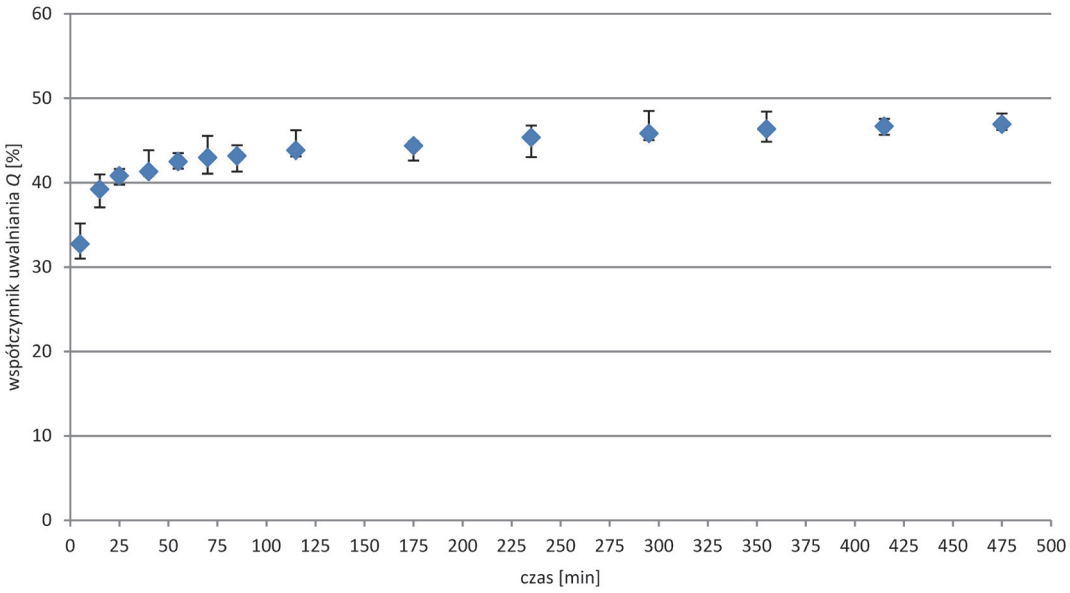
Ryc. 11. Krzywa uwalniania ketoprofenu z tabletek formulacji I w 500 mL buforu fosforanowego pH 7,4 + + Tween 80

Fig. 11. Curve of ketoprofen release from tablets – formulation I in 500 mL of phosphoric buffer pH 7.4 + Tween 80



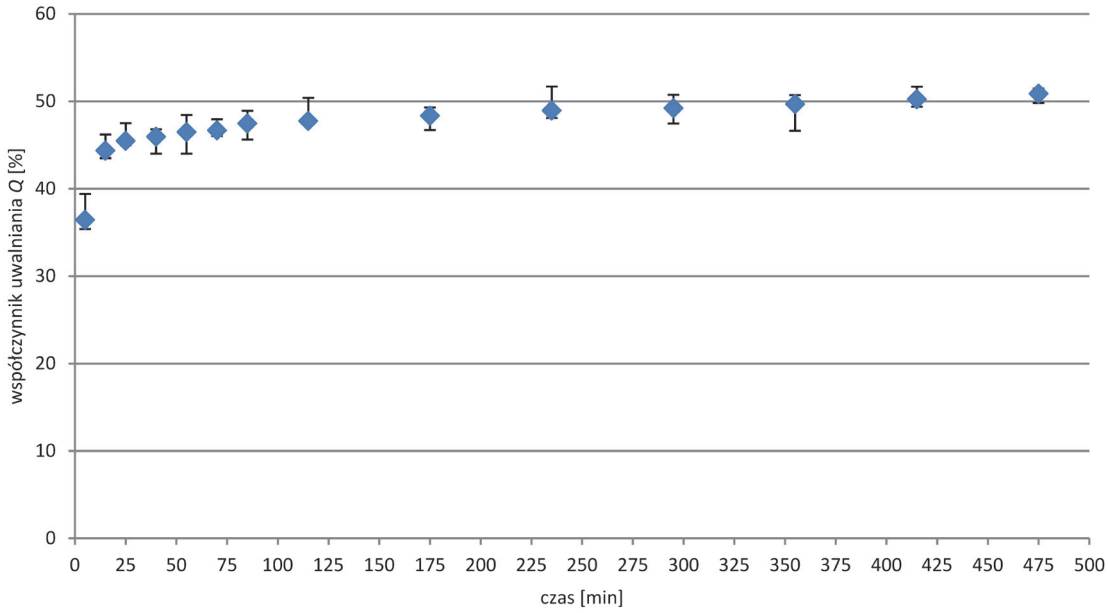
Ryc. 12. Krzywa uwalniania ketoprofenu z tabletek formulacji I w 500 mL buforu fosforanowego pH 7,4 + + Rofam 70

Fig. 12. Curve of ketoprofen release from tablets – formulation I in 500 mL of phosphoric buffer pH 7.4 + Rofam 70



Ryc. 13. Krzywa uwalniania ketoprofenu z tabletek formulacji IV w 500 mL buforu fosforanowego pH 7,4 + + Tween 80

Fig. 13. Curve of ketoprofen release from tablets – formulation IV in 500 mL of phosphoric buffer pH 7.4 + Tween 80



Ryc. 14. Krzywa uwalniania ketoprofenu z tabletek formulacji IV w 500 mL buforu fosforanowego pH 7,4 + Rofam 70

Fig. 14. Curve of ketoprofen release from tablets – formulation IV in 500 mL of phosphoric buffer pH 7.4 + Rofam 70

opartych na fosforanie dwuwapniowym i Kollidonach K25 i K90 (formulacje II i III). Aby uzyskać optymalne pod względem technologicznym matryce, konieczny jest udział hydroksyetylocelulozy. Użyte surfaktanty w przedstawionym modelu badawczym nie wpłynęły istotnie statystycznie na poprawę dostępności farmaceutycznej ketoprofenu.

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Influence of sodium starch glycolate, croscarmellose sodium and crospovidone on disintegration and dissolution of stevia-loaded tablets

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D – writing the article; E – critical revision of the article; F – final approval of the article

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Abstract

Background. Sugar substitutes are used by diabetic, obese and calorie-conscious people. As artificial sweeteners are harmful to the body, natural sweeteners are more suitable. Sugar substitutes are available on the market in tablet forms, which are added to hot or cold drinks. Rapid disintegration and dissolution of sugar substitute-loaded tablet is desired. However, the tablets should be hard enough to maintain their integrity during mechanical shocks.

Objectives. The objective of this research was to develop rapidly disintegrating and dissolving stevia-loaded tablets with appropriate wetting, hardness and friability.

Material and methods. Several tablets were prepared using different superdisintegrants using the direct compression method. Flowability tests of the powder blends were performed before compression; these test took into account such physical parameters as bulk density, tapped density, angle of repose, compressibility index, and Hausner's ratio. Evaluation of the compressed cores was accomplished with weight variation, hardness, thickness, friability, disintegration time, wetting time, and dissolution.

Results. The disintegration time and wetting time of the tablets were in the following order: sodium starch glycolate > croscarmellose sodium > crospovidone containing tablets. A powder blend consisting of stevia extract, crospovidone, lactose, and magnesium stearate at the optimized ratio of 15/2.5/32/0.5 (w/w/w/w) showed the best flow, rapid disintegration (38 ±0.894 s), wetting (30 ±1 s), and dissolution (~ 95% in 1 min). Moreover, this formulation showed more rapid wetting (30 ±1 s vs 91 ±1.9 s), disintegration (38 ±0.894 s vs 143 ±1.276 s) and dissolution (~ 95% vs 60% in 1 min) than a commercial product.

Conclusions. The tablet consisting of stevia, crospovidone, lactose, and magnesium stearate at the weight ratio of 15/2.5/32/0.5 showed excellent results with regards to dissolution and disintegration; accordingly, this formulation could be a potential sugar substitute for diabetic, obese and/or calorie-conscious individuals.

Key words: superdisintegrants, sugar substitute, hydrophilic polymers, wetting time

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Introduction

Sweetness is a pleasing sensation produced by the presence of sugars, which are an important substance of daily human life. Sugar beet and sugarcane are the main sources of sugar. However, sugar obtained from these sources is not suitable for diabetic patients, obese and/or calorie-conscious people, as sugar-sweetened food is highly caloric and results in high glycemic index.[1,2] Consumption of such meals disturbs glucose and insulin levels, alters normal metabolism and hormonal balance, and promotes obesity.[1] Accordingly, different sugar substitutes are extensively consumed by individuals who are cautious about their health but want to fulfill their craving for sugar. Consumption of diet and drinks which have non-nutritive sweeteners has substantially increased over the past few decades. It is estimated that about 15% of the US population consumes non-nutritive sweeteners.[3]

A sugar substitute is a food additive which has the taste of sugar but contains few or no calories.[4,5] It may be obtained from a natural or a synthetic source. Examples of natural sugar substitutes include mannitol, lactitol, xylitol, maltitol, isomalt, sorbitol, etc., while synthetic sugar substitutes include aspartame, calcium cyclamate, thaumatin, saccharin, neotame, acesulfame potassium, sodium cyclamate, sucralose, etc.[6] On the basis of caloric values, a sugar substitute may be nutritive or non-nutritive. Nutritive sugar substitutes, such as monosaccharides (e.g., sorbitol, xylitol, mannitol, erythritol, etc.), disaccharides (e.g., isomalt, maltitol, isomaltulose, trehalose, etc.) and polysaccharides (e.g., hydrogenated glucose syrup), are caloric sweeteners.[7,8] Non-nutritive sugar substitutes, such as saccharin, aspartame, neotame, acesulfame-K, cyclamate, dulcin, stevia, and sucralose, are usually non-caloric and produce more intense sweetening sensation than the regular sugar.[9] Natural sugar substitutes are becoming more popular owing to their harmless nature, while artificial sweeteners possess some documented health hazards.[10]

Stevia, a non-caloric natural sugar substitute, is extracted from leaves of *Stevia rebaudiana* (Bertoni). Amongst 200 species of genus *Stevia*, only *Stevia rebaudiana* possesses property of sweetness.[11] Stevia contains alkaloids, flavonoids, caffeic acid, chlorogenic acid, oligosaccharides, amino acids, etc.[12] The chief active sweetening agents in stevia are steviosides, rebaudioside A, rebaudioside C, dulcoside A, and other glycosides of the diterpene steviol.[13] Steviol (Fig. 1) is the basic structural unit of these glycosides. Stevia is very cheap and easily available; therefore, it has been extensively used for decades to sweeten various foods in Brazil, Korea and Japan.[14] Stevia enhances insulin sensitivity.[8] Moreover, it possesses antihypertensive,[15,16] antihyperglycemic[17,18] and antiviral[19] properties. It also has been used in masking the bitter and obnoxious taste of some drugs.[20]

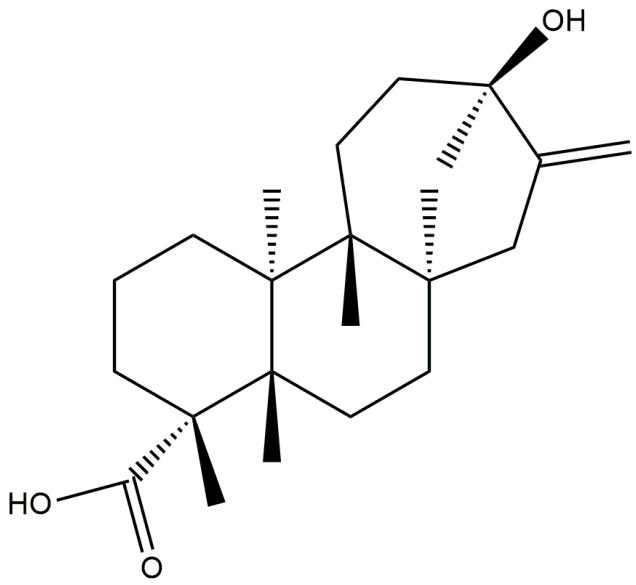

Fig. 1. Structural formula of steviol

Tablets of a sugar substitute undergo in vitro disintegration and dissolution; accordingly, their rapid disintegration and dissolution is desired as soon as they are added to a beverage, coffee or tea. Superdisintegrants, usually hydrophilic polymers, are the excipients which are added to solid dosage forms such as tablets, pellets or granules to help in breaking up the compact mass as it comes in contact with the liquid environment. These are frequently employed for immediate release products, where quick release is the basic requisite.[21] Superdisintegrants, such as crospovidone, sodium starch glycolate, croscarmellose sodium, etc., can play a significant role in the rapid disintegration and dissolution of such tablets due to their swelling and wetting characteristics. Nevertheless, the tablets should also be hard enough to maintain their integrity during handling, mechanical shocks, blistering, packaging, and transportation. Inadequately friable tablets may crumble during these processes.

Tablets may contain an active ingredient and a number of excipients. In direct compression of tablet formation, all raw constituents are blended well before being subjected to compression under optimized conditions. Adequate flow of powder blend from hopper to die of a tablet machine is necessary for proper formation of tablets. Insufficient flow of powder blend may result in incomplete or very friable tablets.

In the present research, rapidly disintegrating and dissolving tablets were formed using stevia, lactose, magnesium stearate, and different quantities of selected superdisintegrants. The superdisintegrants tested in this study were croscarmellose sodium, crospovidone and sodium starch glycolate. Before direct compression, each powder blend was tested for its flowability by measuring bulk density, tapped density, angle of repose, Hausner's ratio, and compressibility index.[22] Evaluation of the compressed cores was performed by determining their assay, hardness, friability,

weight variation, disintegration time, wetting time, and dissolution rate. Fourier transform infrared (FTIR) spectrum of the selected tablet was compared with that of its corresponding powder blend in order to determine the potential chemical interaction among the constituents upon compression. Moreover, wetting time, disintegration time and the dissolution rate of the selected formulation were compared with those of a commercial product.

This research does not involve exploitation of human, animals or other living things as experimental subjects.

Material and methods

Material

Stevia extract (Rebaudioside *A*) was obtained from Xinghua GL Stevia Co. (Taizhou, China). Sodium starch glycolate was acquired from Hangzhou Zhongbao Co. (Hangzhou, China). Crospovidone was procured from Eurotrade World Commerce, S.L., (Madrid, Spain). Croscarmellose sodium was purchased from Accent Microcell Co. (Ahmedabad, India). Magnesium stearate was bought from Linghu Xinwang Chemical Co. (Huzhou, China). Spray-dried Lactose was purchased from DMV–Fonterra GmbH and Co. (Goch, Germany). Nocal tablets, the commercial product, were kindly gifted by NovaMed Pharmaceutical Co. (Lahore, Pakistan).

Preparation of powder blends for compression

Each powder blend consisted of stevia extract, spray-dried lactose, magnesium stearate, and a superdisintegrant (croscarmellose sodium, crospovidone or sodium starch glycolate) for a batch of 500 tablets. Each superdisintegrant was tested at 2%, 3% and 5% concentrations. The detailed composition of each powder blend is given in Table 1. For each formulation, all the ingredients were weighed individually on a calibrated electronic weighing balance. At first, lactose was passed through European sieve #600. Subsequently, stevia extract was sifted from the same sieve and both were thoroughly mixed for 5 min. Then, the selected superdisintegrant, at 2%, 3% or 5% concentration, was sieved and added to this binary blend and mixed for 5 min again. Finally, magnesium stearate was sieved and poured into the ternary blend and mixed for 5 min again to achieve a final powder blend for direct compression.

Pre-compression flowability of powder blends

Prior to direct compression, each powder blend was tested for its flow property. Flowability was assessed using Hausner's ratio, compressibility index and angle of repose.[22] Bulk density (D_B, g/cm^3) and tapped density (D_T, g/cm^3) for each powder blend were determined using the KYT-4000 instrument (Seishin Co., Tokyo, Japan). The compressibility index and Hausner's ratio were determined using the following formulas: compressibility index (I_C) = $(D_T - D_B) / D_T \times 100$ and Hausner's ratio (H_R) = D_T / D_B, respectively. The angle of repose was measured using an ABD-72 powder peculiarity tester (Tsutsui Scientific Instruments, Tokyo, Japan). Each powder blend was allowed to flow through the funnel to form a stable symmetrical cone. The formula for the angle of repose is $\theta = \tan^{-1}(2h / d)$, where h – height of the pile and d – mean diameter of the periphery of the cone base.

Formation of tablets

Nine batches, each comprised of 500 tablets, were prepared via the direct compression method using a ZP-17 rotary tablet press (Shanghai, China). The composition of each tablet is listed in Table 1. For each formulation, the powder blend was subjected to direct compression. The circular tablets of about 5 mm diameter and 2.5 mm thickness with both sides plain were obtained for further evaluation.

Evaluation of compressed cores

Assay of tablets

Twenty tablets were ground thoroughly using a pestle and mortar. The resultant powder, equivalent to 15 mg stevia extract, was poured into a 50 mL volumetric flask

Table 1. Composition of powder blends or tablets

Constituents [mg]	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Stevia extract	15	15	15	15	15	15	15	15	15
Croscarmellose sodium	1.0	1.5	2.5	–	–	–	–	–	–
Crospovidone	–	–	–	1.0	1.5	2.5	–	–	–
Sodium starch glycolate	–	–	–	–	–	–	1.0	1.5	2.5
Lactose (spray dried)	33.5	33.0	32.0	33.5	33.0	32.0	33.5	33.0	32.0
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total weight per tablet	50	50	50	50	50	50	50	50	50

and completely dissolved in 20 mL diluent with magnetic stirring for 15 min at room temperature. The diluent consisted of distilled water and acetonitrile (68/32, v/v). Then, the final volume was made up to 50 mL and filtered (0.45 µm). The theoretical concentration of the resultant solution was 300 µg/mL. The actual concentration in the filtrate (20 µL) was measured using an HPLC system (LC 20-AT; Shimadzu, Kyoto, Japan). The column used in the analysis was Capcell Pak C18 column (Shiseido, 4.6 mm I.D. × 25 cm, 5 µm) at 40°C. The mobile phase, 0.01 M sodium phosphate buffer and acetonitrile (68/32, v/v), was eluted at a rate of 1 mL/min. The eluent was analyzed at 210 nm for measuring stevia titer. The inter-day and intra-day variances in the precision and accuracy of the method were within the acceptable limits ($r^2 = 0.9999$). For each formulation, the assay was performed in triplicate. The assay was determined using the following formula: $S_C = S_A/S_T \times 100$, where S_C is the assay (%), S_A is actual concentration (µg/mL), and S_T is the theoretical concentration (300 µg/mL).

Weight variation

Twenty tablets were taken randomly for each formulation. Each tablet (50 mg) was weighed on a calibrated weighing balance (ATV 224 Model, Shimadzu, Japan). The requirements were met if the average weight of the tablets is within ±10% range, with no more than 2 tablets differing from the average weight by more than ±10% and with no tablet differing in weight by ±20%.[23]

Hardness test

Hardness of the tablet is reflected by the minimum force required to break the tablet in a diametric compression. The hardness of 10 randomly selected tablets was determined using a digital PortTAB-01 portable tablet hardness tester (Torontech™, Markham, Canada). Each tablet was carefully placed between the 2 jaws. Then, the movable jaw was screwed towards the fixed jaw. For each tablet, the minimum force at which the tablet broke was recorded and the average force of all the tablets was calculated.

Thickness

Ten tablets were selected randomly from each batch. The thickness of each tablet was measured using a Vernier calipers. Then, the average thickness was calculated and recorded for each batch.[24]

Friability test

The friability test of tablets was carried out using a Pharmatest PTF3DR 3-drum automated friability testing instrument (Pharma Test Apparatebau AG, Hainburg, Germany). For each formulation, 130 randomly taken tablets were dedusted and weighed carefully. These tablets were placed in the friabilator drum. The friabilator drum was rotated at 25 rpm for 4 min. Then, after the screening of fines, tablets were reweighed. Friability (%) was determined by the following formula: Friability (f) = $(W_i - W_f) / W_i \times 100$, where W_i is the initial weight of the tablets before being subjected to the friability test and W_i is the final weight of the tablets after the test. The weight of the tablets lost during the test should not exceed 1%.[25] The test was performed in triplicate for each batch.

Wetting time

An aqueous solution of eosin (a water-soluble dye) was prepared using distilled water. Ten milliliters of this solution was poured into a petri dish and spread evenly. Three filter papers, cut in accordance with the inner dimensions of the petri dish, were placed over the spread solution in layers. The solution rapidly seeped across the filter papers due to capillary action. For each formulation, 6 tablets were randomly selected for this test. Each tablet was carefully placed on the soaked filter papers and observed visually for the spreading of blue colour across the tablet. The minimum time for the tablet to become completely blue was noted and regarded as the wetting time of the corresponding tablet.[24] The average time of wetting for each formulation was calculated.

Disintegration test

Disintegration test was accomplished using a disintegration tester (Torontech). For each formulation, 6 tablets were randomly taken for this test. One tablet was inserted in each tunnel of the basket and a disc was subsequently introduced. The disintegration was performed using 900 mL of distilled water as a disintegration medium. The basket speed was set at 30 cycles/min. The test was performed 3 times for each batch. The average disintegration time was calculated along with standard deviation (SD).

Dissolution test

Dissolution test was performed using the USP dissolution apparatus II (Vision® classic 6™; Hanson Research Co., Los Angeles, USA). For each formulation, 6 tablets were randomly selected for testing. Each 50 mg tablet, containing 15 mg of stevia extract, was dropped in a dissolution vessel containing 500 mL of distilled water. The temperature of the dissolution medium was maintained at 37 ±0.5°C by the surrounding water-bath. The paddle rotation was set at 50 rpm. From each dissolution vessel, 1 mL of the dissolution medium was sampled at each pre-set time intervals (0.5 min, 1.0 min, 3.0 min, and 4.5 min), centrifuged at 5000 × g for 5 min (5417-R; Eppendorf AG, Hamburg, Germany) and filtered (0.45 µm) separately. Each filtrate was analyzed using the HPLC method as described above.

FTIR spectroscopic analysis

The Alpha FTIR Spectrometer (Bruker Optik GmbH, Ettlingen, Germany) was used for the FTIR spectroscopic analyses of the selected formulation and its corresponding powder blend or physical mixture. On the sample disc, a minute quantity of the formulation or powder blend was placed in the cavity below the scanning lens. The sample was scanned over a range of 400–4000 cm^{-1}. The selected formulation or the corresponding powder blend consisted of stevia extract, crospovidone, spray-dried lactose, and magnesium stearate (15/2.5/32/0.5, w/w/w/w).

Results and Discussion

Because tablets containing a sugar substitute are added to a drink or food, their immediate disintegration and dissolution are desired. However, endeavours to achieve rapid disintegration may lead to decreased hardness and increased friability of the tablets. The tablets must be hard enough to endure the mechanical shocks connected with handling, manufacturing, packaging, and transportation. Utilization of superdisintegrants for enhancing disintegration and dissolution rates of tablets, without substantially disturbing hardness and friability, is a good idea.

Superdisintegrants such as crospovidone, sodium starch glycolate and croscarmellose sodium are used as excipients in a solid dosage form to help with the quick dispersal of bound particles, thereby accelerating the dissolution rate; accordingly, they are frequently used as excipients in immediate release products.[21] The aim of our study was to develop a stevia-loaded tablet which, when added to a drink or food, immediately disintegrates and dissolves to make it sweeter as soon as possible. Therefore, crospovidone, sodium starch glycolate and croscarmellose sodium were used as superdisintegrants in the present research.

Direct compression is the most convenient method to manufacture tablets. It has several advantages including cost-effectiveness, stability, quick dissolution, and simplified process validation.[26,27] Moreover, the active ingredient and excipients need to be properly mixed before direct compression to enhance content uniformity. Thus, in our research, all the constituents were appropriately blended for each formulation before direct compression. The detailed composition of each batch is shown in Table 1.

Sufficient flow of powder from hopper to die of a tablet machine is essential in the manufacturing of tablets. Otherwise, highly friable tablets are formed, which may crumble during handling and mechanical shocks. Thus, in the present study, powder flowability was assessed. For each powder blend, the values of bulk density, tapped density, angle of repose, Hausner's ratio, and compressibility index are shown in Table 2. The angle of repose, Hausner's ratio, and compressibility index of a powdered substance with a flowability from excellent to fair are 25–36°, 1.00–1.25 and ≤10–20%, respectively.[22] All the powder blends exhibited good or excellent flowability, as the values of these parameters were within the prescribed limits.[22] Thus, the combinations of constituents in the powder blends were perfect for hinderless flow.

Adequate blending of the constituents and flowability of powder blends result in more apposite content uniformity in the tablets. For batch F1, F2, F3, F4, F5, F6, F7, F8, and F9, the average assay (n = 3) was 99.21%, 98.80%, 99.20%, 99.79%, 99.63%, 99.19%, 99.06%, 98.91%, and 99.76%, respectively. This confirmed that the blending of constituents and flow of powder blend from hopper to die during tablet manufacturing was adequate in our study.

In the weight variation test, the acceptable difference is ±10% if the average weight of tablets is less than 130 mg, ±7.5% if the average weight of tablets is 130–324 mg and ±5% if the average weight of tablets is greater than 324 mg.[25] The values of weight variation (n = 20) for all the batches are shown in Table 3. For each formulation, the difference in weight of each tablet from the average weight was within ±10%. Thus, all our formulations passed the weight variation test in accordance with the abovementioned criteria.[25]

Table 2. Pre-compression flowability of powder blend

Formulations	Bulk density [g/cm³]*	Tapped density [g/cm³]*	Angle of repose [°]*	Hausner's ratio*	Compressibility index [%]*
F1	0.526 ±0.003	0.625 ±0.005	25.523 ±0.050	1.180 ±0.005	15.840 ±0.013
F2	0.551 ±0.007	0.588 ±0.002	25.566 ±0.100	1.068 ±0.020	6.290 ±0.063
F3	0.550 ±0.002	0.580 ±0.005	28.053 ±0.050	1.056 ±0.015	5.171 ±0.033
F4	0.550 ±0.003	0.625 ±0.007	25.066 ±0.060	1.130 ±0.001	12.082 ±0.060
F5	0.526 ±0.007	0.555 ±0.006	25.733 ±0.060	1.050 ±0.007	5.229 ±0.005
F6	0.520 ±0.008	0.580 ±0.006	31.290 ±0.150	1.124 ±0.006	10.346 ±0.001
F7	0.555 ±0.013	0.600 ±0.006	25.446 ±0.100	1.080 ±0.005	7.533 ±0.057
F8	0.526 ±0.003	0.580 ±0.005	25.516 ±0.030	1.100 ±0.050	9.324 ±0.078
F9	0.571 ±0.010	0.660 ±0.002	25.076 ±0.130	1.150 ±0.050	13.487 ±0.042

* Each value denotes the mean ±SD (n = 6).

Hardness of tablets should be appropriate. Very hard tablets may fail to disintegrate, while inadequate hardness may result in enhanced friability. Moreover, inappropriate thickness of tablets can create problems during packaging. The mean values of hardness (n = 10), thickness (n = 10) and friability (n = 3) are shown in Table 3. In our study, each tablet demonstrated sufficient hardness for it to be used as a rapidly dispersible tablet. In the friability test, the weight of the tablets lost was <1%; thus, the tablets passed the test.[25] Furthermore, thickness values should not be outside ±5% variation. Thickness values of all the tested tablets were within the acceptable limits.

When a tablet comes in contact with an aqueous medium in vitro or in vivo, water seeps into the tablet, making the superdisintegrants swell in volume, which facilitates disintegration. Thus, wetting is a prerequisite for disintegration and dissolution of a tablet. In our study, all the tablets exhibited complete wetting time results within ~1.5 min. The result of average wetting time (n = 6) of each formulation is shown in Table 3. At each concentration level (2%, 3% or 5%), superdisintegrants with respect to their wetting time were in the order as follows: sodium starch glycolare > croscarmellose sodium > crospovidone. Thus, amongst the 3 superdisintegrants, crospovidone furnished quicker wetting of the tablets than sodium starch glycolate and croscarmellose sodium at all concentration levels. In addition, for each disintegrant, wetting time was reduced as the concentration was increased from 2% to 5%. In particular, crospovidone at a concentration of 5% resulted in the quickest wetting of the tablets. Furthermore, the average wetting time of formulation F6 was 30 ±1 s vs 91 ±1.9 s as compared to the commercial product.

The disintegration time results were in accordance with the results of wetting time. The result of average disintegration time (n = 6 × 3 = 18) of each batch is shown in Table 3. All the formulations showed quicker wetting than the commercial product. At each concentration level, superdisintegrants with respect to their disintegration time were in the order as follows: sodium starch glycolate > croscarmellose sodium > crospovidone. Moreover, for each disintegrant, disintegration time was decreased as the concentration was increased from 2% to 5%. Among the 3 superdisintegrants, crospovidone exhibited quicker disintegration of the tablets than sodium starch glycolate and croscarmellose sodium at all concentration levels. In particular, crospovidone at a concentration of 5% demonstrated the quickest disintegration of all the tablets. Furthermore, the average disintegration time of formulation F6 was 38 ±0.894 s vs 143 ±1.276 s as compared to the commercial product.

All the superdisintegrants exerted a positive influence on the dissolution rate of stevia in water. At each concentration level, superdisintegrants with respect to their positive influence on the dissolution rate of stevia in water were in the order as follows: crospovidone > croscarmellose sodium > sodium starch glycolate. Moreover, dissolution rate of stevia was improved as the concentration of a superdisintegrant was increased from 2% to 5%. At 1 min, the average dissolution rate of formulation F3, F6 and F9 was 72.64 ±3.95%, 95.26 ±3.70% and 57.53 ±2.87%, respectively (Fig. 2). In particular, the dissolution rate of formulation F6 was 95.26 ±3.70% vs 60.54 ±4.38% in 1 min as compared to the commercial product.

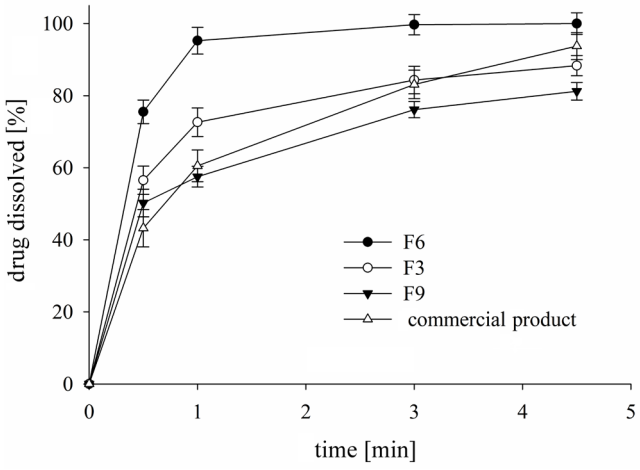

Fig. 2. A comparison of dissolution profiles of selected formulations and the commercial product. Each value of dissolution rate represents the mean ±SD (n = 6)

Table 3. Evaluation of compressed cores

Formulation	Weight variation [mg]*	Hardness [kg]*	Thickness [mm]*	Friability [%]*	Disintegration time [s]*	Wetting time [s]*
F1	50.136 ±0.457	2.948 ±0.256	2.458 ±0.041	0.404 ±0.045	100 ±0.983	90 ±1.303
F2	50.976 ±0.445	3.019 ±0.267	2.481 ±0.012	0.493 ±0.023	79 ±0.752	67 ±0.836
F3	51.741 ±0.664	2.984 ±0.271	2.481 ±0.019	0.580 ±0.075	59 ±1.264	50 ±1.341
F4	51.356 ±0.571	3.119 ±0.464	2.427 ±0.020	0.660 ±0.052	75 ±0.752	65 ±0.836
F5	50.786 ±0.892	3.087 ±0.214	2.428 ±0.022	0.576 ±0.064	59 ±0.727	57 ±1.516
F6	50.391 ±0.680	3.290 ±0.384	2.475 ±0.023	0.448 ±0.058	38 ±0.894	30 ±1.000
F7	49.690 ±0.808	3.285 ±0.352	2.440 ±0.023	0.430 ±0.112	110 ±0.632	95 ±0.489
F8	50.338 ±0.925	3.315 ±0.307	2.420 ±0.022	0.536 ±0.118	97 ±0.983	86 ±1.643
F9	51.251 ±0.800	3.330 ±0.286	2.460 ±0.034	0.516 ±0.076	80 ±1.048	65 ±1.732

* Each value represents the mean ±SD.

The FTIR spectra of formulation F6 and its corresponding powder blend are shown in Fig. 3 and Fig. 4, respectively. The FTIR spectral analysis revealed that there was no appearance, disappearance or shift of major peaks after compression. Both the spectra overlapped each other. This suggested the absence of potential chemical interactions among constituents.

Thus, on the basis of the most accelerated wetting, disintegration and dissolution rate, formulation F6 containing stevia, crospovidone, lactose, and magnesium stearate at the weight ratio of 15/2.5/32/0.5 was selected as the final formulation in our studies. Moreover, it exhibited better wetting, disintegration and dissolution rate as compared to the commercial product. Thus, it can be an effective sugar substitute for diabetics, obese and calorie-conscious people.

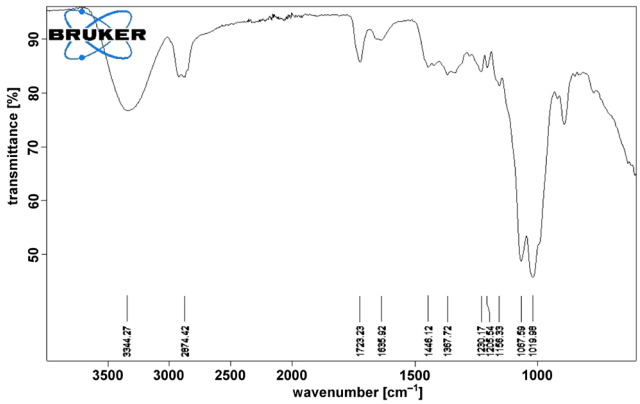

Fig. 3. FTIR spectrum of formulation F6

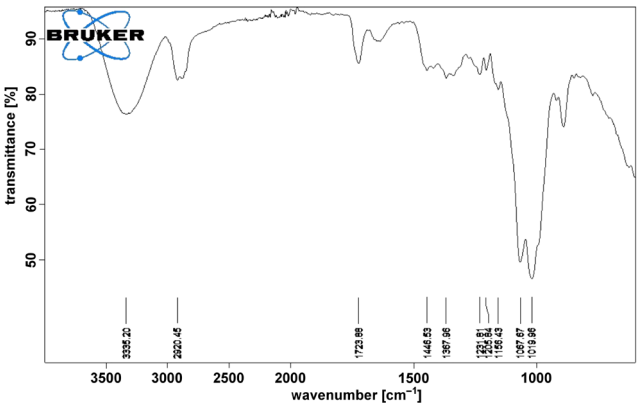

Fig. 4. FTIR spectrum of the powder blend corresponding to formulation F6

Conclusions

Powder blends of all the formulations exhibited good-excellent flow. Assay, weight variation, hardness, thickness, and friability of all the tablets were within the acceptable limits. All the superdisintegrants affected the wetting, disintegration and dissolution rate of stevia extract positively. At each concentration level, superdisintegrants with respect to their positive effect on the wetting, disintegration and dissolution rate of stevia in the aqueous medium were in the order as follows: crospovidone > croscarmellose sodium > sodium starch glycolate. Moreover, wetting, disintegration and dissolution rate of stevia were improved as the concentration of a superdisintegrant was increased from 2% to 5%. In particular, the formulation F6 containing stevia, crospovidone, lactose and magnesium stearate at the weight ratio of 15/2.5/32/0.5 resulted in the most accelerated wetting, disintegration and dissolution rate of stevia. Also, it exhibited better wetting (average wetting time: 30 ±1 s vs 91 ±1.9 s), disintegration (average disintegration time: 38 ±0.894 s vs 143 ±1.276 s) and dissolution rate (average percent dissolved: 95.26 ±3.70% vs 60.54 ±4.38% in 1 min) as compared to the commercial product. Accordingly, this formulation can be an effective sugar substitute for diabetics, obese and calorie-conscious individuals.

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Relationship between compression pressure, mechanical strength and release properties of tablets

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

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Abstract

Tablets are a complex drug delivery system consisting of the active pharmaceutical ingredients and excipients. Tablet production involves a series of unit operations in which drugs and excipients are subjected to mechanical stresses, such as compression pressure, thus imposing changes in the properties of these materials. Variations in the compression pressure and other processing parameters may affect the mechanical strength and release properties of the final tablet. It is generally expected that an increase in compression pressure should lead to an increase in mechanical strength and a decrease in release properties of tablets, but this may not be true in some practical situation, since tablet production is the result of complex interaction between many factors involving the drug, excipient, the formulation, and processing variables. The degree and extent of interaction of these variables are not absolutely dependent on one factor. The aim of this review is to study the interaction between compression pressure, mechanical strength and release properties of immediate and controlled release tablets. The effect of compression pressure on tablets is complemented by such factors as the material properties of the drug and excipient, the formulation and processing factors, which in turn affects mechanical strength and release properties.

Key words: mechanical properties, dissolution, compression pressure, release properties, crushing strength

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Introduction

Tablets are a complex drug delivery system consisting of the drug substance and adjuvants known as excipients, which aid the formulation of the desired drug product. Polymers as excipients in tablet production play an important role in determining the properties of a finished tablet. They have been extensively used in the design of various drug delivery systems as binders, disintegrants, drug release modifiers, directly compressible excipient, film coating, emulsifiers, suspending agents, thickeners, gelling agents, nanoparticles, etc.

Tablet production involves a series of unit operations usually consisting of mixing, blending and compaction. Other operations, such as granulation, coating, etc., may also be used depending on the type and desired properties of the finished product. During each unit operation process, drugs and excipients are subjected to mechanical stresses, which impose changes in the properties of these materials. This process is complex, because the knowledge of the properties of these starting material is often not complete, and their relationship to formulation factors and processing parameters is frequently not understood well; hence the essence of preformulation characterization to predict quality of the end product.[1] Also, producing a tablet of desirable quality requires understanding of the physics of compression.[2] Slight variations in formulation factors, processing parameters and material properties may affect the quality of the final tablet. The active pharmaceutical ingredients (APIs) and excipients, especially the binders,[3] disintegrants[4] and lubricants[5] used in tablet production, determine tablet properties. Compression pressure[6] and method of production[3,7] also contribute to the final tablet properties.

In general, tablet production involves the application of pressure (i.e., compression pressure) to a powder bed, compressing it into a cohesive compact through a process known as compaction.[8] Compaction is a simultaneous process of compression and consolidation of a particulate solid–gas system as a result of applied force.[9,10] While compression involves a reduction in bulk volume as a result of reduced gaseous phase with an increase in pressure within a powder bed, thereby resulting in closer packing of the powder particles, consolidation occurs simultaneously as force is increased to a point where further rearrangement becomes difficult and particle deformation occurs, leading to an increase in mechanical strength as a result of particle–particle interactions which result in bond creation. Consolidation is mainly responsible for increasing the mechanical strength of a powder bed under a rising compressive force.[11]

The aim of this review is to study the interaction between compression pressure (independent variable), mechanical strength and release properties (dependent variables) of immediate and controlled release tablets produced through wet granulation or direct compression techniques.

Compression pressure

Compression pressure is an external axial force which occurs when a physical force is pressed inward on the solid surface of an object, deforming it either permanently or temporarily, depending on the material and the magnitude of the force. The extent, degree and the direction of the deformation depend on such factors as the properties of the APIs and excipients, the type and concentration of ingredients in the formulation, particle size, particle shape, molecular weight, solubility, formulation processes, wetting properties, polymer properties, type of binding force that exist during consolidation, etc.

These are the critical quality attributes that determine the optimized force needed to make a tablet of good quality. This force is determined mostly during preformulation studies. The United States Pharmacopeia and the European Pharmacopeia did not specify a limit of compression pressure required to produce a cohesive compact, and therefore its determination is often empirical depending on the critical quality attributes of the material to be compressed. Compression pressure is an important control parameter, because it influences almost every tablet property, such as density, porosity, surface area, hardness, friability, disintegration, dissolution, etc.[12]

Density increases with the increase in compression force, while porosity decreases. Hardness increases with the increase in compression force, while friability decreases.[13] In many cases, an exponential relationship exists between disintegration time and compression pressure. The disintegration time increases with the increase in pressure. There is no clear-cut trend with dissolution. This may depend on the type of tablet, such as immediate release (disintegrating tablets) and controlled release (non-disintegrating tablets).

Tablet hardness, crushing strength or tensile strength is used in many cases as a surrogate measure for compression pressure during tablet production, since tableting machines are unable to determine and measure the compression force that is desired.[14]

The effect of compression pressure on tablets is complemented by the material properties and the formulation factors, which in turn may affect mechanical strength and release properties.

Mechanical properties of tablets

The ability of a tablet to withstand mechanical handling and transport is a measure of tablet mechanical strength, which is an important and widely used parameter to control the production process. The major tests available for the assessment of the mechanical properties of tablets are the hardness (N or Kgf), tensile strength (kg/cm^2) and friability (% loss). Mechanical strength assessment generally begins with mechanical testing of particles of drugs and excipients with compression parameters derived from

Heckel[15] and Kawakita and Lüdde,[16] which are the most commonly used compaction equations. These compaction equations are based on the relationship between applied load and volume reduction of materials in the die and none has been found to be fully satisfactory.

Some of the factors generally affecting tablet mechanical strength are:

Particle size – a decrease in particle size will result in increased tablet mechanical strength; powders of very fine particles are cohesive even in their uncompressed form.

Moisture content – a small proportion of moisture is essential for the production of a cohesive tablet. In some cases, wet granulation process with hydrophilic polymer was reported to yield tablet with stronger mechanical strength,[3,7] and, thus, there should be optimum moisture content for the production of a good quality tablet.

Lubricants – they act as a physical barrier which prevents particle–particle interactions affecting inter-particulate bond formation, thereby decreasing tablets mechanical strength.

Compression pressure – during compression, an external force is introduced which causes fragmentation, resulting in the formation of new surfaces with increased surface area; thus, more area and particles are available for bond formation. A linear relationship exists between tablet crushing strength and compression pressure, except at high forces.

Hardness

Tablet hardness or breaking strength is a measure of tablet strength. It is the force required to break a tablet from which tensile strength is determined. It assesses how strong a tablet has to be to withstand breakage, crumbling or chipping under the conditions of storage, transportation and handling.[17] It generally depends on the type and concentration of binder in a formulation,[18] tablet height to diameter ratio[12] and compression force.[6,19]

Friability

Tablet friability is a measure of the resistance of tablets to fracture. The test is generally used to assess the ability of tablets to withstand shock and abrasion, which will unavoidably be encountered during manufacturing, packaging, transportation, and handling.[20]

Effect of compression pressure on mechanical strength

Generally, there is an increase in mechanical strength with increased compression pressure. Sun and Hao[21] observed that the tensile strength of caffeine tablets was reasonably and substantially higher than that of methyl gallate produced under the same compression pressure gauge. They also observed a sharp reduction in tablet tensile strength of both tablets at a point with increasing pressure, suggesting that the detrimental effect of elastic recovery on tablet strength supersede the bonding strength gained from increased compression pressure. However, the formation of 1:1 cocrystal of caffeine and methyl gallate exhibited superior compaction properties due to the presence of slip planes in crystal structure, thereby improving tablet strength with increasing pressure. Changes in the tensile strength of caffeine tablets, methyl gallate tablets and the co-crystal combination of caffeine and methyl gallate tablet was due to the material properties of the drugs, since that was the only variable in the study.[21]

A study carried out by Adeleye et al.[6] established that compression pressure is a strong variable which has a great impact on the hardness of tablets when all other manufacturing processes are kept constant. Statistical analysis revealed a significant increase in tablet hardness with increase in compression pressure. This was due to gas displacement from the powder bed in the die as compression pressure increases, bringing particles in close contact, thereby leading to the formation of a strong bond, which, in turn, increases the mechanical strength of the tablet at high compression pressure. They also observed a decrease in friability with increase in compression pressure. The decrease was attributed to the formation of more solid bonds, which increases hardness, thus making tablets more resistant to fracture and abrasion.[17]

Nanjwade et al.[22] reported an increase in the breaking force and pellet hardness of cefuroxime axetil along with an increase in compression pressure as a result of the existence of a very firm intrinsic compact binding property between the individual particles of the drug and the excipient, which ultimately resulted in a decrease in in-vitro dissolution.

Shipar et al.[23] and Vodáčková et al.[12] concluded that compression pressure has an intense effect on tablet hardness and disintegration time. Tablet hardness and disintegration time increases with increasing compression pressure. According to Ordu et al.,[24] excess amounts of binders and compression pressure may lead to the production of tablets that are too hard, which may affect disintegration taking place within the desired time.

Release properties of tablets

The significance, magnitude and extent of the effect of variables on the release properties lie mostly in the nature of materials in the formulation rather than in compression pressure. Ordu and Onyemelukwe[25] reported that the nature or form of excipient, especially the binder, had a considerable influence on the release properties of a tablet. The concentration is the most important independent variable, as it had more influence on other variables, such as compression pressure, affecting the release properties of tablets. In some cases, compression pressure does not have a significant effect on the release properties of tablets.

Tablet disintegration

The first step towards dissolution is breaking down the tablet into smaller particles or granules in conventional tablets. This process is known as disintegration. It exposes a greater surface area of tablets to the dissolution medium; hence, it plays an importance role in tablet dissolution for the active drug substance to be released into the absorption site.[26]

The disintegration time of tablets usually depends on formulation factors such as the nature, type and amount of drug and the excipients used (this could be referred to as internal variables), as well as on the actual tablet manufacturing conditions such as compression force, speed of compression and environmental conditions of the room where the compression is taking place (this could be referred to as the external variables). Often, disintegration time increases exponentially with an increase in compression pressure. Tablets made with high compression pressure exhibit low porosity with strong inter-particulate bond, thereby increasing the time required for penetration of water into the tablet, thus increasing the disintegration time. In tablets made with low compression pressure, there is large porosity and the bond is weak, thereby decreasing the time required for penetration of water into the tablet, thus decreasing the disintegration time. Mistry et al.[27] reported that binder concentration has a direct relationship with hardness and disintegration and an inverse relationship with friability. As the amount/concentration of the binder increases, the hardness and disintegration times also increases, while the friability decreases.

Tablet dissolution

Dissolution is the process by which a solid drug goes into solution in a solvent. Drug dissolution is an important condition for the bioavailability of drugs. The dissolution rate of a drug is the most important factor determining drug absorption; it is the rate-limiting step in many formulations.[28] Therefore, dissolution time gives an indication of the time needed for the drug to be absorbed and to induce a therapeutic effect. Dissolution is a multistep process involving different interactions between the drug and the dissolution medium. This process involves the release of drug molecules from the tablet surface with the formation of hydrated molecules at the solid-liquid interface, and the mass transport of the drug molecules from the interphase to the bulk solution.[29]

Controlled drug delivery tablet systems are designed for tablets to remain intact in the gastrointestinal tract, where they gradually erode to release their content. If the structure or design is lost, drug release is no longer controlled and the tablet behaves like a conventional immediate release tablet, causing dose dumping. Tablet hardness has no significant influence on the dissolution rate of this system.[6] It is only important here to guide the formulator to produce tablets that can withstand shock and abrasion during production and handling. Drug release mechanisms are complex processes involving swelling, erosion and diffusion across tablet surfaces, in which hardness and compression force may not have any significant influence.[30]

Effect of compression pressure on release properties

Several authors stated that compression pressure is a statistically significant factor of tablet hardness, but its effect on drug release was found to be minimal.[31] Some authors observed that compression does not have any effect on the release properties of drugs,[32] while some observed that it does.[22,33]

The ideal theoretical relationship between dissolution and compression pressure is dissolution being slowed with an increase in compression pressure; however, the increase in force of compression may not affect the dissolution rate of a drug in that manner. The possible relationships that can occur between dissolution and compression pressure are the following: dissolution being more rapid with an increase in pressure, dissolution being slower with an increase in pressure, dissolution being faster to a maximum with an increase in pressure and later becoming slower with a further increase in compression pressure, and dissolution being slower to a minimum with an increase in pressure and later becoming fast with a further increase in compression pressure. Dissolution mostly depends upon the nature of the drug (solid properties, solubility, etc.) and also upon the nature (compactibility) and the amount of binder present in the formulation. An increase in compression force will result in a slower rate of dissolution of some types of tablets due to factors which include hardness (this increase is a result of high compact arrangement of the particles in the tablet, thus making it difficult for the dissolution medium to penetrate the tablet), surface area (due to the compact arrangement of particles, the surface area of the materials in the tablet is reduced, which means that the exposed surface to the dissolution medium is also reduced, resulting in a reduction in dissolution rate of tablets) and wettability (the wettability of the tablet decreases in the dissolution medium due to the compact arrangement of particles, slowing down the penetrability of the dissolution medium into the tablet core, resulting in a reduction in the dissolution rate of tablets).

Dedhiya et al.[34] reported that the release properties of lithium carbonate did not significantly change with the increasing compression force. Iranloye and Parrott[35] also reported that compression pressure had no effect on the dissolution rates at a certain range.

Adeleye et al.[6] tried to relate compression pressure with the drug release rate, found that drug release is controlled mainly by diffusion and concluded that compression pres-

sure does not have a significant effect on the release rate and release mechanisms, but rather the polymer and the material properties of the drug. This was in agreement with the report of Santos et al.[32]

Generally, drug release from matrix tablets takes place as a result of hydration, when the matrix comes in contact with dissolution medium,[36] which leads to the formation of gel in which drug diffuses out. The viscosity of this gel layer and its diffusional path length determine the release rate rather than the compression pressure or tablet hardness.[37,38] These factors (viscosity and diffusional path length of the gel layer) are the rate-determining step in matrix tablet dissolution.

The effect of compression force on dissolution behavior of a drug may be significant or insignificant. It mainly depends upon the nature of the drug and the excipients included. For example, the effect of compression will be negligible on the dissolution rate of a water-soluble drug. For a water-insoluble drug with low melting point, e.g., erythromycin stearate, compression force has an enormous effect on the dissolution rate of such drug, which could lead to failed disintegration and dissolution tests. Increasing the compression force of such material with low melting point will lead to the formation of a complex due to heat generated during compression, which reduces the dissolution rate. For such material, compression force should be optimized.

Nanjwade et al.[22] reported a sharp decline in the release of cefuroxime axetil with an increase in compression pressure. The release was directly proportional to compression pressure. Cefuroxime axetil has good compression, strong binding and gelling properties. They concluded that compaction by means of compression pressure of cefuroxime axetil is a major reason for a drastic drop of dissolution.

Marais et al.[39] reported that an increase in compression force increased the disintegration times of furosemide tablets, but did not have a significant effect on the dissolution of the tablet. They concluded that dissolution is mainly a reflection of the disintegration time, which depends on the concentration of disintegrant in the formulation. It was assumed that his was due to the higher concentration of disintegrant, which improved the rate and extent of liquid uptake and penetration into the tablets, allowing them to break up easily and rapidly, thus exposing the drug particles to the dissolution medium very quickly. Audu-Peter and Ibrahim[40] observed in their study that some tablet formulations which do not have satisfactory disintegration time could not release up to 50% of their drug content at the end of a 60-minute observation period, while some were able to release up to 100%, despite not having a satisfactory disintegration time. All formulations with satisfactory disintegration time had good release values of up to 95% after 60-minute observation period. The reasons why formulations with unsatisfactory disintegration time had a good release profile was attributed to low binder concentration, high concentration of disintegrant and low compression force, while satisfactory disintegration time with lower release was attributed to high compression force and the proportions of binder and disintegrant in the formulation. Ordu et al.,[24] Ordu and Onyemelukwe,[25] and Onyishi et al.[41] also reported the effect of ratio and the amount of binder and disintegrant concentrations on release properties.

Figure 1 depicts the schematic representation of the theoretical concept of the relationship between compression pressure, mechanical strength and release properties of a tablet as conceived by the researcher. This model has 3 different variables divided into 2 categories: independent and dependent variables. The independent variable is the compression pressure while the dependent variables are the mechanical strength (hardness and friability) and release properties (disintegration and dissolution). Each of the dependent variables is related to compression pressure and to each other as reflected in the model.

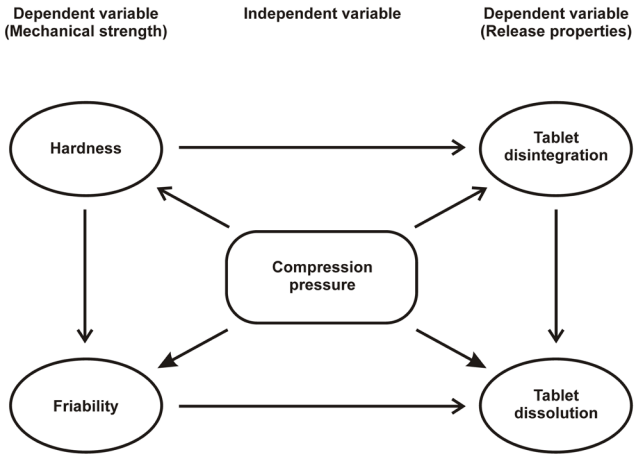

Fig. 1. Schematic representation of the relationship between compression pressure, mechanical strength and release properties of tablet

Discussion

Several factors affecting tablet quality during its preparation come into play. Such factors can be classified as internal and external variables. The internal factors are the nature, properties and concentration of excipient and drug, while the external factors include compression method (direct compression or wet granulation), compression pressure and compression speed. The magnitude of the influence of these variables is important to the pharmaceutical formulator to guide in the careful selection of excipients, formulation factors and processes to produce tablet of good property.

Properties of various tablet formulations vary because of the existence of different forms of interactions between the drug and the excipients as a result of the operations involved during manufacturing. Properties such as the nature, concentration, particle size, particle shape, mo-

lecular weight, solubility, etc. are some of the properties that influence the interaction, together with the external factors as enumerated above. The effect of these interactions can be minimized or maximized by modifying these properties to produce tablets of desired properties. The adhesion between powder materials is a result of the area of close contact between particles and the strength of such interactions. The quantity of the interaction is determined by the degree of compression as well as material properties, such as particle size and morphology, while the quality of interaction is determined by the surface properties, such as free surface energy.[42]

The greatest variables, which have overwhelming effects on tablet properties, generally occurred between type, nature and concentration of the binder, mostly due to the fact that the nature of the binder determines its plastoelastic properties and the magnitude of plastic deformation that will take place under compression forces.[43]

In tablet production, Audu-Peter and Ibrahim[40] reported that there should be a balance between formulation variables for the production of a tablet with good property. Some situations demand an appropriate ratio of binder and compression pressure; otherwise, excessive binder content may produce very hard granules that may not be properly compressed at a given compression pressure. They discovered that binder concentration and compression pressure influenced disintegration time and that a decrease in binder concentration will necessitate increasing the compression pressure to produce satisfactory tablets.

The increase in relative density is a reflection of increased compression pressure, which has a great effect on disintegration time and dissolution. The increase in relative density reduces specific surface area, thereby reducing the rate of penetration of liquid into the core of tablets as a result of increase in the binding force between particles due to their close proximity. This reduces the pore space in which binder particles can swell when wetted before disruption of the tablet.[44]

The effect the concentration of binding agent has on disintegration could be due to the fact that for an immediate release tablet, the tablet needs to disintegrate into granules before deaggregating to fine particles. The deaggregation process involves the removal of the binder layer around the particles, and this is subject to the amount of binder coating the particles; thus, the higher the binder concentration, the slower the removal, since a higher concentration would lead to more binding.[45] Changing the type of binder could have an effect on the disintegration time of tablets irrespective of compression pressure. Alebiowu and Itiola[46] reported the effect of pregelatinized starch on disintegration time as being dependent on its concentration, but in the case of native starch, the effect on disintegration time was dependent on relative density (compression pressure). This was attributed to the fact that pregelatinized starch binders are cold water-swellable.[47] This swellability would overwhelm the effects of compression pressure on the tablets. Concentration had a greater effect, since it leads to the formation of additional bonds.[46] They also found that, with the combination of native/pregelatinized starch, the nature of the starch was completely different, having a stronger effect on dissolution than relative density as expected, because pregelatinized starches are cold water-swellable and have a higher swelling capacity,[46] resulting in decreased dissolution times, unlike native starches in which lower swelling capacity was observed, which extended the dissolution time. The swellability of pregelatinized starches would undermine the effect that relative density would have on the penetration rate of water into the tablets. They concluded that the form or nature of a binder will have considerable influence on the effect that the relative density (compression pressure) of a tablet has on the disintegration and dissolution parameters.

Conclusions

Theoretically, an increase in compression force should lead to an increase in mechanical strength and a decrease in the release properties of tablets. In some practical situations, this trend may be distorted.

Tablet production is the result of a complex interaction between many factors involving the drug, excipient, the formulation, and processing variables. The effect is an interplay between variables, which are not easily understood close**,** because at times it does not follow a particular theoretical trend. The pharmaceutical formulator should try to understand and take advantage of these variables for the production of tablets with desired property. The degree and extent of interaction of these variables are not absolutely dependent on one factor. However, the uniqueness of the material characteristics of ingredients essentially determines the final properties of the finished tablet. It can, therefore, be concluded that the effect of compression pressure on tablets is complemented by factors such as the material properties of the drug and excipient, as well as the formulation and processing factors; all of these properties and factors, in turn, affect the mechanical strength and release properties.

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Influence of levodropropizine and hydroxypropyl-β-cyclodextrin association on the physicochemical characteristics of levodropropizine loaded in hydroxypropyl-β-cyclodextrin microcontainers: Formulation and in vitro characterization

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Abstract

Background. Poorly water-soluble drugs do not dissolve well in aqueous-based gastrointestinal fluid; therefore, they are not well absorbed. Thus, employing a suitable solubility enhancing technique is necessary for such a drug. Drug/HP-β-CD complexation is a promising way to improve solubility and dissolution of a poorly water-soluble drug. Levodropropizine was used as a model drug in this study.

Objectives. The purpose of this research was to enhance the aqueous solubility and dissolution rate of levodropropizine by employing the inclusion complexation technique.

Material and methods. A microparticle formulation was prepared from levodropropizine and hydroxypropyl-β-cyclodextrin (HP-β-CD) in a 1:1 molar ratio through the spray-drying technique. The host-guest relationship between levodropropizine and HP-β-CD was also investigated using the molecular docking computational methodology. The aqueous solubility and dissolution rate of levodropropizine in formulations were assessed and compared with those of the drug alone. X-ray diffraction (XRD), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and Fourier transform infrared spectroscopy (FTIR) were applied for the solid-state characterization of the prepared samples.

Results. According to the research outcomes, the levodropropizine/HP-β-CD formulation had enhanced the aqueous solubility (351.12 ±13.26 vs 92.76 ±5.00 mg/mL) and dissolution rate (97.83 ±3.36 vs 3.12 ±1.76% in 10 min) of levodropropizine, compared to the plain drug powder. The levodropropizine/HP-β-CD formulation had converted the crystalline drug into its amorphous counterpart. Furthermore, no covalent interaction was found to exist between levodropropizine and HP-β-CD. The spray-dried particles were discrete. Each particle had a shriveled appearance.

Conclusions. The levodropropizine/HP-β-CD formulation is, therefore, recommended for the more effective administration of levodropropizine through the oral route.

Key words: dissolution rate, spray-drying, cyclodextrins, amorphous form, phase solubility

Introduction

Acute or chronic coughing is an indicator of various underlying respiratory illnesses. Acute coughing might be caused by a bacterial invasion in the upper respiratory tract during a common cold,[1] while other causes of chronic coughs include gastro-esophageal reflux disease (GERD), asthma, chronic bronchitis, or chronic obstructive pulmonary disease (COPD).[2] Irrespective of whether acute or chronic, coughing often accompanies several uncomfortable symptoms, such as nausea, vomiting, chest pain, headache, insomnia, or lethargy.[3] Antitussives offer much desired relief from the discomforts being caused by dry coughs.[4]

Antitussives either act centrally or peripherally. Centrally acting antitussives, such as codeine, cloperastine, morphine, dihydrocodeine, and dextromethorphan result in a number of adverse effects, including reduced alertness, somnolence, respiratory depression, and constipation.[5] Moreover, their frequent and prolonged use may result in patient tolerance and/or dependence. To circumvent such complications, treatment with peripherally acting antitussives is considered more favorable.

Levodropropizine [(2S) -3-(4-Phenylpiperazin-1-yl) propane-1, 2-diol], an isomer of dropropizine (Fig. 1A), is a peripherally acting cough suppressant that is used in the management of dry coughs, pertaining to various pulmonary morbidities.[6] Its peripheral action involves the inhibition of cough reflexes by the modulation of sensitive C-fibre activity.[7] Levodropropizine is only slightly soluble in water.[8]

Levodropropizine is as effective as dropropizine in relieving cough. Moreover, it has lower risk of somnolence than dropropizine.[9] Levodropropizine is only slightly water-soluble.[10] For improving the potency, absorption and efficacy of a slightly soluble drug, an aqueous solubility improving technique can be adopted.[11] Various techniques have been employed for improving the aqueous solubility and dissolution rates of slightly soluble drugs.[12–15]

The oral route is the most preferred way of drug administration, owing to its higher safety and the convenience of such administration.[16] An orally administered drug achieves its intended pharmacological effects when it is traversed from the gastrointestinal tract, enters the general blood circulation and reaches the target site of action. The dissolution of a drug in the aqueous gastrointestinal fluid is essential for traversing the gastrointestinal–blood barrier as a solid drug cannot cross cell membranes. Thus, on the basis of the aqueous solubility and permeation across cell membranes, Biopharmaceutics Classification System (BCS) has placed drugs under 4 classes.[17] Poorly water soluble drugs are included in BCS class II. Such a drug is insufficiently absorbed from the gastrointestinal tract (GIT)[18]; therefore its oral bioavailability is low. Thus, high doses are required to cross the minimum effective concentration (MEC) level in the blood, as concentration below MEC of a drug cannot illicit the specific receptors to produce particular pharmacological effects associated with it. Moreover, high doses can result in local toxicity in the GIT. Accordingly, aqueous solubility-enhancing techniques are employed for improving the potency, absorption and efficacy of insoluble or slightly soluble drugs.[19]

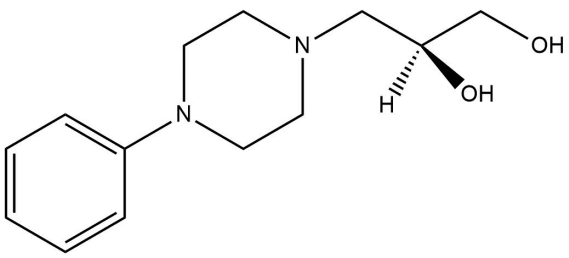

Fig. 1A. Structural formula of levodropropizine (ChemDraw Ultra 12.0)

Several techniques have been adopted for enhancing the aqueous solubility, dissolution rate, absorption, bioavailability, potency, and efficacy of various slightly water soluble drugs.[13,14] Among others, the inclusion complexation technique has been successfully used for augmenting the aqueous solubility and dissolution rate of slightly soluble drugs.[12] Cyclodextrins, such as hydroxypropyl-β-cyclodextrin (HP-β-CD), are hydrophilic oligomeric matrices that can improve the aqueous solubility and dissolution rate of a slightly soluble drug by converting the crystalline form of the drug into its amorphous counterpart.[20] A cyclodextrin molecule possesses a hydrophilic exterior and a lipophilic inner cavity.[21] A poorly water soluble drug molecule resides within the inner cavity during complex formation.[22] Although several weak intermolecular forces may exist between the drug and the cyclodextrin molecules,[23] new covalent bonds are not formed and the pre-existing covalent bonds are not weakened during complex formation.[24,25] Amongst other cyclodextrins, hydroxypropyl-β-cyclodextrin (HP-β-CD) (Fig. 1B) possesses a greater ability to house or accommodate various insoluble, or slightly soluble, drug molecules.[26] Because the cyclodextrins cannot be absorbed from the gastrointestinal tract, they are considered non-toxic when administered orally.[27] Toxicological investigations have proven that HP-β-CD is absolutely non-toxic.[28]

Thus, in the present research, the solubility and dissolution rate of levodropropizine were improved using HP-β-CD in order to increase its potency and oral absorption, and decrease possible local toxicity associated with high doses.[11] A microparticulated sample of levodropropizine and HP-β-CD, in a 1:1 molar ratio,[29] was prepared through the solvent evaporation method, using the spray-drying technique.[30] Spray-drying is considered to be a promising technique for the preparation of a drug/HP-β-CD formulation, allowing the amorphous form of the drug to be contained, due to the rapid evaporation of the solvent.[30] The host–guest relationship between levodropropizine and HP-β-CD was also studied by employing the mo-

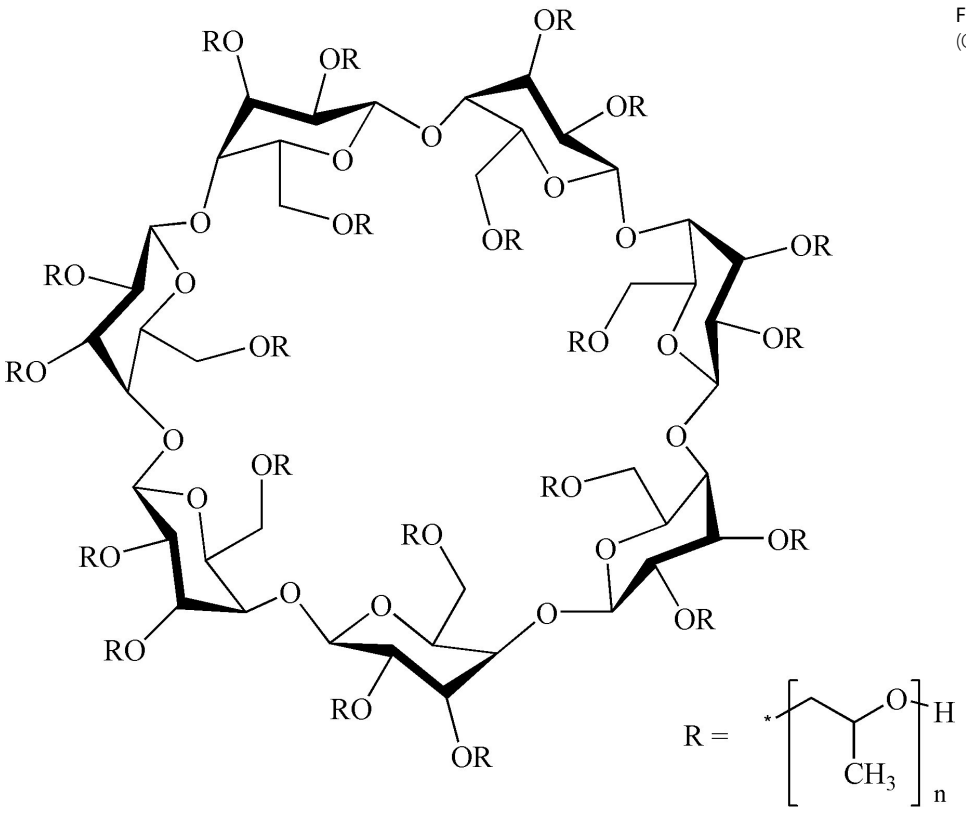

Fig. 1B. Structural formula of HP-β-CD (ChemDraw Ultra 12.0)

lecular docking computational methodology. The aqueous solubility and dissolution rate of levodropropizine were determined and compared with those of the drug alone. X-ray diffractometery (XRD), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and Fourier transform infrared spectroscopy (FTIR) were employed for the solid-state characterization of the preparation.

Material and methods

Material

Hydroxypropyl-β-cyclodextrin (HP-β-CD) was obtained from Sigma-Aldrich Co. (St. Louis, USA). Levodropropizine was procured from Jinan Chenghui-Shuangda Chemical Co. (Jinan, China). All other chemicals were of the reagent grade.

Phase solubility study

Various concentrations of HP-β-CD were prepared by dissolving solid HP-β-CD in water (0.0357 M, 0.0715 M, 0.143 M, 0.214 M, and 0.286 M).The solubility of levodropropizine in each of these aqueous solutions of HP-β-CD was determined using the Higuchi and Connors phase solubility method.[29] An excess amount of levodropropizine was transferred into 1 mL of each aqueous solution of HP-β-CD in 2 mL microtubes and vortexed for 1 min. These tubes were then fixed to an agitator in a water bath (25°C) and the samples mechanically shaken (250 rpm) for 2 days. After centrifugation at ×5,000 for 2 min, the supernatant of each sample was carefully withdrawn by means of 1 mL syringes, filtered and adequately diluted. These dilutions (2 mL) were analyzed on a HALO DB-20 UV-visible spectrophotometer (Dynamica Scientific Ltd., Clayton, Australia) at 240 nm. The complexation efficiency (E_C) and stability constant (K_S) were determined with the following formulas: $E_C = m/1–m$ and $K_S = E_C/S_0$, where m is the slope of the straight line of the phase solubility graph and S_0 is the intrinsic solubility or solubility of levodropropizine in water in the absence of HP-β-CD.

Computational methodology for molecular docking

In order to rationalize the achieved results from the phase solubility study, a molecular docking study for the levodropropizine/HP-β-CD formulation was conducted using the Molecular Operating Environment (MOE) 2015.10 software (Chemical Computing Group, Montreal, Canada). The 3D structure of β-CD was retrieved from the RCSB Protein Data Bank (PDB ID code: 1jl8) and used as a structural template for building the final structure of HP-β-CD by adjusting the corresponding functional group with the Sybyl-X1.3 SKETCH module. Levodropropizine was constructed by also using the SKETCH module, which was employed in Sybyl-X1.3.

Its potential energy was minimalized by means of a Tripos force field and Gasteigere-Huckel atomic charge, which had a distance-dependent dielectric function and a convergence criterion of 0.001 kcal/(mol·Å). All parameters were kept at default values for molecular docking in MOE. The best binding conformations of ligand in oligomer were ranked based upon their docking scores. In conclusion, the best energy model was selected and graphically analyzed.

Preparation of the levodropropizine/HP-β-CD formulation

Levodropropizine and HP-β-CD in a 1:1 molar ratio were dissolved in 90% ethanol to prepare an absolutely transparent solution. Subsequently, the solution was subjected to spray-drying using a mini spray dryer (Büchi B-290, Labortechnik AG Co., Flawil, Switzerland). The feed rate, spraying air pressure, internal diameter of the spraying nozzle, inlet temperature, outlet temperature, aspirator setting, and aspiration pressure in the filter vessel were 3 mL/min, 4 kg/cm^2, 0.7 mm, 95°C, 60°C, 90% and –45 mbar, respectively. The dried formulation was accumulated in the product collector.

Levodropropizine content determination

The formulation, equivalent to 10 mg of levodropropizine, was dissolved in 30 mL of ethanol in a 100 mL volumetric flask and the volume amounted to 100 mL with ethanol. The theoretical concentration of the solution was 100 µg/mL. One milliliter of this clear solution was filtered and adequately diluted. The dilution (2 mL) was analyzed on a HALO DB-20 UV-visible spectrophotometer at 240 nm. The test was performed in triplicate. The levodropropizine content was determined, using the formula: $L_C = L_A/L_T \times 100$, where, L_C is the levodropropizine content [%], L_A is the actual concentration of levodropropizine [µg/mL] as determined on the UV-visible spectrophotometer, and L_T is the theoretical levodropropizine concentration [µg/mL].

Aqueous solubility test

To determine the effect of the levodropropizine/HP-β-CD formulation on the aqueous solubility of the drug, a sufficient quantity of the formulation was transferred into 1 mL of distilled water in a 2 mL microtube and vortexed for 1 min. Each tube was then secured to a mechanical shaker in a water bath (25°C) and agitated (100 rpm) for 5 days.[30] After centrifugation at ×5000 for 2 min, the supernatant of each sample was carefully withdrawn by means of 1 mL syringes, filtered using syringe filters and adequately diluted. Each dilution (2 mL) was assayed on a HALO DB-20 UV-visible spectrophotometer at 240 nm.

Dissolution test

Dissolution studies were performed on both the active ingredient alone and on the formulation. Quantities of the formulation and of the drug powder, equivalent to 30 mg of levodropropizine, were enclosed in Spectra/Por® dialysis pouches (Spectrum Labs, Rancho Dominguez, USA) and placed in the baskets of a Vision® Classic 6™ USP dissolution tester I (Hanson Research Co., Los Angeles, USA). Each rotating basket (100 rpm) was then immersed in 900 mL of a 2% (w/v) aqueous solution of Polysorbate 80 in round bottom dissolution vessels.[31] The dissolution medium temperature was maintained at 37 ±0.5°C by the surrounding water bath. One milliliter of dissolution medium was sampled from each dissolution vessel at each of the following time intervals: 5 min, 10 min, 15 min, 20 min and 30 min. Each sample was filtered using syringe filters and adequately diluted. The levodropropizine in each dilution (2 mL) was quantified on a HALO DB-20 UV-visible spectrophotometer at 240 nm.

Crystallinity test

The intensity of crystallinity of the levodropropizine plain powder and the HP-β-CD separately, of a physical mixture of the 2 components, and of the levodropropizine/HP-β-CD formulation were examined by employing XRD and DSC techniques. The physical mixture was prepared by thoroughly triturating levodropropizine and HP-β-CD in a 1:1 molar ratio, using a pestle and mortar. The samples were scanned on a D/MAX-2500 PC X-ray diffractometer (Rigaku Corporation, Tokyo, Japan), equipped with a Cu $K\alpha_1$ monochromatic radiator. Each sample, mounted on the sample plate, was scanned between 10–80°, using a step-size, scanning mode, scanning speed, current and voltage of 0.02°/s, 2θ, 5°/min, 100 mA, and 40 kV, respectively.[30] A DSC Q20 differential scanning calorimeter (TA Instruments, New Castle, USA) was used for DSC analysis in the range of 30–130°C. Each sample, completely sealed in an aluminum crucible, was heated at a rate of 5°C/min under a nitrogen supply of 30 cm^3/min.

Morphological features study

The shape, size and surface physiognomies of the particulate samples were perused, using an S-4800 scanning electron microscope (Hitachi, Tokyo, Japan). The samples were affixed onto the exposed surface of a double-sided adhesive tape, already clung onto the metallic disc with its one side. The samples were then coated with platinum under 7×10^{-3} mbar pressure, using a K575X EMI Teck Ion Sputter to facilitate electrical conduction for imaging. The current and turbo speed were 25 mA and 100%, respectively.

Fourier transform infrared spectroscopy spectroscopic analysis

For FTIR spectroscopic analysis, a Nicolet-6700 FTIR spectrophotometer (Nicolet Instrument Corporation, Madison, USA) was used. A minute quantity of each sample was transferred into the fixed crucible, or sample slot, located exactly below the compression tip. Before scanning in the range of 600–4000 cm^{-1}, the hollow pin, bearing the scanning lens inside, was adjusted downwards onto the sample for compression between the sample slot and the compression tip.

Results and discussion

Among the cyclodextrins, HP-β-CD possesses a higher affinity for water-insoluble or slightly water-soluble, molecules and was thus chosen for the inclusion complex formation during this research.[26] Since the exterior of the HP-β-CD molecule is hydrophilic, while its inner cavity is lipophilic, it can accommodate the slightly water-soluble levodropropizine molecule within its cavity, where an inclusion complex is formed to possibly improve the aqueous solubility of the drug.[26]

Total degree of substitution (TDS) is defined as the average number of substituted moieties per cyclodextrin molecule.[32] The average molar degree of substitution (MS) is defined as the average number of moles of the substituting agent per mole of glucopyranose.[24,33] The degree of substitution is defined as the average number of substituted hydroxyls per glucopyranose of the cyclodextrin molecule.[34] HP-β-CD used in this research had a molecular weight (MW) of 1400 Da. When no additional reactive moieties are generated as a consequence of substitution reaction, the MS is equal to DS. No net gain or loss of any atom takes place in the hydroxypropylation reaction; therefore, the molecular formula of HP-β-CD can be expressed as $C_{42}H_{70}O_{35} + (C_3H_6O)_n$, where *n* is the number of moles of propylene oxide (substituent of hydroxypropyl) added. Thus, MW = 58.08 × (T.D.S.) + 1135, where 1135 is molecular weight of betadex ($C_{42}H_{70}O_{35}$) and 58.08 is the molecular weight of propylene oxide (C_3H_6O).[32] As the β-cyclodextrin molecule consists of seven glucopyranose units, TDS = 7 × MS. Therefore, MW = 406.56 × (M.S.) + 1135. From this discussion, TDS and MS in our study were 4.56 and 0.65, respectively. Moreover, DS was 0.65.[35]

For determining the apposite composition of the levodropropizine/HP-β-CD formulation, the Higuchi and Connors phase solubility study model was employed.[29] The straight line ($r^2 = 0.9999$) graph obtained during this study is demonstrated in Fig. 2. From the graph, the slope of the line was determined at 576.79, while the y-intercept, representing the solubility of the drug in the absence of HP-β-CD, was 394.47 M. The complexation

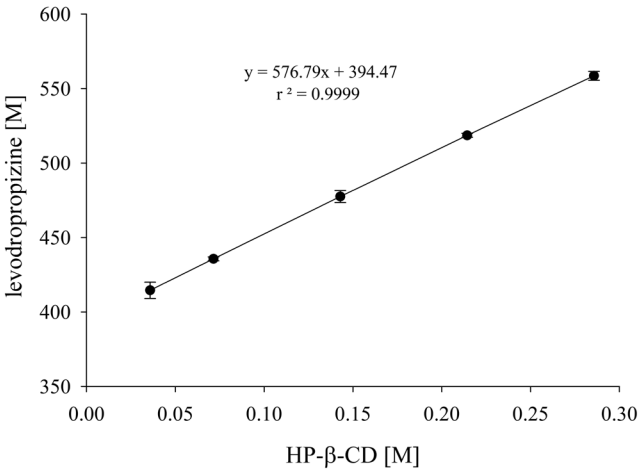

Fig. 2. The levodropropizine/HP-β-CD phase solubility diagram acquired in water at 25°C. Each value represents the mean ±SD; (n = 3)

efficiency (E_C) and stability constant (K_S) were 1.0017 and 2.539×10^{-3} M^{-1}, respectively. According to this phase solubility model, therefore, levodropropizine and HP-β-CD were prepared in a 1:1 molar ratio for this formulation.[29]

The most likely molecular model for the inclusion complex of levodropropizine and HP-β-CD, depicting the possible interaction of the drug molecule with HP-β-CD cavity, is shown in Fig. 3. These results indicate that levodropropizine interacted with HP-β-CD in a 1:1 molar ratio, and thus had the best stability constant (K_S) and complexation efficiency (E_C), which was in agreement with the conclusions of the Higuchi and Connors phase solubility study. Furthermore, with regards to the docking with HP-β-CD, the binding energy was –6.3 kcal/mol. Graphical analyses of the docking results revealed that the phenylpiperazine moiety of levodropropizine was retained at the margin of cavity, while the propane-1,2-diol moiety forming hydrogen bonds to the secondary hydroxyls along the rims of HP-β-CD had an average distance of 2.93Å (Fig. 3).

The spray-drying technique, in conjunction with the solvent evaporation method, is considered the best way to prepare formulations with HP-β-CD.[30] In this method, since the drug and HP-β-CD are completely dissolved in a solvent prior to subjecting them to spray-drying, the drug content is the highest in the solid product, owing to homogeneous intermingling at the molecular level. In this study, the drug content in the solid levodropropizine/HP-β-CD formulation was 100.26 ±1.64% (n = 3).

HP-β-CD has reportedly been successfully used for enhancing the aqueous solubilities and dissolution rates of various drugs, such as tacrolimus,[36] fenofibrate,[30] azithromycin,[37] nimesulide and meloxicam,[38] and apigenin.[37] In this study, the aqueous solubility and dissolution rate of levodropropizine were improved by the levodropropizine/HP-β-CD formulation, compared to those of the levodropropizine powder alone. The improvement

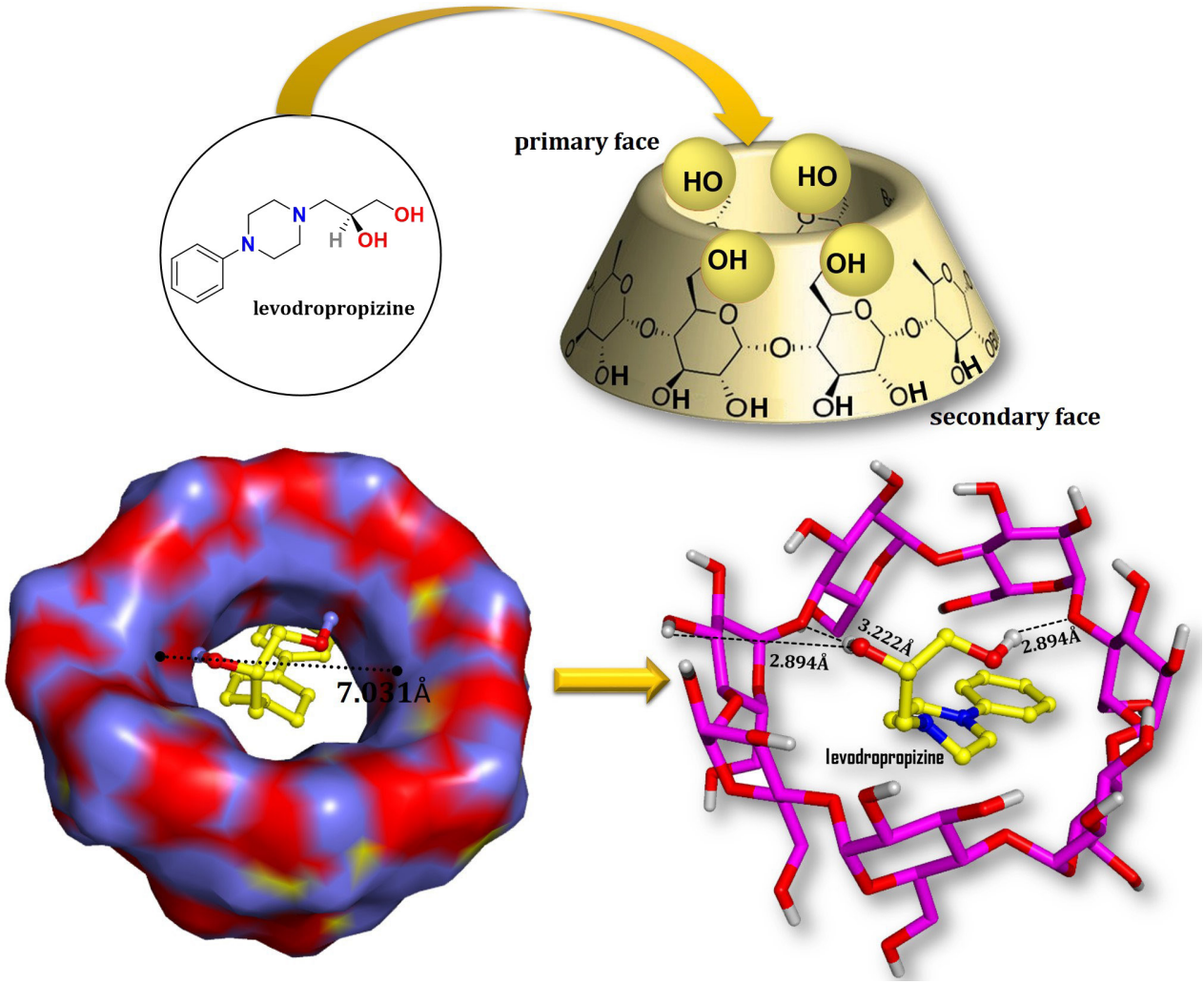

Fig. 3. Binding mode of levodropropizine (yellow ball-sticks) into HP-β-CD (magenta sticks). Possible H-bonds are shown with doted lines

in the aqueous solubility of levodropropizine in formulation was 351.12 ±13.26 vs 92.76 ±5.00 mg/mL, while the enhancement of its dissolution rate was 97.83 ±3.36 vs 3.12 ±1.76% in 10 min (Fig. 4).

The XRD patterns of the test samples are illustrated in Fig. 5. The levodropropizine powder gave typical sharp crystalline peaks in the 10–30° range (Fig. 5A). HP-β-CD did not generate any sharp peaks, suggesting its amorphous nature (Fig. 5B). Levodropropizine-related distinguishing peaks were visible in the XRD pattern of the physical mixture as well (Fig. 5C). These peaks were, however, absent in the diffractogram of the levodropropizine/HP-β-CD formulation (Fig. 5D). This suggested that levodropropizine had changed from its crystalline state into its amorphous state in the spray-dried levodropropizine/HP-β-CD formulation during preparation through the solvent evaporation method.[30]

Likewise, the DSC results were in harmony with the XRD results. The DSC thermograms are shown in Fig. 6. A deep endotherm was present at about 103°C for the levodropropizine powder, suggesting the melting point of the crystals (Fig. 6A). Although no peak appeared

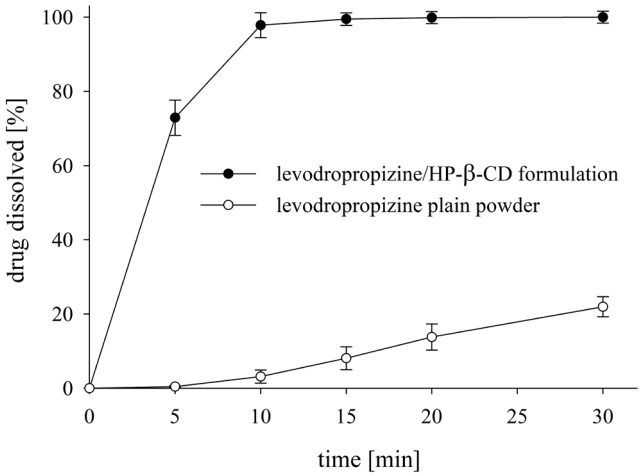

Fig. 4. Effect of levodropropizine/HP-β-CD formulation on the dissolution of the drug compared to plain levodropropizine. Each value of dissolution represents the mean ±SD; (n = 6); $p < 0.05$ at all points

in the HP-β-CD test results, confirming its amorphous nature, an endothermic sliding behavior in the curve was observed, owing to the escape of loosely bound mois-

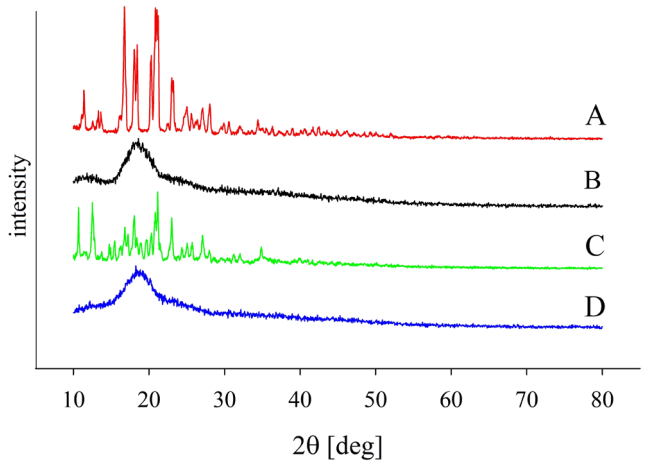

Fig. 5. XRD patterns: (A), levodropropizine; (B), HP-β-CD; (C), physical mixture; (D), levodropropizine/HP-β-CD formulation

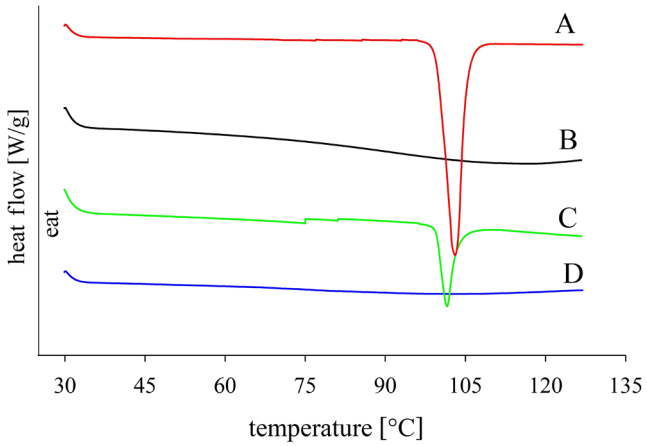

Fig. 6. DSC thermograms: (A), levodropropizine; (B), HP-β-CD; (C), physical mixture; (D), levodropropizine/HP-β-CD formulation

ture from HP-β-CD (Fig. 6B).[30,39] A sharp endotherm, at the melting point of levodropropizine, was also recorded for the physical mixture (Fig. 6C). Neither a sharp endotherm nor a downward curve behavior appeared in the thermogram of the levodropropizine/HP-β-CD formulation (Fig. 6D). This confirmed that the crystalline levodropropizine had changed into its amorphous form and that the formulation had been completely dry after spray-drying.

The scanning electron micrographs are shown in Fig. 7. Levodropropizine exhibited crystalline structures with irregular shapes and surfaces (Fig. 7A). The HP-β-CD particles were of irregular shapes, rough surfaces and large in size (Fig. 7B). The spray-dried particles of the levodropropizine/HP-β-CD formulation were discrete (Fig. 7C). Each particle, about ≤2 μm in size, furnished an elliptical shape and wrinkled surface (Fig. 7C inset).

The FTIR spectra are displayed in Fig. 8. Levodropropizine gave its distinctive peaks in the fingerprint region at 654 cm^{-1}, 740 cm^{-1}, 802 cm^{-1}, 870 cm^{-1}, 920 cm^{-1}, 996 cm^{-1}, 1049 cm^{-1}, 1097 cm^{-1}, 1142 cm^{-1} and

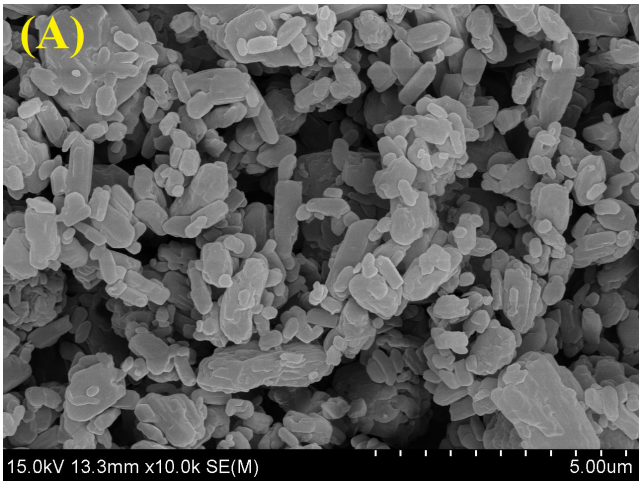

Fig. 7A. SEM image of levodropropizine (×10,000)

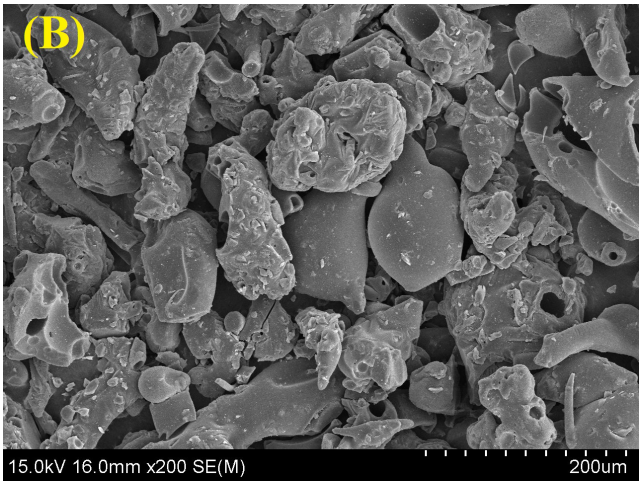

Fig. 7B. SEM image of HP-β-CD (×200)

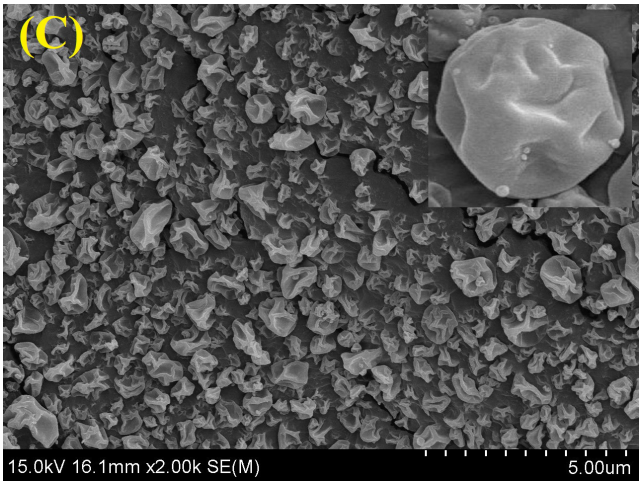

Fig. 7C. SEM image of levodropropizine/HP-β-CD formulation (×2,000)

1387 cm^{-1} (Fig. 8A). These characteristic peaks appeared in both the spectra of the physical mixture (Fig. 8C) and of the spray-dried levodropropizine/HP-β-CD formulation (Fig. 8D). Compared to the physical mixture,

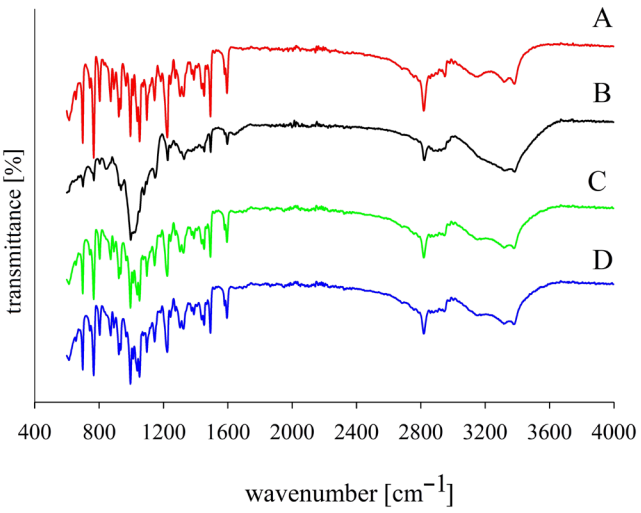

Fig. 8. FTIR spectra: (A), levodropropizine; (B), HP-β-CD; (C), physical mixture; (D), levodropropizine/HP-β-CD formulation

there was no shifting, nor the disappearance of existing peaks, nor the emergence of new peaks in the spectrum of the levodropropizine/HP-β-CD formulation. Moreover, the spectrum of the physical mixture overlaid that of the levodropropizine/HP-β-CD formulation (Fig. 8CD). This suggested that no covalent bonding had existed between levodropropizine and HP-β-CD during the inclusion complex formation process.[40]

From the above discussion, it could be established that the levodropropizine/HP-β-CD formulation had indeed improved the aqueous solubility and dissolution rate of levodropropizine, owing to the following factors: (i) homogeneity and closeness between the levodropropizine and HP-β-CD molecules, which had facilitated wetting,[36] (ii) alteration of the crystalline levodropropizine into its amorphous form,[41] and (iii) reduction in the particle-size of the active ingredient, offering an increased surface area available for dissolution.[42]

Conclusions

The levodropropizine/HP-β-CD formulation (1:1 molar ratio) had increased the aqueous solubility (351.12 ±13.26 vs 92.76 ±5.00 mg/mL) and dissolution rate (97.83 ±3.36 vs 3.12 ±1.76% in 10 min) of levodropropizine, compared to the drug alone. This improvement can be ascribed to (i) the presence of HP-β-CD, which expedited wetting, (ii) alteration of the crystalline levodropropizine into its amorphous state, and (iii) a decrease in the particle-size of the active ingredient, resulting in its increased surface area. Accordingly, this formulation might be a prospective delivery system for administering levodropropizine through the oral route, with improved solubility and dissolution.

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