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Effect of Superdisintegrants on Theophylline Pellets Prepared by Extrusion–Spheronization Technique

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ABSTRACT
The present study was carried out to investigate the effect of superdisintegrants on the drug release characteristics of Theophylline pellets prepared by the extrusion–spheronization technique. Theophylline was selected as a model drug, while microcrystalline cellulose (MCC) was used as the primary pelletizing aid. Three superdisintegrants, namely sodium starch glycolate (Primojel), croscarmellose sodium (Ac-Di-Sol), and crospovidone (Polyplasdone XL10), were incorporated to evaluate their influence on pellet characteristics and dissolution behaviour. Pellets were prepared using suitable granulating liquids and binders, and their physical properties, including particle size distribution, shape, flow properties, friability, drug content, disintegration, and in-vitro dissolution, were evaluated. The prepared pellets exhibited good sphericity with circularity values ranging from 0.968 to 1.00, excellent flow characteristics, low friability (<0.1%), and drug content within acceptable limits (89.06–98.89%). All formulations disintegrated within 30 minutes, with croscarmellose sodium-containing pellets showing faster disintegration than sodium starch glycolate formulations. The incorporation of superdisintegrants significantly enhanced drug release compared to pellets containing only MCC. The dissolution behaviour was found to depend on the type and concentration of superdisintegrant used. Sodium starch glycolate exhibited the highest swelling capacity, croscarmellose sodium provided rapid water penetration and disintegration, while cros povidone showed comparatively lower swelling behaviour.
Keywords: Theophylline, Pellets, Extrusion-spheronization, superdisintegrants, Drug release, Dissolution studies, croscarmellose sodium, sodium starch glycolate

Introduction

Theophylline is an oral bronchodilator with modest anti-inflammatory effects. Given its narrow therapeutic window and frequent adverse events (e.g., gastrointestinal symptoms, loose stools, seizures, cardiac arrhythmias, nausea and vomiting), its use is generally reserved for patients over 12 years of age who are intolerant to or continue to be symptomatic despite other add-on therapies. Extrusion–spheronization is the most widely used pelletization technique in the pharmaceutical industry as it is a robust and reproducible pellet production process. The vital excipient oftenly associated with extrusion–spheronization is microcrystalline cellulose (MCC). It functions as a molecular sponge to absorb water and aid in the binding and lubrication of moistened powder mass during extrusion. There are several techniques to produce pellets e.g. layering in fluid bed equipment or direct pelletisation in high shear mixers and rotary processors. The pelletisation by extrusion-spheronisation is an established technique to produce pellets of a high density and narrow size distribution. This technique includes two steps using specific apparatus. The first step is the extrusion: a paste is pressed through dies of defined diameters resulting in cylindrical extrudates. In the second step these extrudates are transferred to a spheroniser where the beads are formed. Special rheological properties of the paste are required for a successful spheronisation process. These properties like a suitable relation between brittleness and plasticity in spheronising are achieved by the formulation. However, formulations based on MCC as pelletisation aid have some shortcomings. The first disadvantage is the lack of disintegration which results in a prolonged matrix type drug release. For low soluble drugs the time for complete release might be slower than the gastrointestinal passage time results in decreased bioavailability.

Methodology

Materials:

Theophylline was used as the model drug. Microcrystalline cellulose was used as the pelletization aid. Sodium starch glycolate, croscarmellose sodium and crospovidone served as superdisintegrants.

Preparation of pellets

Pellets were prepared by the Extrusion-spherinization technique. The drug and excipients were blended and wetted using a suitable granulating liquid. The wet mass was extruded and subsequently spheronized to obtain spherical pellets.

Results and Discussion

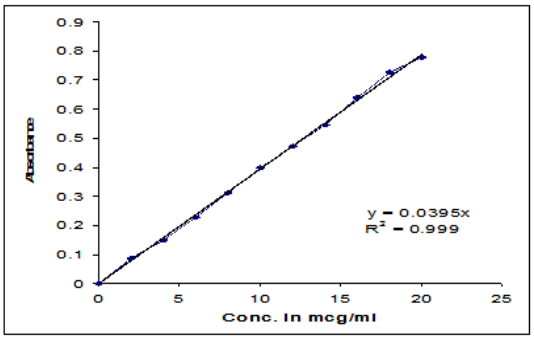

Fig.1: Standard curve of Theophylline in Methanol by UV

Table 1: Data for standard curve of Theophylline in Methanol by UV

Sl. No.	Conc. (mcg/ml)	Absorbance at 278 nm
1	0	0.000
2	2	0.086
3	4	0.149
4	6	0.229
5	8	0.312
6	10	0.400
7	12	0.473
8	14	0.546
9	16	0.640
10	18	0.726
11	20	0.780

Table 2: Solubility of pure Theophylline in various solvents.

Medium	Solubility (mg/ml)
Water	0.026
Methanol	12.5
Chloroform	73.2
Alcohol 90%	43
Propylene glycol	3.1
Isopropyl alcohol	54
pH 1.2 buffer	0.77
pH 7.4 buffer	1.62
Polyethylene glycol 400	0.20
PEG400 : Water (1:4)	0.08
PEG 400 : Water (1:1)	0.09
PEG 400 : Water (4:1)	0.18

Table 3: Absorption maxima, Beer's range and slope of calibration curve of Theophylline in Methanol.

λ_{max} (nm)	Beer's Range	Slope	R^2
230	0-20 µg/ml	0.0395	0.999

Drug Release kinetics

Drug release depended strongly on the type and concentration of superdisintegrants.

Formulation B

The control formulation without superdisintegrant released only 35.11% drug after 9 hours.

Formulation C (5% CCS)

Formulation C exhibited the highest drug release among all 5% formulations, releasing 82.98% after 9 hours.

Formulation D (5% CP)

Drug release reached 62.10% after 9 hours.

Formulation E (5% SSG): Drug release reached 42.75%.

Formulations F, G, and H

Combination formulations produced variable release profiles. Formulation F released 67.07%, formulation G released 60.85%, and formulation H released 38.68%.

Formulation I

The combination of all three superdisintegrants produced 73.73% release after 9 hours.

Formulations J, K, and L

Increasing superdisintegrant concentration from 5% to 10% did not proportionally increase drug release.

- J (10% CCS): 77.26%
- K (10% CP): 42.14%
- L (10% SSG): 38.08%

The results suggest that 5% croscarmellose sodium is the optimum concentration for maximizing drug release.

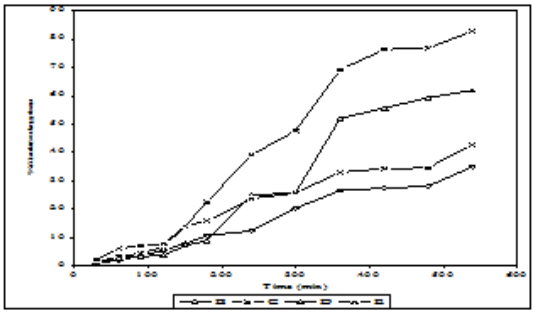

Fig.2: In vitro release of Theophylline from pellets of formulations B, C, D, E.

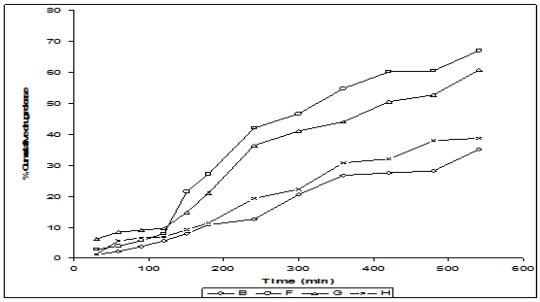

Fig.3: In vitro release of Theophylline from pellets of formulations B, F, G, H.

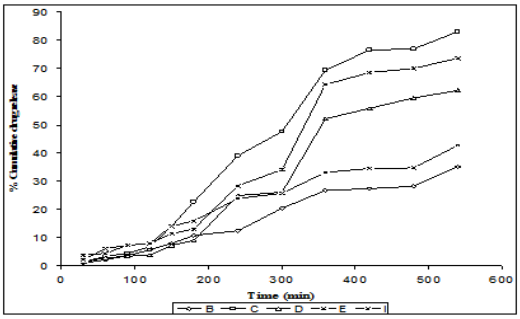

Fig.4: In vitro release of Theophylline from pellets of formulations B,C,D,E, I.

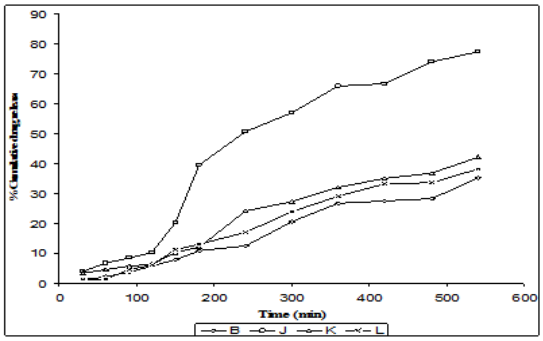

Fig.5: In vitro release of Theophylline from pellets of formulations B, J, K and L.

Data treatment

All the formulations were subjected to mathematical methods to understand the mechanism of drug release. First order, Zero order kinetics, Higuchi and Korsmeyer's-Peppas model given in Table 44. Formulations B, C, D, H, I, PY and D' follows zero order kinetics. Formulations E, F, G, J, K, L and C' follows first order. Formulation B which retained pellets size and shape after 9 hour of dissolution follows zero order kinetics or usually diffusion as a release mechanism which is without any of the superdisintegrants.

Table 4: Composition of Pellets

Quantity of Theophylline (%)	Quantity of MCC (%)	Quantity of Croscarmellose Sodium (%)	Quantity of Crospovidone (%)	Quantity of Sodium Starch Glycolate (%)	Binder Used	Code
-	100	-	-	-	3%NaCMC	A
40	60	-	-	-	3%NaCMC	B
40	55	5	-	-	3%NaCMC	C
40	55	-	5	-	3%NaCMC	D
40	55	-	-	5	3%NaCMC	E
40	50	5	5	-	3%NaCMC	F
40	50	5	-	5	3%NaCMC	G
40	50	-	5	5	3%NaCMC	H
40	51	3	3	3	3%NaCMC	I
40	50	10	-	-	3%NaCMC	J
40	50	-	10	-	3%NaCMC	K
40	50	-	-	10	3%NaCMC	L
40	60	-	-	-	2%PVP	PY
40	55	5	-	-	5%PVP	C'
40	55	-	5	-	5%PVP	D'

Table 5: Image analysis data of pellets

Code	d_{max} (µm)	d_{min} (µm)	Aspect ratio	Area in (μm^2)	Circularity
A	1052.10	1002.80	**1.0491**	1063116.07	**1.00012**
B	1369.66	1304.62	**1.0498**	1253175.12	**1.00012**
C	1291.67	1259.70	**1.0253**	1286370.50	**1.00009**
D	1266.69	1193.37	**1.0614**	1307148.70	**0.99043**
E	1333.93	1291.69	**1.0327**	1642188.80	**1.00012**
F	1292.84	1216.67	**1.0626**	1253175.13	**1.00012**
G	1243.12	1158.36	**1.0731**	1253175.12	**1.00012**
H	1528.15	1500.02	**1.0187**	1816467.72	**0.96812**
I	1157.61	1134.11	**1.0207**	1032958.22	**1.00013**
J	1325.00	1267.98	**1.0449**	1494654.50	**1.00013**
K	1309.50	1283.33	**1.0120**	1220413.70	**1.00012**
L	1751.30	1707.24	**1.0258**	2437790.21	**1.00013**
PY	1463.18	1398.89	**1.0459**	1423490.62	**1.00013**
C'	1050.03	0987.22	**1.0636**	0807317.30	**1.00013**
D'	1234.12	1216.62	**1.0143**	1063116.00	**1.00012**

Table 6: Hausner ratio and Compressibility index of pellets

Code	Bulk density (ρ_p)	Tap density (ρ_t)	Hausner ratio	Compressibility (%)
A	0.714	0.769	1.0770	7.1502
B	0.689	0.740	1.0741	6.8918
C	0.666	0.689	1.0345	3.3422
D	0.645	0.666	1.0333	3.2282
E	0.666	0.712	1.0714	6.6647
F	0.625	0.666	1.0662	6.1561
G	0.666	0.714	1.0714	6.6647
H	0.666	0.714	1.0714	6.6647
I	0.666	0.714	1.0714	6.6647
J	0.625	0.666	1.0662	6.1561
K	0.645	0.666	1.0333	3.1531
L	0.625	0.666	1.0662	6.1561
PY	0.714	0.769	1.0770	7.1541
C'	0.625	0.666	1.0662	6.1561
D'	0.645	0.689	1.0689	6.4530

Table 7: Dissolution profile and pellets morphology

Code	Cumulative % release after 120 min in pH1.2 buffer	Pellet morphology	Cumulative % release after 540 min in pH7.4 buffer	Pellet morphology
A	0.0	Retained pellets size and shape	0.0	Retained pellets size and shape
B	5.66	Retained pellets size and shape	35.11	Retained pellets size and shape
C	6.80	Slight cracks on pellets	82.98	Pellets swells and bursts
D	3.97	Retained pellets size and shape	62.11	Retained pellets size and shape

E	7.96	Retained pellets size and shape	42.75	Retained pellets size and shape
F	7.94	Retained pellets size and shape	67.07	Fully powdered and nicely broken pellets.
G	9.69	Small cracks with slight swelling	60.85	Fully broken with cracks
H	6.82	Retained pellets shape with a slight increase in pellet size	38.68	Retained pellets shape with a slight increase in pellet size
I	7.97	Slight swelling in pellets	73.73	Pellets swells and bursts
J	10.23	Retained pellets size and shape	77.26	Fully powdered and nicely broken pellets.
K	6.26	Retained pellets size and shape	42.14	Rounded in shape with increased size after swelling
L	6.22	Retained pellets size and shape	38.08	Rounded in shape with increased size after swelling
PY	2.82	Retained pellets size and shape	49.80	Retained pellets size and shape
C’	5.6	Retained pellets size and shape	81.79	Fully powdered and nicely broken pellets.
D’	5.11	Retained pellets size and shape	57.50	Retained pellets size and shape

Discussion

Among all formulations investigated, formulation C containing 5% croscarmellose sodium and 3% NaCMC demonstrated the most desirable characteristics:

- Excellent spreadility
- Good flow properties
- Low friability
- High drug content
- Rapid disintegration
- Maximum drug release(82.98%)

Therefore formulation C may be considered the optimized formulation for the development of immediate release Theophylline multiparticulate pellets.

Conclusion

The present study successfully demonstrated that the incorporation of superdisintegrants significantly influences the physicochemical properties and drug release behavior of Theophylline pellets prepared by the extrusion–spheronization technique. All formulations exhibited satisfactory pellet characteristics, including excellent sphericity, good flow properties, low friability, and acceptable drug content, confirming the suitability of the extrusion–spheronization process for multiparticulate dosage form development. Among the superdisintegrants evaluated, 5% croscarmellose sodium (Formulation C) produced the most favorable results, exhibiting rapid disintegration and the highest cumulative drug release (82.98%) without compromising pellet integrity. Increasing the concentration of superdisintegrants beyond 5% did not produce a proportional improvement in drug release, indicating that an optimum concentration is critical for achieving the desired performance. Overall, the study establishes that croscarmellose sodium at an optimized concentration is an effective superdisintegrant for enhancing the dissolution of Theophylline pellets, making Formulation C a promising immediate-release multiparticulate system for improving therapeutic efficacy and patient compliance.

Conflict of Interests

The authors declare no conflict of interest

Ethics Approval

Not applicable

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AI Tool Declaration

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

Data Availability

Data will be available on request

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