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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF METOCLOPRAMIDE HYDROCHLORIDE USING NATURAL AND SYNTHETIC SUPERDISINTEGRANTS

Sumit, Munish, Lovekesh Nagpal*

B.D.M. College of Pharmacy, Chhuchhakwas, Jhajjar, Haryana, India.

***Corresponding Author: Lovekesh Nagpal**

B.D.M. College of Pharmacy, Chhuchhakwas, Jhajjar, Haryana, India.

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ABSTRACT

Background: Fast dissolving tablets (FDTs) of metoclopramide hydrochloride, a dopamine antagonist used for nausea, vomiting and gastroparesis, can serve patients who cannot swallow conventional tablets or have no access to water. **Objective:** To develop and evaluate directly compressed FDTs of metoclopramide hydrochloride using two synthetic superdisintegrants (crospovidone and croscarmellose sodium) and one natural superdisintegrant (ispaghula husk). **Methods:** Swelling indices of the disintegrants were determined in water, 0.1 N HCl and phosphate buffer (pH 6.8). Twelve 200 mg tablets (F1–F12), each containing 10 mg of drug and 5, 10, 15 or 20 mg of a superdisintegrant, were compressed with microcrystalline cellulose as diluent. Blends and tablets were evaluated for flow, hardness, friability, weight and content uniformity, disintegration, dispersion and wetting time, and in vitro dissolution against a marketed tablet (Reglan). Drug–excipient compatibility was examined by FTIR. **Results:** Ispaghula husk showed the highest swelling index (86.70 ± 0.95% in water), followed by croscarmellose sodium (76.26 ± 0.65%) and crospovidone (57.23 ± 1.29%). All blends flowed well (angle of repose 25.96–30.49°; Hausner ratio 1.08–1.16). Disintegration time ranged from 9.33 s (F8, croscarmellose sodium) to 93.66 s (F4, crospovidone); the best ispaghula batch (F12) disintegrated in 15.53 s. After 4 min, F8 and F12 released 99.75% and 99.01% of drug, against 27.76% for the marketed tablet. FTIR revealed no drug–excipient interaction. **Conclusion:** Croscarmellose sodium and ispaghula husk, at 20 mg per tablet, gave rapidly disintegrating, mechanically acceptable metoclopramide FDTs, and ispaghula husk is a credible natural alternative to synthetic superdisintegrants.

KEYWORDS: metoclopramide hydrochloride; fast dissolving tablets; superdisintegrants; croscarmellose sodium; crospovidone; ispaghula husk; direct compression.

1. INTRODUCTION

Tablets remain the most widely used oral dosage form, yet difficulty in swallowing limits their usefulness for a large group of patients. Dysphagia in the elderly, hand tremors, immature neuromuscular control in children, fear of choking, uncooperative or psychiatric patients, and nausea that makes swallowing difficult all lead to missed or incomplete dosing.[1–3] Travellers and patients without ready access to water face a similar problem. Poor adherence in these groups reduces therapeutic benefit and has pushed formulators towards patient-friendly dosage forms that suit existing drugs rather than new molecules.

Fast dissolving tablets (FDTs), also called orally disintegrating tablets (ODTs) or orodispersible tablets, are one such answer. They disintegrate or disperse in saliva within seconds, so the patient needs no water and the dose is swallowed as a suspension or solution.[3] The United States Pharmacopeia and the United States Food and Drug Administration use the term ODT for a solid dosage form that disintegrates rapidly, usually within seconds, on the tongue. The European Pharmacopoeia uses the term orodispersible tablet for a tablet that disperses within 3 min in the mouth before being swallowed.[4,5] A well-designed FDT keeps the stability, dose accuracy and low cost of a solid dosage form while

behaving, at the point of administration, like a liquid.

FDTs also offer pharmacological and commercial advantages. Rapid disintegration promotes fast dissolution and a quicker onset of action, and any absorption through the buccal, pharyngeal and oesophageal mucosa bypasses first-pass metabolism, which can raise bioavailability for susceptible drugs.[1,4] For manufacturers, converting an established drug into an ODT is a recognised lifecycle strategy that extends market exclusivity and widens the treatable patient population.[6,7]

1.1 Technologies for FDTs

The central design challenge is to combine rapid water uptake with enough mechanical strength to survive handling and packaging. Several technologies have been developed for this purpose, including freeze-drying, moulding, spray drying, sublimation, phase-transition processes, mass extrusion, nanonisation and oral thin films.[8–13] Freeze-dried and moulded products disintegrate very quickly but are costly and fragile. Moulded tablets, for example, are soft and porous and need protective packaging.[8,10] Spray drying produces porous, readily compressible powders.[9] Sublimation creates pores by removing volatile adjuvants from compressed tablets and has recently been used to speed disintegration of poorly soluble drugs.[11] Oral films and mini-tablets are alternative formats for patients who cannot take a standard tablet.[12,13]

Direct compression remains the most economical and scalable route because it uses conventional tablet presses, commonly available excipients and few processing steps. It also tolerates higher drug loads and avoids the water and heat that can harm sensitive drugs. In direct compression, disintegration depends on the choice and level of disintegrant, the diluent and the compression force. It is therefore the method of choice in many recent FDT studies, often combined with co-processed excipients, quality-by-design tools and factorial designs.[14–16]

1.2 Superdisintegrants

Superdisintegrants are disintegrants that act at low concentrations (typically 1–10% w/w) through one or more mechanisms: swelling, capillary action (wicking), deformation recovery, particle–particle repulsion and, in effervescent systems, gas release.[17,18] Their performance depends on the type and level used, their position in the tablet (intragranular, extragranular or both), the compression force and the properties of the other excipients.[19] Recent reviews stress that a single mechanism rarely explains disintegration and that excipient choice must be matched to the drug and process.[20,21]

Three superdisintegrants were studied here. Croscarmellose sodium (CCS) is a cross-linked sodium carboxymethylcellulose that swells strongly and also wicks water into the tablet. Crospovidone (CP) is a cross-linked polyvinylpyrrolidone that is insoluble and does not form a gel. Its spongy, porous particles draw water into the tablet by capillary action, and it was introduced as a tablet disintegrant in the early 1970s.[22] Ispaghula husk, the seed husk of *Plantago ovata*, is a natural, hydrophilic, mucilaginous polymer with a high swelling capacity. It is widely consumed, is regarded as safe, and is cheap and biodegradable.[23–25] Natural superdisintegrants are attractive because they are renewable and non-toxic, and recent work with zidovudine and enalapril maleate suggests they can rival synthetic agents in orodispersible tablets.[23,24]

1.3 Metoclopramide hydrochloride as a candidate drug

Metoclopramide hydrochloride (4-amino-5-chloro-N-(2-diethylaminoethyl)-2-methoxybenzamide hydrochloride) is a white to off-white crystalline powder with a molecular weight of 354.3 g/mol, a melting point of 182.5–184.0 °C, a pKa of about 9.3 and a log P (octanol/water) of about 2.6. It is freely soluble in water (about 1 part in 0.7 parts) and not noticeably bitter. Pharmacologically, it is a dopamine D2 receptor antagonist with prokinetic action. It raises the threshold of the chemoreceptor trigger zone, increases lower oesophageal sphincter tone and enhances antral contractions, which accelerates gastric emptying.[26,27] It is used for gastro-oesophageal reflux disease, diabetic gastroparesis, and the nausea and vomiting that accompany gastrointestinal dysmotility, chemotherapy and surgery.[26]

After oral administration the drug is absorbed rapidly. Peak plasma concentrations are reached within about 1 h, oral bioavailability is roughly 75%, plasma protein binding is about 40% and the elimination half-life is 4–6 h.[27–29] It is widely distributed, undergoes sulfate and glucuronide conjugation and CYP2D6-mediated metabolism, and is eliminated mainly by the kidney, so exposure rises in renal impairment.[27,30,31] The usual adult oral dose is 10 mg three times a day, with 0.2–0.5 mg/kg for children. Its safety profile, notably acute dystonic reactions and tardive dyskinesia, calls for the lowest effective dose and careful dosing.[26,31] Earlier formulation work on the drug has focused on sustained-release matrix tablets.[32]

Several properties make metoclopramide a logical FDT candidate. The therapeutic dose is only 10 mg, so tablet size can stay small. The drug dissolves quickly and has no bitter taste, so elaborate taste masking is unnecessary. Its lipophilicity favours mucosal permeation. Most importantly, the patients who need it are often nauseated, vomiting, elderly or travelling, so a tablet that dissolves without water addresses a real clinical need.

1.4 Research gap

Directly compressed FDTs have been reported for many drugs, including famotidine[33], teneligliptin[34],

lacidipine[35], phenytoin[36], salbutamol sulphate[37], amlodipine besylate[38], a hydrophobic model drug[39] and acyclovir.[40] Optimisation by experimental design and machine learning is increasingly used to pick disintegrant type and level.[38,41] Co-processed excipients, which combine several functions in one particle, are another active line of work.[42] Most of these studies compare synthetic superdisintegrants with one another. Few place a natural disintegrant such as ispaghula husk next to croscarmellose sodium and crospovidone at the same four levels in a single antiemetic prokinetic tablet. Comparison with a marketed conventional tablet under identical dissolution conditions is also uncommon.

The aims of this work were to characterise metoclopramide hydrochloride and set up a UV calibration plot; compare the swelling indices of crospovidone, croscarmellose sodium and ispaghula husk; prepare twelve FDT formulations (F1–F12) by direct compression, each with one superdisintegrant at four levels; evaluate blend flow, tablet physical properties, disintegration, dispersion and wetting behaviour, and in vitro dissolution; compare the best formulations with a marketed tablet; and check drug-excipient compatibility by FTIR.

2. MATERIALS AND METHODS

2.1 Materials

A procured sample of metoclopramide hydrochloride was used. Crospovidone, croscarmellose sodium and ispaghula husk were the superdisintegrants. Microcrystalline cellulose (MCC) served as diluent and binder because of its good compactability and flow.[43] Magnesium stearate was the lubricant, a widely used food and pharmaceutical additive of low toxicity.[44] Colloidal silicon dioxide (Aerosil) acted as glidant, improving powder flow by coating cohesive particles.[45] Glycine was added as a dissolution enhancer and sodium saccharin as sweetener. The marketed comparator was a conventional metoclopramide hydrochloride 10 mg tablet (Reglan). Hydrochloric acid and phosphate buffer were used as dissolution and test media.

Equipment comprised a UV–visible spectrophotometer, a single-station hand-operated tablet machine fitted with 9 mm biconvex punches, a Monsanto hardness tester, a Roche friabilator, a tablet disintegration apparatus, a USP type II (paddle) dissolution apparatus and an FTIR spectrophotometer.

2.2 Preformulation studies

Drug characterisation. The drug sample was examined for appearance, odour, melting point and solubility in water, ethanol (95%), chloroform and dichloromethane.

Calibration plot. Metoclopramide hydrochloride (100 mg) was dissolved in 0.1 N HCl to give a 1000 µg/mL stock solution. One millilitre of stock was diluted to 100 mL with 0.1 N HCl (10 µg/mL). Aliquots of 2–10 mL of this solution were made up to 10 mL with 0.1 N HCl, and absorbance was read at 309.6 nm against a blank. The calibration line was fitted with PCP Disso v3 software and used to calculate unknown concentrations.[46]

Swelling index. One gram of each superdisintegrant was placed in a 25 mL stoppered measuring cylinder with 25 mL of the test medium (distilled water, 0.1 N HCl or phosphate buffer pH 6.8). The cylinder was shaken every 10 min for 1 h and then left for 3 h at room temperature. The volume occupied by the swollen material was recorded, and the determination was done in triplicate.

2.3 Preparation of tablets

Twelve formulations (F1–F12) were prepared by direct compression (Table 1). Each 200 mg tablet contained 10 mg of drug, one superdisintegrant at 5, 10, 15 or 20 mg (2.5–10% w/w), and MCC to make up the weight. Drug, superdisintegrant and MCC were mixed thoroughly, and glycine, sodium saccharin, Aerosil and magnesium stearate were added in turn. The blends were compressed with 9 mm biconvex punches, and at least 50 tablets were made per batch.

Table 1: Composition of formulations (mg per tablet).

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Metoclopramid e HCl	10	10	10	10	10	10	10	10	10	10	10	10
Crospovidone	5	10	15	20	–	–	–	–	–	–	–	–
Croscarmellose sodium	–	–	–	–	5	10	15	20	–	–	–	–
Ispaghula husk	–	–	–	–	–	–	–	–	5	10	15	20
Microcrystallin e cellulose	177	172	167	162	177	172	167	162	177	172	167	162
Glycine	2	2	2	2	2	2	2	2	2	2	2	2
Sodium	1	1	1	1	1	1	1	1	1	1	1	1

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
saccharin												
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4	4
Aerosil	1	1	1	1	1	1	1	1	1	1	1	1
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

2.4 Evaluation of powder blends

Flow behaviour was assessed by the fixed-funnel method for angle of repose (θ), where h is the fixed funnel height (1 cm) and r the radius of the powder cone.

$$\tan\theta = \frac{h}{r}$$

Loose bulk density (LBD) and tapped bulk density (TBD) were measured in a 100 mL cylinder tapped from a height of 2.5 cm at 2 s intervals until the volume was constant. Carr's compressibility index, Hausner ratio and percentage porosity were then calculated.[47,48]

$$\text{Carr's index}\ (\%) = \frac{TBD - LBD}{TBD} \times 100, \qquad \text{Hausner ratio} = \frac{TBD}{LBD}$$

$$\%\varepsilon = \left(1 - \frac{V_t}{V_b}\right) \times 100$$

Here V_b is the bulk volume and V_t the tapped volume. Specific bulk volume was the reciprocal of LBD, and void volume was V_b − V_t.

2.5 Evaluation of tablets

Hardness was measured on 10 tablets per batch with a Monsanto tester. Friability was measured on six tablets in a Roche friabilator for 100 revolutions at 25 rpm. Weight variation used 20 tablets and thickness used six tablets (vernier callipers). Disintegration time was measured on six tablets in phosphate buffer pH 6.8 at 37 ± 0.5 °C. In vitro dispersion time was measured on three tablets dropped in 50 mL of phosphate buffer pH 6.8.

For wetting time, a folded tissue paper was placed in a Petri dish (6.5 cm) with 6 mL of Sorensen's buffer pH 6.8, and the time for complete wetting of a tablet placed on it was recorded (n = 3). The water absorption ratio R was obtained from the weights of the tablet before (W_b) and after (W_a) wetting.

$$R = \frac{W_a - W_b}{W_b} \times 100$$

For content uniformity, 20 tablets were powdered, a portion equivalent to 10 mg of drug was extracted and processed according to the Indian Pharmacopoeia, and the absorbance of the chloroform extract was read at 309.6 nm.[46]

2.6 In vitro dissolution

Dissolution was carried out in a USP type II (paddle) apparatus with 900 mL of 0.1 M HCl at 50 rpm, as described in the pharmacopoeial method for tablets.[46] Samples (10 mL) were withdrawn at 1, 2, 3 and 4 min, filtered, and read at 309.6 nm. The marketed tablet was tested under identical conditions with additional sampling to 20 min. Dissolution testing of rapidly disintegrating dosage forms is discussed in the FIP/AAPS workshop report.[49] All dissolution values are means ± SD (n = 3).

2.7 Drug–excipient compatibility

FTIR spectra (KBr pellets) were recorded for the pure drug, each superdisintegrant, MCC, and the physical mixtures in the selected formulations F3, F8 and F12.

3. RESULTS AND DISCUSSION

3.1 Drug characterisation and calibration

The drug sample was a white or almost white, odourless, crystalline powder that melted at 181–186 °C, close to the reported 182.5–184.0 °C. It was very soluble in water, freely soluble in ethanol (95%) and chloroform, and sparingly soluble in dichloromethane. These findings agree with the reference profile and support identity and purity. The drug's high water solubility, absence of bitterness and low dose suit an FDT, because no taste masking or solubility enhancement is needed and the tablet can stay small.[26,27] Standard solutions of 2–10 µg/mL in 0.1 N HCl gave a linear absorbance–concentration relationship at 309.6 nm, which was used to calculate drug released in dissolution testing and drug content.

3.2 Swelling index of the superdisintegrants

Ispaghula husk had the highest swelling index in all three media, followed by croscarmellose sodium and then crospovidone (Table 2). Swelling fell slightly from water to 0.1 N HCl to Ph 6.8 buffer for every agent. The fall was largest for crospovidone (57.23% to 48.23%) and smallest for ispaghula husk (86.70% to 81.94%).

Table 2: Swelling index (% v/v, mean ± SD, n = 3).

Superdisintegrant	Water	0.1 N HCl	Phosphate buffer pH 6.8
Ispaghula husk	86.70 ± 0.95	83.22 ± 0.57	81.94 ± 1.04
Croscarmellose sodium	76.26 ± 0.65	73.18 ± 1.43	70.53 ± 1.00
Crospovidone	57.23 ± 1.29	54.77 ± 2.07	48.23 ± 1.79

The ranking is consistent with the known behaviour of the three materials. Ispaghula husk is a mucilage-forming polysaccharide that hydrates and expands, croscarmellose sodium swells and wicks, and crospovidone is insoluble and acts mainly through capillary uptake and shape recovery rather than bulk swelling.[17,18,22] A low swelling index therefore does not rule out crospovidone as a disintegrant, but it shows that swelling alone cannot predict tablet disintegration. The swelling data justified including the natural agent alongside the two synthetic ones.[23,24]

3.3 Flow properties of the blends

All twelve blends had acceptable flow (Table 3). Angles of repose ranged from 25.96° to 30.49°, and only F3, F6 and F12 (30.02–30.49°) were marginally above 30°.

Bulk density was 0.428–0.441 g/mL and tapped density 0.469–0.499 g/mL. Carr's index was 8.10–13.82%, below the 15% limit usually taken to indicate good compressibility, and Hausner ratios were 1.08–1.16, well under the 1.25 threshold for free-flowing powders.[47,48] Porosity (8.0–13.7%) and void volume (2.2–3.8 mL) show that the powder beds contain enough pore space for saliva to penetrate the compacts, which favours fast disintegration. Good flow, aided by Aerosil and magnesium stearate, gave uniform die filling and the tight weight control reported below.

Table 3: Micromeritic properties of the blends.

Batch	Angle of repose (°)	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner ratio	Porosity (%)
F1	27.74	0.437	0.491	10.79	1.12	11.2
F2	29.55	0.428	0.490	12.24	1.14	12.6
F3	30.49	0.428	0.483	12.85	1.12	11.5
F4	27.11	0.433	0.490	13.06	1.13	13.1
F5	28.89	0.433	0.475	8.84	1.09	8.9
F6	30.02	0.429	0.494	13.15	1.15	13.1
F7	28.28	0.430	0.499	13.82	1.16	13.7
F8	25.96	0.441	0.498	11.44	1.12	11.4
F9	27.69	0.428	0.489	12.47	1.14	12.6
F10	27.15	0.433	0.478	9.41	1.10	9.5
F11	28.81	0.428	0.477	10.27	1.11	10.3
F12	30.02	0.431	0.469	8.10	1.08	8.0

3.4 Physical properties of the tablets

All batches met the usual quality limits (Table 4). Mean weights were 197.0–201.0 mg against a 200 mg target, thicknesses 4.015–4.228 mm and hardness 4.13–4.53 kg/cm². These hardness values are modest, as expected for tablets compressed at low force to keep them porous, yet they are adequate for careful handling. Friability was 0.20–0.73%, below the 1% limit. Drug content was 95.38–99.83%, within the 90–110% window commonly applied to tablet assay.[46]

Two trends stand out. First, the ispaghula batches, particularly F11 and F12, were thicker (4.195 and 4.228 mm) and more friable (0.68% and 0.73%) than the others. A likely explanation is the bulky, fibrous and moisture-attracting nature of the husk, which gives a more elastic compact, but this was not examined directly. Second, the content of F1 (95.38%) was the lowest, with no obvious cause, which suggests minor blending variation at the lowest superdisintegrant level.

Table 4: Physical properties of the tablets (mean ± SD).

Batch	Hardness (kg/cm²)	Friability (%)	Weight (mg)	Thickness (mm)	Drug content (%)
F1	4.25 ± 0.226	0.20	197.00 ± 1.87	4.015 ± 0.021	95.38
F2	4.23 ± 0.207	0.23	198.00 ± 1.58	4.018 ± 0.019	96.83
F3	4.26 ± 0.455	0.22	199.20 ± 2.38	4.025 ± 0.026	97.36
F4	4.53 ± 0.372	0.31	197.80 ± 1.64	4.033 ± 0.025	97.81
F5	4.21 ± 0.293	0.28	197.60 ± 3.20	4.088 ± 0.155	97.78
F6	4.16 ± 0.314	0.27	199.00 ± 2.34	4.042 ± 0.025	97.83
F7	4.13 ± 0.242	0.28	198.20 ± 2.16	4.045 ± 0.041	99.36
F8	4.25 ± 0.274	0.29	197.20 ± 1.92	4.063 ± 0.027	98.81
F9	4.40 ± 0.303	0.30	197.60 ± 2.07	4.082 ± 0.015	99.83
F10	4.30 ± 0.405	0.29	200.80 ± 2.28	4.153 ± 0.132	98.83
F11	4.35 ± 0.409	0.68	199.40 ± 2.70	4.195 ± 0.131	97.36
F12	4.33 ± 0.207	0.73	201.00 ± 3.53	4.228 ± 0.156	99.61

3.5 Disintegration, dispersion and wetting

Disintegration time (DT) separated the three superdisintegrants clearly (Table 5). CCS tablets disintegrated fastest (9.33–12.50 s), ispaghula husk tablets were intermediate (15.53–26.25 s) and crospovidone tablets were slowest (52.00–93.66 s). In vitro dispersion times followed the same order. Wetting time ranged from 4.80 to 15.0 s and water absorption ratio from 79.97 to 101.02% across the series, and the wetting results mirrored the disintegration trends.

For CCS and ispaghula husk, raising the level from 5 to 20 mg shortened DT, dispersion time and wetting time. For CCS the gain was large between 5 and 10 mg (12.50 to 10.66 s) and small thereafter (9.58 and 9.33 s at 15 and 20 mg). This suggests a plateau above about 5% w/w, where extra disintegrant adds little. Ispaghula husk showed the same shape, with DT falling from 26.25 s

(F9) to 19.00 s (F10) and then flattening at 16.00 s (F11) and 15.53 s (F12). Similar dose–response curves are typical of superdisintegrants, whose effect saturates once a continuous swelling or wicking network has formed.[17,19]

Crospovidone behaved differently. DT fell modestly from 63.33 s (5 mg) to 52.00 s (15 mg) but jumped to 93.66 s at 20 mg (F4), and dispersion and wetting times rose in parallel. At this level the extra insoluble polymer may have made the compact more cohesive or blocked pores, but the mechanism was not tested, and the practical message is that crospovidone should not be used at 10% w/w in this formulation. Even the best crospovidone tablet (F3, 52 s) disintegrated more slowly than every CCS and ispaghula batch. Disintegration times under about 30 s for the best CCS and ispaghula batches fall in the range expected of a true orally disintegrating tablet and are comparable with directly compressed FDTs of other drugs prepared with these disintegrants.[33–35,40]

Table 5: Disintegration and dispersion times (s, mean ± SD).

Superdisintegrant	Batch	Level (mg)	Disintegration time (n = 6)	In vitro dispersion time (n = 3)
Crospovidone	F1	5	63.33 ± 4.71	69.00 ± 4.58
Crospovidone	F2	10	55.50 ± 5.89	66.66 ± 2.08
Crospovidone	F3	15	52.00 ± 3.40	59.33 ± 2.51
Crospovidone	F4	20	93.66 ± 3.83	97.33 ± 2.08
Croscarmellose sodium	F5	5	12.50 ± 1.41	17.33 ± 2.08
Croscarmellose sodium	F6	10	10.66 ± 1.25	15.33 ± 1.52
Croscarmellose sodium	F7	15	9.58 ± 0.73	13.66 ± 1.52
Croscarmellose sodium	F8	20	9.33 ± 1.08	10.66 ± 1.52
Ispaghula husk	F9	5	26.25 ± 1.56	30.33 ± 2.08
Ispaghula husk	F10	10	19.00 ± 1.58	21.66 ± 2.08
Ispaghula husk	F11	15	16.00 ± 0.70	18.66 ± 1.52
Ispaghula husk	F12	20	15.53 ± 0.95	17.33 ± 1.52

The natural superdisintegrant was therefore clearly better than crospovidone and, although slower than CCS, reached a DT of 15.53 s. This supports the view that natural superdisintegrants can substitute for synthetic ones in directly compressed orodispersible tablets.[23,24] Ispaghula husk is cheaper, renewable and edible, and its safety is well documented.[25] The cost is a rise in friability and thickness, as noted above.

3.6 In vitro dissolution

Drug release was very fast for every formulation (Table 6). Between 91.13% (F1) and 99.75% (F8) of the drug was released within 4 min, and release rose with superdisintegrant level in the CCS and ispaghula series. At 4 min, F8 released 99.75 ± 0.08% and F12 released 99.01 ± 0.18%, compared with 94.37% for the best crospovidone batch (F3). CCS and ispaghula husk therefore gave higher and more complete release than crospovidone, in line with their shorter disintegration times. The rapid release of F8 and F12 at 2 min (65.11% and 63.66%) shows that the tablet fragments into fine particles almost at once, exposing a large surface area of a drug that is already highly soluble.

F4 is again the outlier. Only 16.64% of the drug was released at 1 min and 34.19% at 2 min, against 34.00% and 56.09% for F3, although F4 caught up by 3 min (82.32%). This initial lag matches its long disintegration time and confirms that 20 mg of crospovidone is detrimental here.

Table 6: Cumulative drug release (%, mean ± SD, n = 3) in 0.1 M HCl.

Batch	1 min	2 min	3 min	4 min
F1	32.85 ± 0.34	54.63 ± 0.14	80.98 ± 0.21	91.13 ± 0.11
F2	33.42 ± 0.24	55.21 ± 0.40	81.86 ± 0.27	92.31 ± 0.18
F3	34.00 ± 0.33	56.09 ± 0.41	83.33 ± 0.29	94.37 ± 0.21
F4	16.64 ± 0.14	34.19 ± 0.34	82.32 ± 0.29	93.93 ± 0.31
F5	35.16 ± 0.38	54.94 ± 0.26	81.88 ± 0.31	95.22 ± 0.21
F6	36.61 ± 0.12	55.82 ± 0.28	82.77 ± 0.11	97.28 ± 0.14
F7	36.90 ± 0.07	57.56 ± 0.19	84.82 ± 0.31	98.49 ± 0.09
F8	38.63 ± 0.11	65.11 ± 0.14	87.24 ± 0.19	99.75 ± 0.08
F9	34.58 ± 0.19	54.07 ± 0.21	81.29 ± 0.12	94.04 ± 0.09
F10	36.32 ± 0.14	54.95 ± 0.17	81.89 ± 0.25	96.68 ± 0.11
F11	36.90 ± 0.31	56.41 ± 0.16	84.23 ± 0.19	97.60 ± 0.07
F12	38.34 ± 0.28	63.66 ± 0.41	86.06 ± 0.28	99.01 ± 0.18
Reglan (marketed)	5.38 ± 0.19	11.43 ± 0.09	15.80 ± 0.21	27.76 ± 0.16

3.7 Comparison with the marketed tablet

The marketed tablet released only 27.76 ± 0.16% of its drug in 4 min, compared with 99.75% for F8 and 99.01% for F12, a release about 3.6 times higher at that time. The marketed tablet reached 50.93% at 6 min, 63.65% at 8 min, 75.34% at 12 min, 89.75% at 16 min and 99.59% at 20 min. The FDTs therefore reached in 4 min the extent of release that the conventional tablet needed about 20 min to achieve. For a patient who is nauseated, this faster availability could mean a more rapid onset of antiemetic action, although only in vivo studies can show whether it does.

3.8 FTIR compatibility

The spectrum of pure metoclopramide hydrochloride showed its characteristic bands at about 3396 and 3310 cm^{-1} (N–H/O–H stretching), 2942 cm^{-1} (aliphatic C–H), 1597 cm^{-1} (amide C=O), 1540 cm^{-1} (N–H bending) and 1269 cm^{-1} (C–O–C stretching). These bands were still present, without new peaks or marked shifts, in the spectra of the physical mixtures F3, F8 and F12. The drug is therefore compatible with crospovidone, croscarmellose sodium, ispaghula husk and MCC under the conditions used. Because FTIR only detects gross interactions, long-term stability studies under accelerated conditions remain necessary.

3.9 Selection of formulations and limitations

On the combined evidence, F8 (20 mg CCS) is the best overall formulation, with the shortest disintegration (9.33 s), dispersion (10.66 s) and highest release (99.75% at 4 min), and a friability of only 0.29%. F12 (20 mg ispaghula husk) is the best natural-polymer formulation, with a 15.53 s disintegration and 99.01% release, but a higher friability (0.73%).

The study has limits. Dissolution was run in 0.1 M HCl, whereas disintegration and wetting were measured in pH 6.8 buffer, which better mimics saliva. Taste, mouthfeel and residue were not rated by volunteers, and no stability or in vivo work was done. The batches were made on a single-station press, and no statistical test was applied to compare formulations. Finally, the very small volume of saliva in the mouth is not matched by the 50 mL used in the dispersion test, so true in-mouth disintegration may be slower than the in vitro values.

4. CONCLUSION AND FUTURE PERSPECTIVES

Fast dissolving tablets of metoclopramide hydrochloride can be made by simple direct compression using croscarmellose sodium, crospovidone or ispaghula husk with microcrystalline cellulose as diluent and binder. All twelve formulations had good flow, uniform weight, adequate hardness, friability below 1% and drug content of 95.38–99.83%, and FTIR showed no drug–excipient incompatibility.

The superdisintegrants ranked croscarmellose sodium > ispaghula husk > crospovidone for disintegration, dispersion, wetting and early drug release. F8 (20 mg croscarmellose sodium) disintegrated in 9.33 s and released 99.75% of its drug in 4 min. F12 (20 mg ispaghula husk) disintegrated in 15.53 s and released 99.01% in 4 min. The marketed tablet released only 27.76% in the same time and needed about 20 min for complete release. Crospovidone at 20 mg (F4) was markedly worse than at 15 mg, so its level must be controlled. The natural superdisintegrant ispaghula husk outperformed crospovidone and approached croscarmellose sodium, which supports its use as a low-cost, renewable alternative.

Future work should address the limits listed above.

1. accelerated and long-term stability studies, with moisture-protective packaging, because FDTs are sensitive to humidity;
2. taste, mouthfeel and in-mouth disintegration tests with human volunteers or a validated in vitro model;
3. optimisation of superdisintegrant level and compression force by factorial or quality-by-design approaches, to lower the friability of the ispaghula formulation;
4. dissolution testing in simulated saliva and at several pH values; and
5. in vivo pharmacokinetic studies to confirm faster onset and to test whether any pre-gastric absorption occurs.

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