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Research Article

Melt-in-Mouth Pellets of Fexofenadine Hydrochloride Using Crospovidone as an Extrusion–Spheronisation Aid

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Abstract. Microcrystalline cellulose (MCC) is well established as an extrusion spheronisation aid for the preparation of pellets. Crospovidone (Polyplasdone® XL-10) is compared with microcrystalline cellulose for the preparation of melt-in-mouth pellets. Taste-masked fexofenadine hydrochloride was incorporated in the melt-in-mouth formulation. Crospovidone was found to be well suited as extrusion–spheronisation aid for the preparation of melt-in-mouth pellets. The great advantage of crospovidone is, however, the disintegrating properties of the pellets after only a short time of exposure to liquid. Crospovidone was successfully employed as an extrusion–spheronisation aid to produce melt-in-mouth pellets obviating the need of a traditional extrusion–spheronisation aid, MCC. Dual properties of Crospovidone were explored viz. as an extrusion–spheronisation aid and a disintegrant.

KEY WORDS: Crospovidone (Polyplasdone® XL-10); fexofenadine hydrochloride; ion exchange resin; melt-in-mouth pellets; microcrystalline cellulose; taste masking.

INTRODUCTION

Various processes which can be utilised to prepare pellets are: extrusion–spheronisation, powder/solution/suspension layering and melt extrusion. Amongst all the above techniques, extrusion–spheronisation is the most robust and reproducible technique and, hence, widely used. Microcrystalline cellulose, the commercial grade Avicel® PH-101 in particular, is considered as an indispensable extrusion–spheronisation aid. This material, when dry-mixed in adequate concentration with a drug, acts as a molecular sponge for the added water, usually forming a plastic mass, which may extrude well prior to forming well-rounded pellets in a spheroniser (1,2). However, MCC formulations show some disadvantages like non-disintegration of pellets, which results in prolonged, matrix-type dissolution (3). This undesired property can be overcome by addition of large quantities of disintegrating aids (4). Other approaches to get fast disintegrating pellets are use of powdered cellulose (5) and use of ethanol water mixture as the granulating fluid (6). But both the abovementioned methods give pellets with weaker mechanical strength. Thus, the production of orally fast disintegrating pellets by extrusion–spheronisation using MCC is difficult. In addition, some drugs may adsorb to MCC, altering their dissolution time (7). Some drugs like ranitidine decompose in presence of MCC (8).

During the last few years, several other excipients like crospovidone (9), carrageenan (10–13), chitosan (14–17), pectin (18–20), hydroxypropyl methylcellulose and hydroxyethylcellulose (21), Eudragit® (22), poly(ethyleneoxide) (23) and modified starch (24–26) were exploited as extrusion–spheronisation aid alternate to MCC.

Crospovidone is a synthetic water insoluble cross-linked homopolymer of *N*-vinyl-2-pyrrolidone. It is available in several grades differing mainly in the particle size, for example Polyplasdone® XL is a coarser grade while Polyplasdone® XL-10 and Polyplasdone® INF-10 are finer grades. It is commonly used as a disintegrant at a concentration ranging from 2–5% in solid dosage forms (27–33).

Liew *et al.* (9) evaluated three different grades of Polyplasdone® as extrusion–spheronisation aids; two finer grades Crospovidone and Polyplasdone® INF-10 were efficient as extrusion–spheronisation aids. The mechanism of pellet formation using crospovidone as a spheronisation aid has been postulated by the authors (9) as such: added water is readily taken up by crospovidone, forming a hydration layer around the particles. With increasing water levels, its internal pores are gradually filled and saturated. The cross-linked structure of crospovidone behaves as a mesh to prevent the loss of water trapped within the internal pores, thus providing a repository for water, like a reservoir. In these aspects, its mechanism of action resembled the sponge model proposed for MCC. Although both crospovidone and MCC are capable of hydrogen bonding, the binding ability of crospovidone is comparatively lower, perhaps owing to the lack of mechanical interlocking. This gives rise to compensatory increases in water requirements before crospovidone could demonstrate appreciable binding properties. The weaker binding ability of crospovidone is demonstrated in its torque rheological properties, greater ease of mixing and extrusion, as well as the inability of its pellets to withstand high-spheronisation

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speeds. The mesh-like structure possesses both rigidity and flexibility to allow the absorption-release reabsorption of water during wet massing (moistening), extrusion (lubrication and moistening) and spheronisation (surface plasticity) (9). This phenomenon resembles the sponge model proposed for MCC (34).

Fexofenadine hydrochloride, the major active metabolite of terfenadine, is an antihistamine with selective peripheral H_1-receptor antagonist activity. Fexofenadine hydrochloride is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults or persons aged 6 years and older. It is also used in treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (35,36). Its bitter taste (37) makes it poor candidate for mouth dissolving dosage form. Literature (38) reports use of crospovidone as an agent for masking bitter taste of the drug. Hence, the objective of this project was to prepare melt-in-mouth pellets of fexofenadine hydrochloride using crospovidone as disintegrant, taste masking agent and an alternate extrusion–spheronisation aid. Crospovidone could not effectively mask the taste of fexofenadine hydrochloride; hence, ion exchange resins with pineapple flavour were used to enhance the mouth feel and patient compliance.

MATERIAL AND METHODS

Materials

Crospovidone (Polyplasdone® XL-10) was obtained as a gift sample from Anshul agencies (India) as an extrusion spheronisation aid, Indion® 234s (cross-linked acrylic polymer with $COO^- K^+$ functional group), Indion® 204 (o) (cross-linked acrylic polymer with $COO^- H^+$ functional group), Indion® 414 (cross-linked acrylic polymer with $COO^- K^+$ functional group), Indion® 254 F (polystyrene cross-linked with divinyl benzene with $SO_3^- Na^+$ as functional group) were obtained as a gift sample from Ion Exchange (India) Limited (India) as taste masking agent. Extrusion–spheronisation aids like Avicel® PH-101 and Avicel® RC-591 (mixture of MCC and sodium carboxymethylcellulose); xylitol (Xylisorb® 300; bulking agent) were obtained as a gift sample from Signet Chemicals Corporation (India). Fexofenadine hydrochloride was obtained as a gift sample from S. A. Pharmachem (India). Pineapple flavour (Instacoat® IC-F-105) was obtained as gift sample from Idealcures Ltd. (India). Citric acid, mannitol and dextrose were purchased from s. d. fine chemicals and aspartame was purchased from Ajinomoto Co., Japan. Purified water was used as wet massing liquid.

Taste Masking of Fexofenadine Hydrochloride

Taste Masking Using Polyplasdone® XL-10

Triturating drug with Crospovidone (Polyplasdone® XL-10) causes physical interaction between them. Drug was triturated with crospovidone (Polyplasdone® XL-10) for 30 min using mortar and pestle.

Taste Masking Using Ion Exchange Resin

As the drug is a salt of weak base and strong acid, there are groups which can interact with cation exchange resins. The procedure adopted for the complexation of the drug and resin was a batch method. Resin was stirred with water for 15 min to make a uniform dispersion using overhead stirrer. Drug was slowly added to the above dispersion with continuous stirring. The stirring was continued for 4 h. Resinate was poured in the stainless steel trays and dried in the hot air oven at 40°C and sieved through 40# sieve. Differential scanning calorimetric (DSC) studies were carried out by heating separately drug, resin and resinate from 32°C to 300°C at the heating rate of 10°C/min in nitrogen environment. The instrument used was Perkin Elmer Differential scanning calorimeter with Pyris 6 software.

Characterisation of Crospovidoneand Avicel® PH 101 (10)

Crospovidone and Avicel® PH 101 were characterised for the following parameters (Table I): bulk density and tap density (Veego Densitometer, India), viscosity and torque (Haake Rheometer, Thermo Fisher, USA), particle size (Mastersizer 2000, Malvern, UK), crystallinity (Rigaku, Miniflex X-ray Diffractometer, Japan) and swelling capacity. Viscosity and torque measurements for both the excipients were determined using Haake Rheometer having a stationary plate and rotating cone. Each excipient was granulated with different concentration of water and measured for viscosity at different levels of water content. Torque is directly proportional to viscosity. So torque (Tmax) was calculated in relative terms with maximum viscosity (η max) as 100%. Both the excipients were soaked in a cylinder in specific quantity of water and percent swellability (volume occupied) for each of the excipients was calculated from the initial volume of powder and the final volume of powder obtained after swelling. For measuring particle size, both materials were dispersed in the liquid paraffin. For measuring the crystallinity, the material was passed through 40 μm sieve, filled in the holder and charged to the instrument. The instrument falls over the sample, and the

Table I. Characterisation of Polyplasdone® XL-10 and Avicel® PH 101

	Physical properties						
	Density		Rheology				
Excipients	Tap density (g/mL)	Bulk density (g/mL)	η max (P)	T max (%)	Particle size (μ)	Crystallinity (%)	Swelling capacity (percent)
Avicel® PH 101	0.4494	0.333	69000	76.66	50–75	70	No swelling
Polyplasdone® XL-10	0.4255	0.2985	64466	71.62	30–50	5	23.5

reflected light is measured by the X-ray detector. The instrument automatically gives percentage of crystallinity of the sample.

Preparation of Pellets

Pellets were prepared from the raw materials as obtained from the manufacturer (25% of these extrusion spheronisation aids and 75% lactose). Both raw materials were wetted using purified water. The wet mass extruded using single screw extruder (Naomi Enterprises, India) equipped with an axial screen with perforation of 0.8 mm diameter. Immediately after extrusion, the extrudates were rounded in the spheroniser (Naomi Enterprises, India) with cross-hatched plate of diameter 150 mm in a batch size of 50 g each time. The spheronisation of MCC and crospovidone extrudates were carried out at 750 rpm for 1–2 min and 500 rpm for 30 s, respectively. The pellets were dried in fluid bed drier (S.B. Panchal and Co.) at 40°C for 30 min. The quality control parameters of the pellets prepared using both the extrusion spheronisation aids were compared (Table II)

All the melt-in-mouth formulations prepared were as shown in Table III. For preparation of the pellets (Batch size of 300 g); all the ingredients as mentioned in Table III were mixed in a planetary mixer for 15–20 min. Purified water was added to the above mix along with stirring until the appropriate mass was formed. The wet mass was extruded through single screw extruder as specified above. The extrudates were spheronised in batches of around 50 g at 500 rpm for 20–30 s. The pellets were dried in fluid bed drier (S.B. Panchal and Co.) at 40°C for 30 min and passed through appropriate sieves. The quantity of Polyplasdone® XL-10, other excipients and binder was varied so as to obtain spherical and melt-in-mouth pellets.

Evaluation of the Pellet

Size and Shape of the Pellets (9)

The pellets were characterised using LEICA GALEN™ III image analyser (USA) which consisted of a computer system connected to a camera mounted on a stereo microscope. The magnification was ×4. Projected area and perimeter were determined using Biovis image plus software. Prior to processing of the images, care was taken to assure that all pellets were detected as single entities. All the measurements were performed on 400±50 pellets. Sphericity/circularity emphasise on the spherical shape of the pellets. Perfectly spherical pellets will have value 1 or close to 1. Aspect ratio is the ratio of maximum diameter and the diameter perpendicular to the maximum diameter. Ideally spherical pellets will have value 1, but pellets with aspect ratio less than 1.2 are considered as spherical. The aspect ratio that describes the elongation of the pellets was calculated using: Aspect ratio = Major axis/minor axis or length/breadth ; where the minor axis was the shortest distance perpendicular to the major axis. Sphericity/circularity emphasises the spherical shape of the pellets using the equation:

$$\text{Sphericity} : 4\,\pi A/P^2$$

where A is the projected area of the individual pellet and P is the perimeter of that image, a perfectly spherical pellet would yield a sphericity of 1. Any value less than 1 indicates a less spherical image.

Friability Test

Friability test ($n=3$) was performed using Roche friabilator (Labindia, India). A pre-weighed sample (5 g, 16/25 mesh fraction) was placed in the friabilator along with 25 steel balls, each 2 mm in diameter. After 100 revolutions at 25 rpm, the mass retained on 25-mesh sieve was weighed, and friability was calculated as the percentage loss of mass between the initial and final weights of each bead sample (23).

Gustatory Sensation Test

Gustatory sensation test was performed by modifying a previously described method (39). In brief, quinine hydrochloride solution 1 mM was considered as standard for bitterness with a bitterness score of 5 and purified water as 0. The human volunteer study was done according to ethical guidelines for biomedical research on human subjects by Indian Council of Medical Research (www.icmr.nic.in/ethical.pdf). The protocol for the test was approved by institutional ethical committee. The test was performed with ten well-trained volunteers. The developed pellets were rated between 0 and 5 depending upon intensity of bitterness, 0 being tasteless and 5 very bitter. After tasting each sample, volunteers gargled well with water and waited for at least 20 min before tasting the next sample. Also, the volunteers rated the pellets for mouthfeel and dispersion in mouth (how fast polymeric material disperses the saliva) on the scale of 1 to 5.

Table II. Comparison of Polyplasdone® XL-10 as Spheronisation Aid with Avicel® PH 101

Parameters	Avicel® PH101	Polyplasdone® XL-10
Size	Around 70% in the range of 425–850 μ	More than 90% in the range of 425–850 μ
Water requirement	43–45%	55–60%
Extrusion rate	30 g/min	50 g/min
Spheronisation	More time along with high speed, hence more loss due to attrition	Less time with lower speed, hence less loss
Surface	Rough	Smooth
Drying Time	2–3 h	4–6 h
Aspects ratio	1.112	1.113

Table III. Formulation Development

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredients	Quantities in mg								
Fexofenadine Hydrochloride	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Indion® 234s	90.0	90.0	90.0	90.0	90.0	90.0	90.0	90.0	90.0
Indion® 414	30.0	30.0	–	–	–	–	–	–	–
Polyplasdone® XL – 10	–	–	75.0	75.0	75.0	75.0	30.0	62.5	75.00
Avicel® PH101	30.0	30.0	–	–	–	–	–	–	–
Avicel® RC591	45.0	45.0	–	–	–	–	–	–	–
Pineapple flavour	9.0	9.0	9.0	9.0	9.0	9.0	9.0	7.5	9.0
Citric acid	15.0	15.0	15.0	15.0	15.0	15.0	15.0	12.5	15.0
Aspartame	6.0	6.0	6.0	6.0	–	3.0	3.0	2.5	3.0
Mannitol	45.0	–	75.0	–	–	–	–	–	–
Xylitol (Xylisorb® 300)	–	45.0	–	75.0	81.0	78.0	123.0	45.0	–
Dextrose	–	–	–	–	–	–	–	–	78.0
Sugar syrup (20% *w/v*)	–	–	–	–	q.s.	–	–	–	–
Purified Water	q.s.	q.s.	q.s.	q.s.	–	q.s.	q.s.	q.s.	q.s.
Total	300.0	300.0	300.0	300.0	300.0	300.0	300.0	250.0	300.0

Flow Properties (USP 30)

Flow behaviour was assessed in terms of parameters like angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio as per USP 30.

Dissolution Test

Dissolution test was carried out as described below: Medium used was 900 mL 0.1 M hydrochloric acid, USP dissolution apparatus type 2 at 37°C and 50 rpm; 300 mg of the pellets was added to each vessel, and aliquots were withdrawn at regular interval of 15 to 45 min and analysed by an HPLC method (the liquid chromatographic system consisted of a Jasco PU-980 Intelligent pump (Jasco, Japan) coupled with a Jasco MD-2015 (Plus) Multiwavelength Detector (Jasco, Japan) and a Rheodyne injector (model 7725) fitted with a 20-μL sample loop. Data integration was done using Borwin Chromatography software version 1.50 for LC peak integration. Chromatography was performed on Thermo® RP-18 (5 μm) ODS Hypersil (4.6×250 mm) analytical column in the reverse phase mode. Chromatography was performed at room temperature under isocratic conditions at a flow rate of 0.8 mL/min. Detection was done at 220 nm). The time to form a uniform dispersion in 5 mL water is *in vitro* dispersion time. *In vitro* dispersion time was calculated by putting a sachet of pellets in 5 mL of water with slow swirling and calculating the time to form the uniform dispersion.

Stability Studies

The developed formulation was filled in aluminium sachets and subjected to accelerated stability studies as per ICH guidelines (at 40±2°C and 75±5% RH). The samples were withdrawn from the stability chambers at 1, 2, 3 and 6 months time points and analysed for assay and dissolution test.

RESULTS AND DISCUSSION

Taste Masking of Fexofenadine Hydrochloride

Taste Masking Using Polyplasdone® XL-10

Drug/crospovidone was taken in the ratio 1:1 and 1:2. Drug/Crospovidone in the ratio 1:2 (weight basis) gave complete taste masking of the drug. A bigger batch was prepared in ball mill; the drug could not be taste-masked even after triturating for 72 h in a ball mill. The hand trituration had more impact pressure on drug and Polyplasdone® as compared to the impact of balls on these; this could be reason for incomplete masking of the drug. Drug was also stirred with crospovidone in presence of water, in the ratio of 1:2, but it could not help in masking the bitter taste of the drug. Hence, other methods of masking the taste of the drug were tried.

Taste Masking Using Ion Exchange Resin

Indion® 234s in the ratio 2.5:1 (weight basis) with drug could mask the bitter taste of the drug. When this complex was incorporated in mouth dissolving pellets, the formulation tasted bitter. Indion® 204 (o) and Indion® 414 in the ratio 3:1 with drug, the bitterness of the drug could not be masked. Indion® 254 F at the ratio of 2.5:1 with drug could effectively mask the bitterness of the drug. This resinate after incorporation into mouth dissolving pellets gave pellets with poor mouthfeel. The *in vitro* release studies showed 45% of the drug release in 60 min. The reason for the slow release of the drug was slow elution of drug from strong cation exchange resin Indion® 254 F. Resinate with the drug: resin ratio of 1:3 was prepared with Indion® 234s. Thermograms obtained were as shown in Fig. 1. As shown in Fig. 1, thermogram D represents the DSC thermogram of pure drug fexofenadine hydrochloride, exhibiting a sharp endotherm at 198.6°C. Disappearance of this peak in the thermogram C indicates complete complexation of the drug with the resin. Thermo-

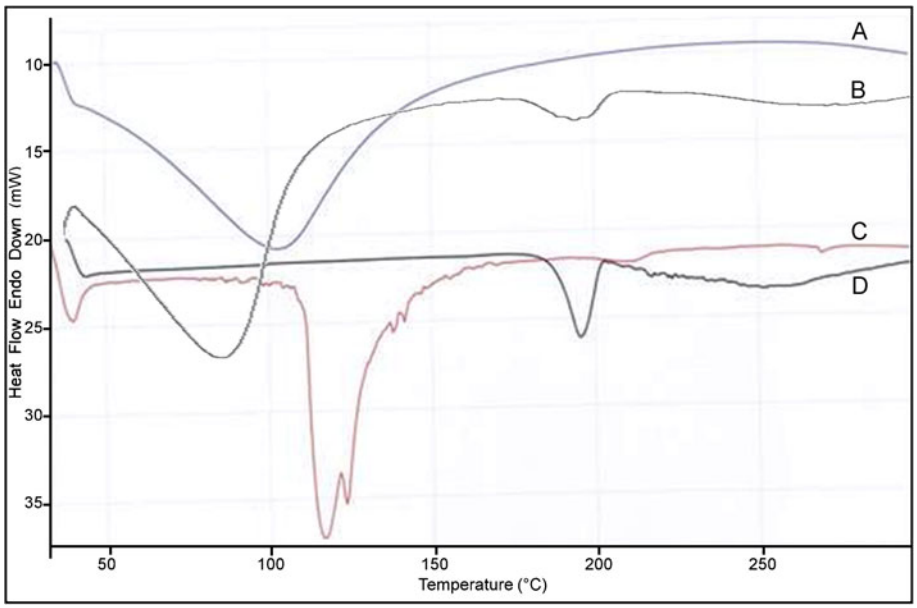

Fig. 1. DSC thermograms of drug, resin and resinates. **a** Resin, **b** Resinate (1:2.5—drug–resin), **c** Resinate (1:3.0—drug–resin), **d** Drug

gram A is of pure resin Indion® 234s. Thermogram B shows thermogram of resinate with the drug: resin ratio of 1:2.5. A small peak at 198.6°C was seen which indicates incomplete complexation of the drug.

Characterisation of Crospovidone and Avicel® PH 101

The raw materials as obtained from the manufacturer were found to be insoluble in water. Table I shows the characteristics of crospovidone and Avicel® PH 101. From Table I, it was clear that the rheology properties of crospovidone were equivalent to that of Avicel® PH101. Crospovidone swells by 23% which helps in the faster disintegration of the pellets. It also forms a smooth slurry/dispersion in saliva which gives smooth mouthfeel to the formulation.

Preparation of Pellets

The pellets with Avicel® PH101 and crospovidone were prepared (Fig. 2), and comparison of the quality-control parameters was as shown in Table II. Crospovidone was found to be better extrusion–spheronisation aid as compared to Avicel® PH101 since it gave pellets with narrower particle size distribution, faster extrusion and spheronisation rates and a smoother surface.

Initial trials were done with Avicel® PH101 and Avicel® RC591 as the extrusion spheronisation aids. Both formulations (F1 and F2; Table III) gave poor *in vitro* dispersion (around 2 min). In addition, both formulations released only 50% of the drug at the end of 45 min in *in vitro* release studies. Replacement of Avicel® and Indion® 414 with Crospovidone (F3) gave pellets with good dispersion in mouth but with poor mouthfeel. Replacement of mannitol with xylitol (F4) gave pellets with good dispersion in mouth as well as good mouthfeel. The improvement in mouthfeel could be due to negative heat of solution and instant dissolution of xylitol. Batch F5 was without sweetener, and granulation was carried out using sugar syrup 20% *w*/*w*; the pellet surface was very rough. It exhibited poor dispersion in mouth. It was not properly spheronised. The aspartame concentration was reduced to 1% *w*/*w* in batch F6 from batch F4. The sweetness of the formulation was accepted by all healthy human volunteers. Reduction in concentration of crospovidone to 10% *w*/*w* (F7) gave pellets with poor sphericity as well as *in vitro* dispersion. The reason could be lack of an ingredient which has water-holding capacity as well as disintegrant concentration. Reduction in overall weight of the formulation so as to reduce the concentration of the excipients (F8) with 25% *w*/*w* crospovidone exhibited pellets with poor dispersion as well as mouthfeel. This could be due to reduction in concentration of diluent–xylitol. Replacement of xylitol with dextrose (F9) gave pellets with poor dispersion in mouth as well as mouthfeel. The probable reason could be slow dissolution of dextrose as compared to xylitol. The optimum formulation was F6 which was well accepted by the healthy human volunteers.

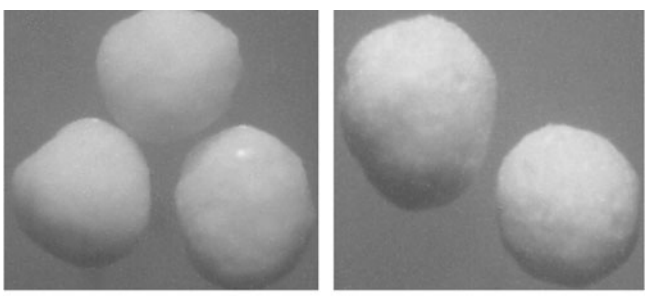

Fig. 2. Photographs of the pellets

Evaluation of Pellets

Size and Shape of the Pellets

In cases where pellets are prepared using Avicel® PH 101 and Polyplasdone® XL-10, the extrusion–spheronisation aids had no impact on the shape of the pellets. Spherical pellets resulted from both these extrusion spheronisation aids (Table II). This was confirmed by the aspect ratio of 1.11 for pellets of both the extrusion–spheronisation aids. The results of the mouthfeel, swelling capacity, flow properties, friability, roundness and *in vitro* release of drug from the formulation F6 are presented in Table IV.

Friability Test

Friability of pellets is influenced by spheronisation residence time and speed (40). The friability of the optimised formulation was 1.6% *w*/*w* which was lower than abundantly reported in the literature (41–43).

Gustatory Sensation Test

Masking of unpleasant taste by using matrix type systems has been studied previously (44). However, in the current study, pellets showed no bitter taste as evident from the bitterness score. The mean bittereness score of 0.3 of the pellets was not significant ($P<0.05$). The significant bitterness score is 5 when tested with quinine hydrochloride. Further, pellets were soft to swallow which may be due to formation of polyacrylic acid (backbone of Indion® 234s) gel in presence of saliva (pH=6.8).

Flow Properties

The free surface of the static heap of powder, when gravity is the only external force acting upon it, can assume various forms, but one limitation persists, the angle to the horizontal cannot exceed a certain value—this is the angle of repose. Difference between tapped density and bulk density indicated cohesiveness of the powder and greater the difference, the more cohesive the powder and poorer the flow (45). The Carr's index was 7.88% (less than 15% indicates excellent flow) and Hausner's ratio was 1.08 (less than 1.25 indicates excellent flow). In this study, the flow properties as evident from the values of Carr's index, Hausner's ratio and angle of repose indicated in Table IV indicated that flow behaviour of the optimised formulation is good. Since the flow behaviour aids in downstream pharmaceutical processes like filling in sachet, it further reduces weight variation.

Dissolution Test

Dissolution test showed more than 90% drug release in 15 min. *In vitro* dispersion time was found to be 20–25 s.

Stability Studies

The formulation was found to stable during the 6-month stability testing period. The assay was found to be 97% *w*/*w* after 6 months at 40±2°C and 75±5% RH condition, and it released more than 90% of the drug in 15 min.

CONCLUSION

In conclusion, crospovidone is well suited as an extrusion–spheronisation aid and an efficient disintegrant. Patient-friendly mouth-dissolving pellets of fexofenadine hydrochloride were developed for paediatrics. The bitterness of the drug was very well masked using an ion exchange resin. The developed formulations were found to be stable during the 6-month stability testing period.

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Table IV. Quality Control Parameters of the Developed Formulation (F6)

Parameter	Results
Appearance	Yellow coloured, spherical, uniform pellets
Taste	Sweet–sour
Mouthfeel	Good
Flavour	Pineapple
Swelling capacity (%)	2.35
Particle size (microns)	Between 425 and 850
Density	
Bulk density (g/cm^3)	0.645
Tap density (g/cm^3)	0.710
Carr's index (%)	7.88
Hausner's ratio	1.08
Angle of repose (°)	16.87°
Friability (%)	1.6±0.09%
Sphericity	0.96
Aspect ratio	1.116
In vitro dispersion	20–25 s
Assay of fexofenadine hydrochloride (%)	99.236±1.26
In vitro release	More than 90% in 15 min

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