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FORMULATION OF MOUTH-DISSOLVING TABLETS CONTAINING A SPRAY-DRIED SOLID DISPERSION OF POORLY WATER-SOLUBLE FENOPROFEN CALCIUM DIHYDRATE AND ITS CHARACTERIZATION

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The aim and objective *of this investigation focus on the formulation of mouth-dissolving tablets of Fenoprofen calcium dihydrate spray dried solid dispersions.*
Materials and methods. *Spray drying is a well-recognized manufacturing technique that can be used to create amorphous solid dispersions, which are an effective delivery method for poorly water-soluble pharmaceuticals such as Fenoprofen calcium dihydrate (FCD). In addition to skimmed milk powder (SMP) and FCD, the carrier β-cyclodextrin was used to produce solid dispersions.*
Results and discussion. *The production of solid dispersions yielded reproducible results. Solid dispersion with β-cyclodextrin and skimmed milk powder is one way to increase disintegration time by increasing the water solubility of inadequately water-soluble FCD. In-vitro dissolution experiments of FCD mouth-dissolving tablets revealed significant differences. Stability studies should evaluate drug product characteristics that are susceptible to change during storage and are anticipated to impact quality, safety, and efficacy to demonstrate that the optimal formulations remain stable over the course of the study. The results of stability experiments were statistically significant at $p<0.05$ using one-way ANOVA followed by Dunnet's test. During in-vivo anti-inflammatory experiments, the formulation SDC6 demonstrated a greater percentage of inhibition than the purified drug and super disintegrant, and the results were statistically significant using one-way ANOVA followed by the Bonferroni test.*
Conclusions. *The solid dispersions were prepared with β-cyclodextrin, and skimmed milk powder improved the solubility of the poorly water-soluble fenoprofen calcium dihydrate. In vitro dissolution experiments of fenoprofen calcium dihydrate mouth dissolving tablets and controlled tablets revealed significant differences*
Keywords: *fenoprofen calcium dihydrate, spray drying, β-cyclodextrin, skimmed milk powder, mouth-dissolving tablets, anti-inflammatory*

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1. Introduction

The oral route of medication administration for illness is considered the most conventional route [1]. Tablets are a commonly prescribed dosage form because of their accessibility in terms of self-administration, solidity, and simplicity of development. Patients, particularly paediatric and geriatric patients, often experience trouble swallowing conventional tablets, and this problem may prove worse during travel conditions due to the non-availability or restricted availability of water. These problems with conventional dosage forms can be overcome by the development of mouth-dissolving tablets [2, 3]. Mouth-dissolving tablets (MDT) are solid dosage forms containing drugs that disintegrate in the oral cavity within less than one minute. The convenience of administration and improved patient compliance are important in the design of the oral drug delivery system, which remains the preferred route of drug delivery in spite of various disadvantages [4]. One such problem can be solved in the novel drug delivery system by formulating MDT, which disintegrates or dissolves rapidly without water within a few seconds in the mouth due to the action of a super disintegrant or by maximizing pore structure in the formulation. These dosage forms are placed in the mouth and allowed to disperse or dissolve in the saliva. They release the drug as soon as they come into contact with the saliva, thus obviating the need for water during administration [5]. Many patients, especially the elderly, find it difficult to swallow tablets, capsules, and fluids and thus do not comply with prescriptions, which results in a high incidence of non-compliance [6]. Compliance-oriented research has resulted in many safer and new drug delivery systems. Rapidly disintegrating or dissolving tablets are one such example, either for the reason of rapid disintegration or even with saliva. Considering the quality of life, most of these efforts have been focused on ease of medication. Among the various dosage forms developed to improve the ease of administration, the MDT is the most widely preferred commercial product [7, 8].

Spray drying is a well-established manufacturing technique that can be used to formulate amorphous solid dispersions. It is an effective strategy for delivering poorly water-soluble drugs like Fenoprofen calcium dihy-

drate [9, 10]. The solid dispersions consist of drug molecules dispersed in amorphous polymeric carriers. Spray drying is an energy-intensive, continuous and scalable drying process which can generate nano to micron-size particles that have a narrow distribution in a very short span of time [11]. The process was meant to exhaust moisture and prevent destructive chemical change.

The process of formation of solid dispersions by using a spray drying process schematically involves several steps involving various processes, as shown in Fig. 1. The feed solution or suspension is pumped into the drying chamber through a nozzle from the feed container followed by a feed pump [12, 13]. During exit from the tip of the nozzle, the droplets come in contact with the drying fluid, i.e. hot air inside the drying chamber. The residence time within the drying chamber is based on the process of components and the equipment dimensions and typically lasts for a few milliseconds. During the transit through the drying chamber, energy-mass transfer takes place at the dynamic droplet surface. Finally, the dried material is separated from the drying medium using a cyclone separator and is collected in a collector. The exhaust gases are filtered through HEPA filters.

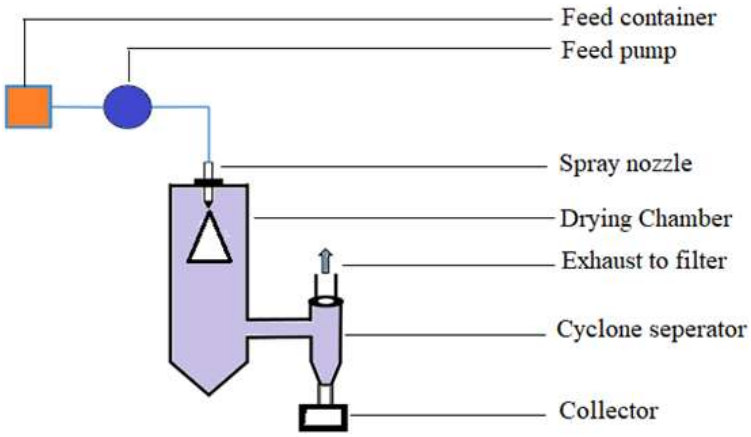

Fig. 1. Illustrations of Spray drying process

2. Planning (methodology) of research

The use of solid dispersions incorporating skimmed milk powder (SMP) and β-cyclodextrin in the formulation of MDT of poorly soluble fenoprofen calcium dihydrate (FCD). The research was well organized and carried out in order to achieve the following goals using appropriate methods:

1. The formulation of solid dispersions by spray drying process.

2. The evaluation of micromeritics properties of solid dispersions.

3. The formulation of MDT of Fenoprofen calcium dihydrate using solid dispersions.

4. To evaluate the post-compression parameters of MDT.

5. To perform in vitro drug release of all sets of prepared formulations.

6. To perform stability studies of the best formulation.

7. To carry out in vivo anti-inflammatory activity.

3. Materials and Methods

Fenoprofen calcium dihydrate is an anti-inflammatory analgesic used to treat mild to moderate pain in addition to the signs and symptoms of rheumatoid arthritis. It was procured from Bal Pharma Ltd (Bangalore, India); β-cyclodextrin (Carrier and solubilizing agent) was purchased from RP Chemicals (Mumbai, India); DMSO (dimethyl sulfoxide) (Solvent for FCD) was brought from Qualigens chemicals (Maharashtra, India); Amul skimmed milk powder (SMP) used as an excipient and calcium supplement were purchased from local market (Gwalior, India); Indion414, SSG (sodium starch glycolate), and CCS (croscarmellose sodium) were used as a superdisintegrants and obtained from Drugs India (Hyderabad, India); Aspartame (Sweetener), Magnesium stearate (Lubricant), Methyl cellulose (Binder and disintegrant) and MCC (Diluent) was procured from SD fine chemicals (Mumbai, India); D-mannitol (Bulking agent) is supplied from Chemkart (Mumbai, India). The rest of the chemicals and reagents employed were of analytical grade.

3. 1. Formulation of solid dispersions (SD) by spray drying process

The calculated amount of FCD is dissolved in 10 ml of DMSO. The different ratio of SMP was dissolved in 10 ml of distilled water. Whereas β-cyclodextrin is practically insoluble in water and hence dissolved in a ratio of 5 ml of ethanol to 5 ml of water with the aid of low heating. Both solutions were mixed together and then sprayed through the nozzle at a feed rate of 4 ml per minute with an inlet temperature of 120 ºC. The set of SDs was prepared by using β-cyclodextrin along with skimmed milk powder and FCD using well-suited spray drying technology [14]. The SD-containing drug, SMP and β-cyclodextrin from varying proportions are given in Table 1.

Table 1

Varying proportions of SD containing drug, SMP and β-cyclodextrin

Formulation code	Drug: SMP:βCD Ratio	DMSO in ml	Water in ml	Water: Ethanol 1:1	Feed Rate of Solution ml/min	Inlet temperature, ºC
C1	1:1:1	10	10	5:5	4	120
C2	1:1:0.5	10	10	5:5	4	120
C3	1:0.5:1	10	10`	5:5	4	120
C4	1:0.5:0.5	10	10	5:5	4	120

3. 2. Micromeritic properties evaluation of solid dispersions

Bulk density and tapped density.

Bulk density is defined as the mass of the powder divided by the bulk volume. An accurate weight quantity of an SD, which was previously passed through sieve number 10, was carefully poured into a graduated cylinder, and the volume occupied was measured. Then, the graduated cylinder was closed with a lid and set into the density determination apparatus. After that, the volume was measured, and the operation was continued till the difference between the two readings was less than 2 %. The bulk and tapped density was calculated by using the formula [15]:

$$\text{Bulk density} = \frac{\text{Weight of SD}}{\text{Bulk volume of SD}};$$

$$\text{Tapped density} = \frac{\text{Weight of SD}}{\text{Volume of SD after tapping}}.$$

The angle of repose (θ).

Weighed quantity of the SD was passed through a funnel kept at a height of 2 cm from the surface. The SD was passed, till it formed a heap that touches the tip of the funnel [16]. The radius was measured and the angle of repose was calculated using the formula mentioned below:

$$\theta = \tan^{-1}\left(\frac{h}{r}\right),$$

where θ – angle of repose; *h* – height of the heap formed from the surface; *r* – radius of the heap in cm

Hausner's ratio.

The Hausner's indicates the flow property of the powder material. It is the ratio of tapped density to bulk density of the powder and is calculated by using the formula:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{bulk density}}.$$

Carr's index.

Compressibility is an important measure that can be obtained from bulk and tapped densities [17]. It is calculated by using the following formula and expressed in terms of %:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100.$$

Drug content uniformity.

Drug content uniformity was determined as triplicate by dissolving the SDs equivalent to 100 mg of FCD in distilled water and filtering with Whatman filter paper (0.45 μm, Whatman, Maidstone, UK). The filtrate was evaporated, and the drug residue dissolved in 100 ml of phosphate buffer (pH 6.8). The 5 ml solution was then diluted with phosphate buffer up to 20 ml, filtered through Whatman filter paper and analyzed at 270 nm using a UV spectrophotometer.

3. 3. Formulation of MDT of FCD using SD

The optimized C2 SD formulations are selected for the preparation of MDT based on the micromeritic results. MDT of FCD was prepared by direct compression method [18] using SDs prepared by spray drying technology as per the formula given in Table 2. An accurately weighed 200 mg equivalent of FCD SD is mixed with super disintegrants like Indiaon414, SSG and CCS. All other ingredients were mixed well using the geometric dilution technique and compressed into the form of tablets of 8 mm in size and flat round punch using a Rimek Compression machine. The compressed tablets were evaluated for various physico-chemical evaluation parameters. The controlled tablets without super disintegrants were also prepared using the same process above.

Table 2

Formulation of MDT by using optimized formulations of C2 SD

Ingredients in mg	SDC1	SDC2	SDC3	SDC4	SDC5	SDC6	SDC7	SDC8	SDC9	SDC10	SDC11	SDC12	Controlled tablet
SD equivalent to 200 mg of FCD	500	500	500	500	500	500	500	500	500	500	500	500	500
Indion414	22.5	18	12.5	8	–	–	–	–	–	–	–	–	–
SSG	–	–	–	–	22.5	18	12.5	8	–	–	–	–	–
CCS	–	–	–	–	–	–	–	–	22.5	18	12.5	8	–
Aspartame	4	4	4	4	4	4	4	4	4	4	4	4	4
Mg stearate	2	2	2	2	2	2	2	2	2	2	2	2	2
Methyl cellulose	3	3	3	3	3	3	3	3	3	3	3	3	3
MCC	38.5	34	29.5	25	38.5	34	29.5	25	38.5	34	29.5	25	51
D-Mannitol	30	30	30	30	30	30	30	30	30	30	30	30	40
Total weight in mg	600	600	600	600	600	600	600	600	600	600	600	600	600

3. 4. Post-compression parameters evaluation of MDT

All the prepared formulations were evaluated for their post-compressional parameters [19], such as hardness, friability, thickness, weight variation and drug content, as per the procedure mentioned for conventional oral tablets in the accredited pharmacopoeia.

3. 5. In vitro disintegration time

The disintegration time is performed using a disintegration test apparatus [20]. One tablet was placed in each tube of the basket. This basket was immersed in a water bath at 37+0.5 °C. The time required for complete disintegration was measured, and the same procedure was repeated for another set of formulated tablets.

3. 6. In vitro drug release study

In vitro dissolution studies of the MDT of FCD formulations and controlled tablets prepared without super disintegrants were performed according to USP XXIII Type-II dissolution apparatus (Electrolab, model TDT-06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5 °C as dissolution medium [21]. One tablet was used in each test. Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals and replaced immediately with an equal volume of fresh medium. The samples were filtered through a 0.22 μm membrane filter disc and analyzed for drug content by measuring the absorbance at 270 nm. Drug concentration was calculated from the standard calibration curve and expressed as the cumulative percentage of drug dissolved. The release studies were performed in replicates of three. The dissolution rate was studied by using a USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rpm) using 900 ml of phosphate buffer pH (6.8) as a dissolution medium. The temperature of the dissolution medium was maintained at 37±0.5 °C; the aliquot of the dissolution medium was withdrawn at every 10 min interval and filtered. The absorbance of the filtered solution was measured by the UV spectrophotometric method at 270 nm, and the concentration of the drug was determined from the standard calibration curve.

3. 7. Stability studies

Stability studies should involve the assessment of drug product properties that are sensitive to change during storage and are anticipated to have an impact on quality, safety and efficacy [22]. The ICH stipulates the duration of the investigation as well as the storage conditions: Accelerated stability experiments for the selected formulation SDC6 were carried out in the current study at accelerated conditions of 40±2 °C, 75±5 % RH over a particular time period of up to 6 months. At regular intervals, the tablets were examined for physical appearance, drug content, disintegration time and in vitro drug release. The acquired values were subjected to a one-way ANOVA followed by Dunnett's test. Differences were considered statistically significant at $p<0.05$.

3. 8. In vivo anti-inflammatory activity

The best formulation SDC6 is prepared with the solid dispersions containing β-cyclodextrin as a carrier along with super disintegrant SSG and other excipients were selected for *in-vivo* anti-inflammatory activity [23].

Animals and treatment.

Healthy albino Wistar rats strain of either sex weighing 190±10 g were selected for the study. The animals were kept under 12:12 h day and light schedules with temperature between 18 to 20 °C. They were housed in large spacious hygienic cage during experimental period. Animals were allowed to free access to water and standard pellet diet up to the end of the study.

Experimental design.

Animals were divided into 5 groups (n=6/group). Group I was kept as normal untreated control (5 ml/kg saline), group II received Carrageenan 0.1 ml of 2 % (w/v) along with saline, group III received standard drug Fenoprofen administered orally 1 h before carrageenan suspension administration, group IV received Carrageenan 0.1 ml of 2 % (w/v) along with formulation SDC6 orally for 7 consecutive days and group V received Carrageenan 0.1 ml of 2 % (w/v) along with super disintegrant SSG orally for 7 consecutive days. The last dose was administered 60 min before the induction of inflammation. Subsequently, all animals received a subcutaneous injection of 0.1 ml of 1 % (w/v) carrageenan solution in the plantar region of the right hind paw to induce oedema. The paw volume was measured initially and then at 60-minute intervals for up to 4 hours after the injection, using a vernier calliper.

Statistical analysis.

Results are provided as Mean±SD (n=6). Results were analyzed statistically using one-way analysis of variance (ANOVA) followed by Bonferroni t-test. $p<0.05$ was considered as the level of significance while comparing between groups.

4. Results

Spray drying is a well-established manufacturing technology that may be used to create amorphous solid dispersions, which is an effective strategy for delivering medications that are weakly water-soluble FCD.

The micromeritic characteristics and drug content percentage of SDs comprising FCD: SMP: β-cyclodextrin, such as C1, C2, C3, and C4, were examined, and the results were presented in Table 3. All the formulations showed reproducible results, indicating good flow properties and SD C2 had a high percentage of drug content compared to the rest of the formulations.

The post-compressional parameters such as hardness, friability, thickness, weight variation, and drug content for the prepared MDT formulations were determined by following the procedure for conventional oral tablets in the accredited pharmacopoeia. The obtained values are shown in Table 4. All the prepared MDT formulations showed results within the limits specified in the accredited pharmacopoeia, but when compared to the formulations SDC6, SDC6 showed better results.

The in vitro disintegration time of MDT formulations was determined by using the disintegration apparatus, and the founded values were graphically represented in Fig. 2. In vitro disintegration time is very important for mouth-dissolving tablets, and it is desired to be less. The rapid disintegration may be due to the rapid uptake of water from the medium, swelling, and burst effect, thus promoting bioavailability. The disintegration times of all the formulations lay in the range of 26 to 32 seconds.

In vitro dissolution studies of the mouth-dissolving tablets of FCD formulations and controlled tablets prepared without super disintegrants were performed in a USP dissolution apparatus employing a paddle stirrer at 50 pm and 900 ml of pH 6.8 phosphate buffers at 37±0.5 °C as dissolution medium. The samples were filtered through a membrane filter disc and analyzed for the amount of drug by measuring the absorbance through a UV spectrophotometer. The cumulative drug release was increased by the use of super disintegrants compared to the controlled tablets prepared without super disintegrants, and the results of controlled tablets, formulations SDC1 to SDC12, were found to be 75.92 %, 95.85 %, 99.41 %, 98.46 %, 97.89 %, 97.23 %, 99.98 %, 98.64 %, 96.42 %, 97.69 %, 99.52 %, 98.25 %, and 97.99 %, respectively. Significant differences were observed, and the results are reproducible with triplicate observations. Data from in vitro dissolution studies of all the prepared MDT formulations (SDC1 to SDC12) and controlled tablets are shown in Fig. 3.

Stability studies should involve the assessment of drug product properties that are sensitive to change during storage and are anticipated to have an impact on quality, safety and efficacy. The ICH stipulates the duration of the investigation as well as the storage conditions: Accelerated stability experiments for the selected formulation SDC6 were carried out in the current study at accelerated conditions of 40±2 °C, 75±5 % RH over a particular time period of up to 6 months. At regular intervals, the tablets were examined for physical appearance, drug content, disintegration time and in vitro drug release. The acquired values were subjected to a one-way ANOVA followed by Dunnett's test. Differences were considered statistically significant at $p<0.05$, and the results are shown in Table 5.

The best formulation of SDC6 with super disintegrant SSG and other excipients was selected for *in-vivo* anti-inflammatory activity. Animals were divided into 5 groups (n=6/group). Group I was kept as normal untreated control (5 ml/kg saline), group II received Carrageenan 0.1 ml of 2 % (w/v) along with saline, group III received standard drug Fenoprofen calcium dihydrate administered orally 1 h before carrageenan suspension administration, group IV received Carrageenan 0.1 ml of 2 % (w/v) along with formulation SDC6 orally for 7 consecutive days and group V received Carrageenan 0.1 ml of 2 % (w/v) along with super disintegrant SSG orally for 7 consecutive days. The last dose was administered 60 min before the induction of inflammation. Subsequently, all animals received a subcutaneous injection of 0.1 ml of 1 % (w/v) carrageenan solution in the plantar region of the right hind paw to induce oedema. The paw volume was measured initially and then at 60-minute intervals for up to 4 hours after the injection, using a vernier calliper. The paw volume at different intervals for different groups is given in Table 6.

Table 3

Micromeritic characteristics of SDs

Formulation code	Bulk density (gm/cc)±SD, n=3	Tapped density (gm/cc)±SD, n=3	Angle of repose(θ)±SD, n=3	Carr's index (%) ±SD, n=3	Hausner's ratio ±SD, n=3	Drug content in %
C1	0.56±0.007	0.65±0.01	25.43±1.36	13.85±1.18	1.16±0.03	99.21±0.004
C2	0.54±0.007	0.63±0.01	23.78±1.28	14.29±1.25	1.16±0.05	99.99±0.001
C3	0.56±0.007	0.66±0.01	26.46±1.48	15.15±1.29	1.19±0.03	98.45±0.005
C4	0.52±0.007	0.63±0.01	26.75±1.46	17.46±2.10	1.21±0.03	99.21±0.005

Table 4

Post-compressional evaluation parameters of MDT prepared with the solid dispersions containing β-cyclodextrin

Formulation code	Hardness (kg/cm^2)±SD, n=3	Friability (%)	Thickness (mm)±SD, n=3	Weight variation (mg)±SD, n=3	Drug content %±SD, n=3
SDC1	3.4±0.12	0.69	6.69±0.15	598±1.77	99.47±0.005
SDC2	3.2±0.22	0.63	6.77±0.15	599±1.36	99.69±0.007
SDC3	3.3±0.15	0.62	6.79±0.18	599±0.54	99.58±0.008
SDC4	3.4±0.16	0.56	6.85±0.12	597±1.88	99.87±0.004
SDC5	3.5±0.16	0.59	6.86±0.15	599±0.64	99.59±0.003
SDC6	3.6±0.17	0.61	6.85±0.13	598±1.89	99.99±0.005
SDC7	3.7±0.18	0.65	5.78±0.15	598±1.37	99.84±0.006
SDC8	3.8±0.19	0.73	6.72±0.102	599±1.55	99.83±0.005
SDC9	3.7±0.15	0.58	6.79±0.18	598±0.17	99.63±0.003
SDC10	3.5±0.16	0.69	6.64±0.29	599±0.44	99.74±0.004
SDC11	3.6±0.16	0.63	6.65±0.19	600±1.66	99.71±0.003
SDC12	3.7±0.18	0.55	6.72±0.13	599±0.92	99.92±0.004

Table 5

Stability studies of best formulation (SDC6)

Parameters	1st Month	3rd Month	6th Month	p-value
Physical appearance	No Change	No Change	No Change	--
Drug Content	99.99±0.005	99.99±0.005	99.99±0.005	0.0452
Disintegration time	26±1.08	27±1.01	27±0.99	0.0468
In-vitro drug release in %	99.98	99.88	99.72	0.0457

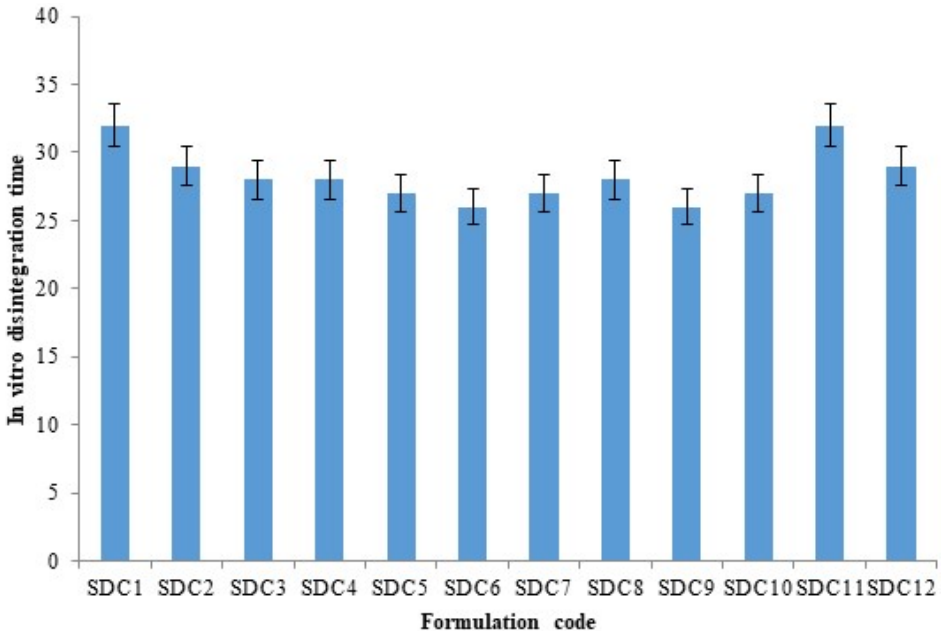

Fig. 2. *In-vitro* disintegration time of SDC1-SDC12

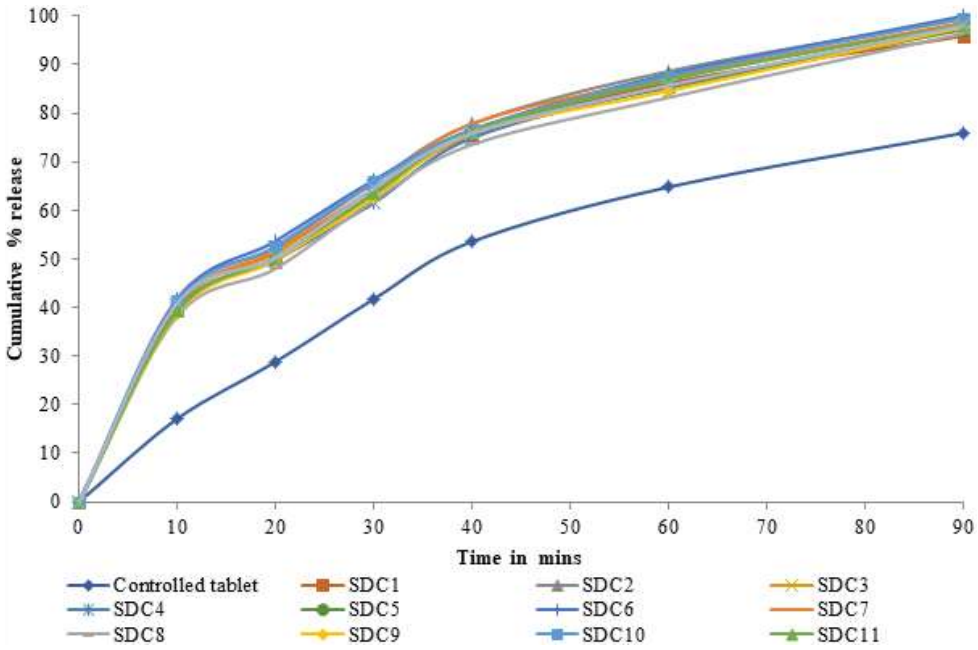

Fig. 3. *In-vitro* drug release data of SDC1 – SDC12 compared with controlled tablet

Table 6

Paw volume at different time intervals

Sl. No.	Group	Time (h)				% Inhibition
		1	2	3	4	
I	Normal Control (5 ml/kg)	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	–
II	Carrageenan control (0.1 ml of 2 % (w/v)	1.81±0.109	1.99±0.107	2.18±0.105	2.32±0.080	–
III	Fenoprofen calcium dihydrate	1.69±0.114^{NS}	1.30±0.100**	0.95±0.165**	0.46±0.124**	80.17
IV	SDC6	1.50±0.081**	1.10±0.092**	0.87±0.091**	0.32±0.085**	86.20
V	Superdisintegrant (SSG)	1.80±0.113^{NS}	1.85±0.107**	1.94±0.110**	1.98±0.094**	14.65

*Note: values are expressed as mean±SD at n=6, One-way ANOVA followed by Bonferroni test, *P<0.050, **P<0.001 and ^{NS}P>0.001 compared to the negative control*

5. Discussion

Spray drying is a well-known manufacturing process that can be used to make amorphous solid dispersions, which are a useful strategy for delivering drugs that are poorly water-soluble [24]. In the solid dispersions, the drug molecules are dispersed in amorphous polymeric carriers. The solid dispersions were created utilizing β-cyclodextrin, as well as skimmed milk powder and FCD. Skimmed milk powder is nutritious and provides bone-building nutrients such as protein, calcium, vitamin D, and vitamin A. It may be added to the composition of SD to increase the amount of protein and calcium for people with rheumatoid arthritis. Cyclodextrins and their derivatives significantly increase drug solubility by forming drug-cyclodextrin complexes during the preparation of SDs, which consist of an inclusion complex where the drug is entrapped within the cavity of β-cyclodextrin. FCD is complexed with cyclodextrins, reducing the hydrophobicity of the drug and enhancing its dissolution rate, absorption, and solubility. When a drug molecule entrapped within the cavity of cyclodextrin prevents degradation upon exposure to oxygen, water, heat, and other chemical reactions. The resulting complex masks the unpleasant odour and bitter taste of the FCD and makes it much more acceptable to the patient.

Micromeritics is the science and technology of small particles because it studies the derived and flow properties of individual powders or granules as well as collections of particles [25]. The

particle size of a drug can influence its release from dosage forms supplied by any route. It is important to know that the above properties of prepared SDs are to be formulated in the form of MDT. The SD formulations C2 with ratios of the drug: SMP: β-cyclodextrin of 1:1:0.5 attained the highest drug content percentage as well as acceptable micrometric characteristics.

FCD mouth-dissolving tablets were made by direct compression using solid dispersions and various proportions of super disintegrants like Indion414, SSG and CCS according to the formulas in the table. The direct compression method is a simplified, shorter process that is well-suited for the manufacture of SDs into MDTs. Post-compression properties such as hardness, friability, thickness, weight variation, and drug content were assessed in the manufactured MDT comprising solid dispersions.

One approach for extending disintegration time by increasing the solubility of weakly water-soluble FCD is solid dispersion with β-cyclodextrin and skimmed milk powder [26]. However, compressing such solid dispersions into a mouth-dissolving tablet dosage form tends to prolong the tablet's disintegration period with the addition of super disintegrants such as Indion414, SSG and CCS. The disintegration time is measured using a disintegration test apparatus.

Indion414 is an ion exchange resin, and the high-purity pharmaceutical-grade weak acid cation exchange resin is available as a dry powder in potassium form that is safe for oral intake and easy to get [27]. It is insoluble in water; the matrix is composed of crosslinked acrylic acid in potassium form with a carboxylic acid functional group, resulting in effective disintegration via a notable swelling propensity upon wetness. It is readily compatible with FCD without having any interaction and does not stick during tablet punching. SSG is the sodium salt of a starch carboxymethyl ether. These are modified starches created by crosslinking potato starch, giving the product excellent disintegration qualities [28]. The crosslinking reduces both the polymer's water-soluble fraction and the viscosity of the dispersion in water. The method by which this action occurs involves quick water absorption, which causes a large rise in the volume of granules, resulting in rapid and uniform disintegration. The inclusion of large hydrophilic carboxymethyl groups disrupts hydrogen bonding inside the polymer structure. Water may now permeate the molecule, and the polymer is cold-water-soluble. CCS is an internally crosslinked carboxymethyl cellulose sodium polymer. It has a high swelling capacity with little gelling, which results in quick disintegration [29]. Croscarmellose particles have wicking properties due to their fibrous structure. All three super disintegrants utilized demonstrated rapid disintegration with minor variances, and SSG was deemed the best based on the results.

In vitro dissolution experiments of all formulations revealed a discernible difference. Stability studies should be conducted on drug product properties that are susceptible to change during storage and are expected to affect quality, safety, and efficacy. The ICH specifies both the duration of the inquiry and the storage conditions: The current investigation involves accelerated stability studies for the selected formulations SDC6 at accelerated temperatures of 40±2 °C and 75 % RH for up to 6 months. At regular intervals, the tablets' physical appearance, drug content, disintegration time, and in-vitro drug release were all evaluated. A one-way ANOVA was performed on the acquired values, followed by Dunnett's test. The statistically processed findings revealed statistically significant differences at $p<0.05$.

The carrageenan test is highly sensitive to nonsteroidal anti-inflammatory drugs and has long been accepted as a useful model to determine the anti-inflammatory effects of natural products. In the present study, the anti-inflammatory activity of FCD and super disintegrant was investigated by an experimental carrageenan animal model. In our study, the induction of carrageenan in the rat hind paw started off the vascular phase of inflammation, which was characterized by temporary vasoconstriction and vasodilatation that generated an increase in the size of the oedema for all groups. The excipients such as polymers, super-disintegrants and multifunctional fillers have been included in dosage forms to increase the apparent solubility of drugs. Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in tablet formulations. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Sodium starch glycolate is modified starch with dramatic disintegrating properties and is available as explotab and primogel, which are low-substituted carboxy methyl starches. The mechanism behind this is the rapid absorption of water, leading to an enormous increase in the volume of granules, resulting in rapid and uniform disintegration. From the data of *in vivo* studies, it was assumed that Group IV formulation containing FCD+SSG (SDC6) formulation exhibited more significant inhibition compared with the other groups, including the control. This significant anti-inflammatory activity may be due to the synergistic action of FCD and Superdisintegrant, resulting in the better suppression of various inflammatory mediators in prostaglandin synthesis, cytokinin production and leucocyte migration. Hence, it can be concluded that the SSG at 4 % acts as a good super disintegranting agent and shows promising additive anti-inflammatory activity with FCD in quick relief of pain.

Study limitations: There are several potential limitations to using DMSO solvent during spray drying technology. As a carrier for fenoprofen calcium dihydrate, we employed solely β-cyclodextrin, coupled with skimmed milk powder, which is a nutritional component. SMP readily absorbs moisture thus storing it is usually a special precaution. Furthermore, including SD into MDT with other excipients may be difficult.

Prospects for further research: This study used only one carrier, and three super disintegrants. In future may be added with more carriers and natural super disintegrants.

6. Conclusions

Solid dispersion with β-cyclodextrin, and skimmed milk powder is the method for increasing disintegration

time by enhancing the solubility of poorly water-soluble FCD, and it is prepared by spray drying technology. The result of micrometric evaluations revealed that the SD formulations showed good flow properties. The SDs C2 was selected for the formulation of MDTs for FCD. The formulation SDC6 showed the highest entrapment of the drug. Significant differences were observed in in vitro dissolution studies of FCD mouth-dissolving tablets. Drug product features that are susceptible to change during storage and are expected to affect quality, safety, and efficacy should be assessed in stability studies to demonstrate that the optimal formulations remain stable during the course of the study. By using one-way ANOVA followed by Dunnett's test, the results of stability experiments were statistically significant at $p<0.05$. During the in vivo anti-inflammatory experiments, the formulation SDC6 demonstrated a higher percentage of inhibition than the pure drug and super disintegrant, and the results were statistically significant using a one-way ANOVA followed by the Bonferroni test.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

Data will be made available at a reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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