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Formulation of Furosemide Oral Disintegrating Tablets Using Natural and Synthetic Superdisintegrants by SeDeM Expert Design System

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ABSTRACT

SeDeM design expert technique used to evaluate the risks of poor flow of pharmaceutical powders under preformulation studies which reveals direct compression suitability and prepare robust composition of active pharmaceutical ingredient (API) and excipient in tablets formulation. The purpose of this study was to develop oral disintegrating tablets of Furosemide using different concentration of natural and synthetic superdisintegrants by means of SeDeM design technique. Oral disintegrating tablets (ODT) of Furosemide were prepared by direct compression technique using isolated banana powder and croscarmellose sodium (Ac-di-sol) together with microcrystalline cellulose as superdisintegrants. SeDeM design was performed to check suitability and deficient of excipients and drug for optimized composition derived based on IPP value. These tablets were evaluated for hardness, friability, drug content, weight variation, wetting time and *in-vitro* dissolution. All the formulations showed low weight variation with dispersion time less than 173.5±0.70 seconds and rapid *in-vitro* dissolution. The drug content of all the formulations was within the acceptable limits. Lubricated blend composition of F4 found average radius value 5.24, 0.66 and 5.509 for IGC, IP and IPP respectively, compressed tablet shown good physical properties. The optimized formulation F4 showed good release profile with 99.25 percentage drug release compared to other trial batches. It was concluded that natural superdisintegrant (banana powder) showed better disintegrating property than synthetic super disintegrant (Ac-di-sol) in the formulations of ODTs.

Keywords: Furosemide, Oral disintegrating tablets, SeDeM expert system, Superdisintegrants

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INTRODUCTION

Oral disintegrating tablets is rapidly gaining acceptance as an important new drug delivery technology. ODTs are intended to disperse, dissolve, or disintegrate quickly in the mouth cavity due to saliva, which results in release of the drug due to rapid absorption of the medium into the tablet core followed by prompt tablet disintegration under the effect of superdisintegrants [1]. Orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. Moreover, patients travelling with little or no access to water, limit utility of orally administered conventional tablets or capsules [2]. Drug candidates that undergo pre-gastric absorption when formulated as ODTs may show increased oral bioavailability. The natural origin polymer is preferred over semi-synthetic and synthetic substances because they are comparatively cheaper, abundantly available, non-irritating and non-toxic in nature [3-4].

A direct compression method has many advantages such as low cost, just enough conventional equipment, less processing steps. In addition high doses of drug, heat and moisture sensitive drugs could be prepared by this method [5]. But due to poor flow property and deficient properties of drug during drug product manufacturing campaigns were faced lot of problems. In direct compression case its recommended to employ excipient which has good flow or which are directly compressible grade qualitatively, to incorporate such excipient quantitatively is always a task for the formulator. While developing the formulation, cautious and specific to select concentration of excipient is important to be achieving by accessing inactive ingredient database of USFDA which provide the safe level of particular excipient as per dosage form and route of administration as well. In the current SeDeM expert system shows the suitability of API and excipient for direct compression process and % concentration of excipient or polymer to be incorporated in the formulation to mask poor flow characteristic of API. This optimization tool is well reported in literature as well as in scientific books [6]. For the present study different excipient

is used to correct the API's poor flow and make it suitable for direct compression using (SeDeM) Secure Development Method expert system. This system provides prediction of flow and a physical profile of drug and excipients intended to be used [7]. SeDeM expert system may be coined as time saving as this technique may reduce no of trials. Due to the ability of prediction for deficient part this technique may serve as economic and choice of technique compared to other time consuming conventional trial and error approach or software based prediction models.

Furosemide (FUR), 5-(aminosulphonyl)-4-chloro-2-[(2-fuanyl-methyl) amino] benzoic acid, is a potent loop (high ceiling) diuretic used in the treatment of edematous states associated with congestive heart failure, cirrhosis of the liver, renal disease and chronic hypertension. According to the biopharmaceutical classification system (BCS), FUR is classified as a class IV drug due to its low solubility (5–20 mg/mL) and low permeability. Therefore, low oral bioavailability of FUR has been reported. Because of its weak acidic properties (pKa 3.8), furosemide is mostly absorbed in the stomach and upper intestine, but also from the oral mucosa following sublingual administration [8]. Therefore, the purpose of this study was to optimize suitable blends using SeDeM expert system, formulate and evaluate a furosemide ODT by means of a direct compression method. The effects of the superdisintegrants i.e. croscarmellose sodium and banana powder on the tablets disintegration, dissolution and swelling properties of ODT were compared.

MATERIALS AND METHODS

Materials

Furosemide was gifted by Glen mark pharmaceuticals Pvt. Ltd. Nashik, India, croscarmellose sodium, aspartame and magnesium stearate were gifted by Gebbs pharmaceuticals Pvt. Ltd, Nashik, India. Banana powder was obtained from Saipro food, Pune, India. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Methods

Drug-excipients compatibility

Compatibility studies of pure drug and excipients were carried out using Fourier transformed infrared spectrophotometer (Shimadzu, Japan) in the range of 400-4000 cm^{-1} by KBr disc method. A base-line correction was made using dried potassium bromide and then the spectrum of the pure furosemide and physical mixture (drug/excipients) were obtained.

Parameters of SeDeM expert system for material properties [9]

Powder material including excipient and drug was evaluated for different parameters according to the SeDeM expert system to determine their suitability for direct compression. Some of them were determined experimentally according to the established procedure and some were calculated from experimental values as per Table 1.

1) Bulk density (Da) and Tapped density (Dc)

Graduated cylinder was employed for density measurements and the volume taken was the value obtained before and after 250 strokes using a settling apparatus.

2) Inter-particle porosity (Ie), Carr index (IC %) and Hausner's ratio (IH)

The inter-particle porosity, Carr index and Hausner's ratio of the drug powder was calculated by the following equation given in Table 1.

3) Cohesion index (Icd)

The cohesion index was determined by directly compressing the drug powder using an eccentric press. The hardness (N) of the obtained tablets was determined.

4) Angle of repose (α)

Angle of repose is the maximum angle possible between the surfaces of apex of the powder to the horizontal plane. The accurately weighed powder and blend it then it was put in the funnel. The height of the funnel was adjusted as per specification in such a way the tip of the funnel just touched to the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The radius of the cone base was measured with a slide caliper and the mean value (r) was calculated. Additionally, the cone height (h) was measured and the angle tangent value (α) of the cone was calculated employing the following equation: $\tan \alpha = h/r$.

5) Flowability (tn)

The flow rate described herein as flowability was determined in accordance with the method described in Section 2.9.16-2 of European Pharmacopoeia as the time for a fixed amount of powder to flow through a glass tunnel with 0.85 cm orifice diameter. It was expressed in seconds and tenths of a second per 100 gm of sample, with the mean value of three determinations always being taken.

Table 1: Parameters of SeDeM expert system along with limits and factors

Incidence factor	Parameter	Unit	Equation (v)	Limits	Radius (r)
Dimension	Bulk density (Da)	g/mL	Da=P/Va	0–1	10v
	Tapped density (Dc)	g/mL	Da=P/Vc	0–1	10v
Compressibility	Inter-particle porosity (Ie)	-	Ie=Dc-Da/Dc×Da	0–1.2	10v/1.2
	Carr index (Ic)	-	Ic= (Dc-Da/Dc)×100	0–50	v/5
	Cohesion index (ICD)	N	Experimental	0–200	v/20
Flowability/ powder flow	Housners ratio (IH)	-	IH=Dc/Da	3–1	(30-10v)/2
	Angle of repose (α)	°	tan θ=h/r	0–50	10-(v/5)
	Powder flow (t^n)	S	Experimental	0–20	10-(v/2)
Lubricity/ stability	Loss of drying (% HR)	%	Experimental	0–10	10-v
	Hygroscopicity (%H)	%	Experimental	0–20	10-(v/2)
Lubricity/ dosage	Particle <5µm (%Pf)	%	Experimental	0–50	10-(v/5)
	Homogeneity index (Iθ)	-	Iθ=Fm/100+Fmn	0-2×10^2	500v

6) Loss on drying (% HR)

Excipient was dried in a convection oven at 105°C ± 2°C until a constant weight is obtained.

7) Hygroscopicity (% H)

The hygroscopicity of a powder is its equilibrium moisture content after being exposed to air humidity under given conditions. It was determined by calculating the increase in sample weight after being kept in a humidifier at ambient relative humidity of 76% ± 2% and a temperature of 22°C ± 2°C for 24 h.

8) Percentage of particles measuring < 50 µ (% Pf)

Particle size was determined by means of the sieve test in accordance with the General method 2.9.12 of European Pharmacopoeia and was expressed as the % of particles that pass through a 0.05 mm sieve, when vibrated for 10 min at speed 10 using a sieve vibrator.

9) Homogeneity index (Iθ)

The method for determination of Iθ was based on General method 2.9.12 of European Pharmacopoeia for determining particle size by means of the sieve test. The grain size of a 100 g sample was determined by submitting a sieve stack to vibration for 10 min at the speed 10 using a sieve vibrator. Sieve sizes used were: 0.355, 0.212, 0.100 and 0.05 mm. The percentage of product retained in each sieve and the quantity that passes through the 0.05 mm sieve were calculated. The percentage of fine particles (<50µ) determined previously in a separate operation was considered. The following equation 1 was then applied to the data obtained:

$$I\theta = Fm/(100 + (dm - dm - 1)Fm - 1(dm + 1 - dm)Fm + 1(dm - dm - 2)Fm - 2(dm + 2 - dm)Fm + 2 \ldots . (dm - dm - n)Fm - n(dm + n - dm)Fm + n) \ldots\ldots\ldots\ldots (1)$$

Where, Iθ= Relative homogeneity index, Fm= % of particles in the majority range, Fm−1=% of particles in the range immediately below the majority range, Fm+1= % of particles in the range immediately above the majority range, n= order number of the fraction studied under a series, with respect to the major fraction, dm= mean diameter of the particles in the major fraction,dm−1= mean diameter of the particles in the fraction of the range immediately below the majority range, dm+1= mean diameter of the particles in the fraction of the range immediately above the majority range.

Table 2: Distribution of particles in the determination of Iθ

Sieve mm	Corresponding fraction	Average of the diameter of the fraction	Corresponding diameter (dm ... dm ± n)	Dif dm with the mayor component
0.355-0.500	Fm+2	100	dm+2	25
0.212-0.355	Fm+1	90	dm+1	15
0.100-0.212	Fm	75	dm	0
0.050-0.100	Fm-1	66	dm-1	9
< 0.050	Fm-2	52	dm-2	23

Conversion of experimental values to radius value for graphical presentation of SeDeM diagram

The numerical values for different parameters of the material obtained by experimental determination were converted into a radius value 'r' of the SeDeM expert system diagram. For the conversion of experimental value of each parameter, specific factors were applied4 as listed in Table 1. SeDeM diagram was drawn on the basis of 12 parameters [10]. Results obtained from the experimental determination of various parameters were converted and presented as a SeDeM diagram (figure 1).

Calculation of acceptance values of indices

For determination of suitability of the material for direct compression the following indices are calculated on the basis of the SeDeM system [11].

Parameter index

$$I.P. = No.\ P \geqslant / 5\ No.\ Pt \ldots\ldots\ldots (2)$$

Where, No. P ⩾ 5 = Parameters with values equal to or more than 5; No. Pt = Total number of parameters.

Parameter profile index

I.P.P. = Average of radius all parameters

Average (r) = mean radius value of all parameters/ no. of parameters..... (3)

Good compressibility index

$$I.G.C. = I.P.P. \times f \ldots\ldots\ldots\ldots\ldots (4)$$

Where, f = Reliability factor = Polygon area / Circle area

The acceptability limit is greater than and equals to 5 in all cases. For 12 parameters f value = 0.952, for 8 parameters f value =0.900

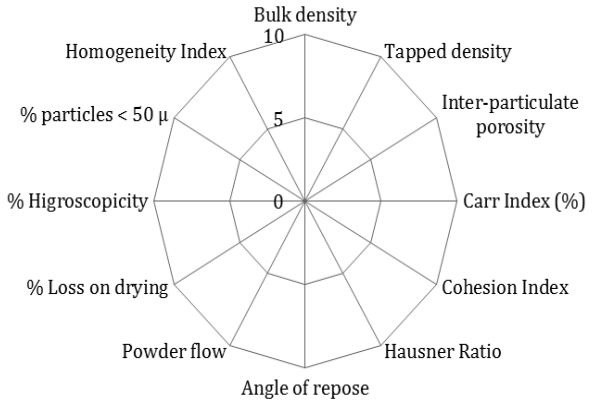

Figure 1: SeDeM diagram for 12 parameters

Application of SeDeM expert system to overcome deficient API properties [9]

For correction the deficiency of poor flow API required amount of excipient was determined using equation 4. This equation allows calculation of the amount of excipient required to compress the API on the basis of the SeDeM radius considering 5 (min) for each parameter of incidence which allows correct compression;

$$CP = 100 - [(RE - R)/(RE - RP) \times 100] \ldots\ldots\ldots\ldots (4)$$

Where CP = % Corrective Excipient; RE = mean-incidence radius value (compressibility) of the corrective excipient; R = mean-incidence radius value to be obtained in the blend; RP = mean-incidence radius value (compressibility) of the API to be corrected.

Blending and tableting for oral disintegrating tablet

Oral disintegrating tablet of furosemide were prepared by using direct compression method based on the radius values obtained on API and excipient as well as % corrective excipient requirement formulation F1 to F6 derived according to the formulae as shown in Table 3. This method involves a simple procedure of blending of API with other ingredients and the resulted mixture is subjected to direct compaction. The required ingredients were taken in a mortar and the powder blend was mixed for a time period of 15-20 min by using mortar and pestle. Then each mixture was passed through sieve no.60 and finally magnesium stearate was added as lubricant and thoroughly mixed. The blend were subjected to 12 test of SeDeM as per Table 1, result obtained were calculated for radius values, on the basis of radius values SeDeM diagram was plotted, acceptance values were calculated using parameter index, parameter profile index and good compressibility index equations of composition whose blend yielding higher IPP value (mean r of all parameters) was considered as optimized batch for further evaluation. The ooptimized powder blend was compressed in to tablets on twelve station rotary punch-tableting machine (Karnavati, Rimek Mini Press- 2) using 8 mm concave punches.

Table 3: Formulation of Furosemide ODT by direct compression method

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Furosemide	20	20	20	20	20	20
Microcrystalline cellulose	100	120	115	121	117	110
Cross carmellose sodium	8	10	15	-	-	-
Banana powder	-	-	-	9	13	20
Mannitol	44	44	44	44	44	44
Magnesium Stearate	4	4	4	4	4	4
Aspartame	2	2	2	2	2	2

Evaluation of Furosemide ODT

Quality control tests such as thickness, diameter and hardness, weight variation, friability, wetting time and water absorption ratio, disintegration and dissolution were performed on the ODTs.

Thickness, diameter and hardness determination

The thickness and diameter of 10 tablets from each formulation was measured using a Vernier caliper. The hardness of tablet of each formulation was measured by Monsanto hardness tester. Thickness, diameter and hardness tests were performed on ODTs using Pharma Test PTB, Germany. Thickness, diameters (mm), and hardness (kg/cm^2) values were expressed as an average of 10 measurements.

Weight variation

20 tablets were chosen randomly and then weighed individually using an analytical balance. The mean weight was calculated, and individual tablet weight was compared to the mean weight to assure whether it was within permissible limits or not.

Friability test

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the Roche friabilator, rotating at 100 rpm for 4 min. The tablets are then taken out, dedusted and were weighed. The difference in the weight is noted and expressed as percentage.

Content uniformity

Twenty tablets were crushed and powder equivalent to weight of one tablet was dissolved in phosphate buffer 6.8. Then suitable dilutions were made and absorbance at 276 nm wavelength was taken by using a UV visible spectrophotometer.

Wetting time and water absorption ratio

For measurement of wetting time and water absorption ratio of ODTs, a piece of tissue paper folded twice was placed in a petri dish with a 10 cm diameter containing 6 mL of purified water. A previously weighed tablet was placed on the surface of the tissue paper, and the time to wet the tablet completely was noted as the wetting time [12]. The fully wetted tablet was weighed and the water absorption ratio, R, was calculated as follows,

$$R = 100 (Wa-Wb)/Wb \quad (5)$$

Where, Wb is weight of tablet before water absorption Wa is weight of tablet after water absorption.

Disintegration time

Disintegration test was performed according to the Ph. Eur. 8th with six tablets, and distilled water as the medium. The time required for complete disintegration of each tablet was recorded individually.

***In-vitro* dissolution tests for ODT**

Dissolution test was performed on six ODTs in 900 mL of pH 5.8 phosphate buffer at 37±0.5°C using Apparatus 2 (paddle method, 50 rpm). At predetermined time intervals (5, 10, 15, 20, 30, 45, 60 min); samples (2 mL) were withdrawn and replaced with fresh dissolution medium. The samples were filtered through 0.45 µm membrane filter and analyzed on UV spectrophotometer (Shimadzu 1800) at 276 nm to determine drug content.

Stability study

Stability studies at 40°C ±2°C /75% ± 5% RH was carried out for 3 months for optimized tablets (F4). The oral disintegrating tablets were observed for colour, friability, hardness, disintegration time, *in-vitro* drug release and assay 3 months respectively [13].

RESULTS AND DISCUSSION

FTIR studies were conducted and the spectrum was recorded in the range of 4000-400cm^{-1}. The study of IR spectra of Furosemide shows Carboxylic acid (COOH), S=O stretching vibrations of sulphonamide group, N-H stretching vibration of secondary amine, C=O stretching, and C-Cl stretching vibrations appeared at 1440-1395, 1370-1335, 3350-3250, 1310-1250 and 550-850 cm^{-1} respectively [14]. The major peaks of physical mixture of formulation F4 after compression was found to be 1570.12, 1319.37, 3398.72, 1249.93, 668.97 cm^{-1} for Carboxylic acid (COOH), S=O

stretching vibrations of sulphonamide group, N-H stretching vibration of secondary amine, C=O stretching, and C-Cl stretching vibrations respectively. It was observed that there were no changed in these main peak in IR spectra of mixture of drug and polymer after compression of tablet, which show there were no physical interaction. The peak obtained in the spectra of each formulation correlate with the peak of drug spectrum.

The choice of excipients is very important for the development of a tablet formulation and also for the quality control of dosage forms. A very limited number of excipients are used for direct compression due to flowability, compressibility, and stability properties. MCC is widely used as filler in tablets but cause an increase in the dissolution rates and hardness of tablets compared to other fillers. ODTs disintegrate in the mouth in a short period of time, so that taste masking is very important especially for bitter tasting active ingredients. Various parameters of a powder blend according to SeDeM system estimated for suitability of direct compression. 12 parameters values determined for the ODT powders are listed in figure 2. Furosemide is white a poor flow powder by 12 parameters as per SeDeM system. The flow property of the Furosemide was improved by addition of excipients which have 5 and above radius values. The radius values of API shows that the bulk density (3.846), tapped density (4.166), inter particle porosity (1.66), cohesive index (4.35), angle of repose (2.65), flow property (2), and homogeneity index (4.35). Firstly, improved the dimension (bulk density, tapped density) of the Furosemide that shows mean radius under the value 5 which improved by addition of the mannitol in it because it's mean radius value is above 5 (6.427) which is largest in all excipients. Void fraction of tapped and loosely packed powder particles have been used for determination of size, void space and shape of particles (Figure 2).

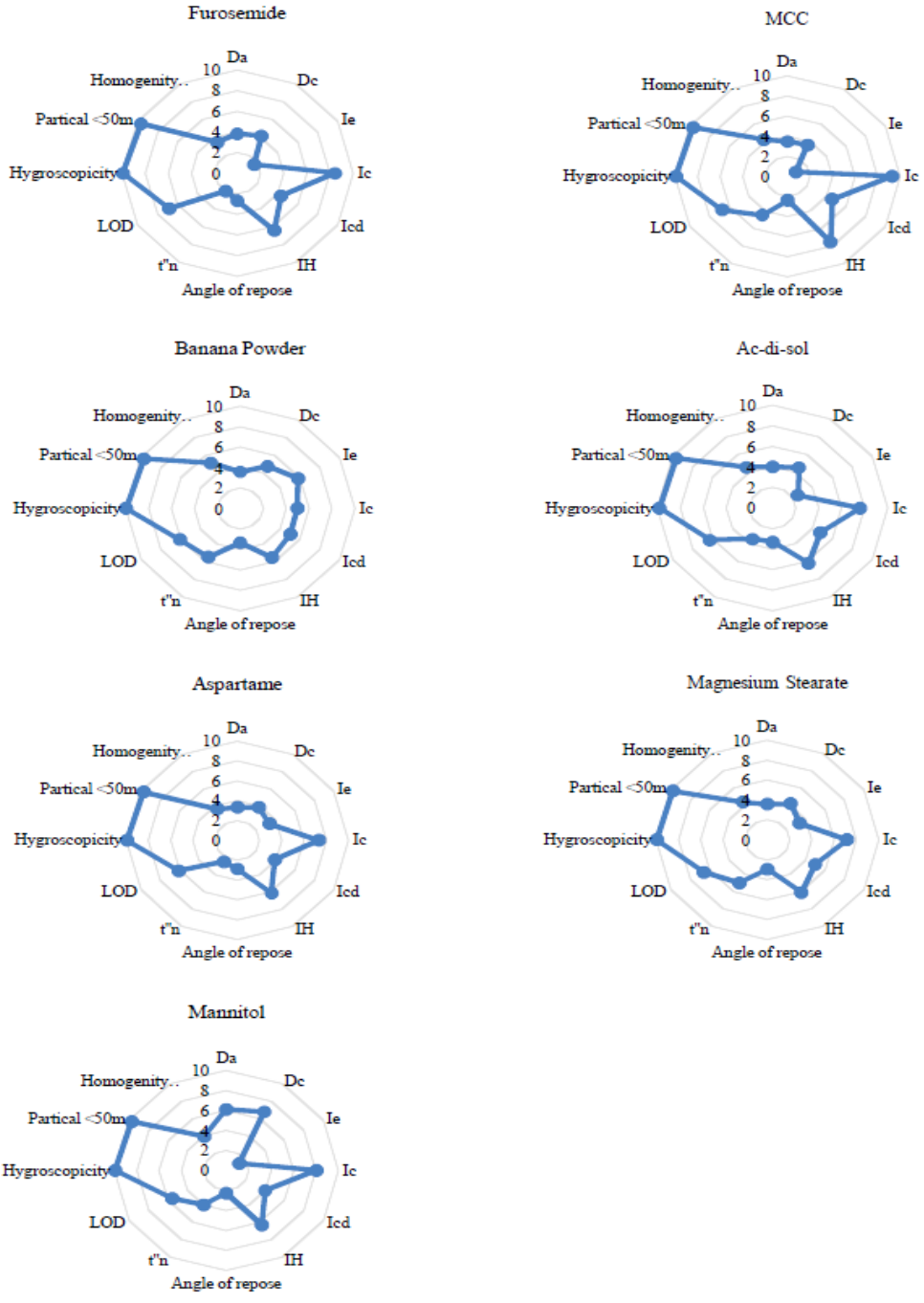

Figure 1: SeDeM diagram of excipients and furosemide

Then improved the compressibility (inter particular porosity and cohesive index) of Furosemide by addition of the MCC and cross carmellose sodium that they shows the compressibility parameters (Ie & Icd) near to the acceptable mean values 4.914 and 4.97 respectively and banana powder shows 5.29 which was largest mean value in all among and improve the compressibility of Furosemide. Cohesive index for the stability of drug and by addition of this above excipients stability of drug also improved. The flow property (angle of repose & flow property) was improved by addition of MCC and banana powder. LOD of all parameter were good enough, and it measured the amount of water and volatile matter present in the sample when the sample was dried under specific temperature condition. High hygroscopicity is undesirable for many reasons that include handling problem, storage conditions, physical stability and chemical stability problem. By addition of excipients having mean value above the acceptable limit were fulfil the requirement of the API and increases the compressibility and flow rate of Furosemide. Index value by SeDeM required amount of excipient was calculated and shown in Table 4.

Table 4: Index Value

Parameter	IPP	IP	IGC
Furosemide	**5.21**	**0.42**	**4.96**
Mannitol	5.66	0.66	5.39
MCC	5.57	0.5	5.3
Aspartame	5.23	0.5	4.98
CCS	5.57	0.5	5.3
Magnesium Stearate	5.65	0.58	5.38
Natural Polymer	5.79	0.75	5.51

Formulations and development of Furosemide oral disintegrating tablets

Two different Furosemide containing ODT formulations were developed by using cross carmellose sodium and banana powder as a super disintegrants. All six formulation blend was further processed through SeDeM parameters in order to finalized optimized formulation, values reported in Table 5.

Table 5: Radius parameters, mean incidence and parametric index for blend

Formulation		F1	F2	F3	F4	F5	F6
Radius values	Da	5	5	4.8	5	5	4.55
	Dc	5.6	6.3	5.9	6.7	6.3	6.25
	Ie	1.7	3.3	3.3	4.2	3.3	5
	Ic	8	6	6.2	5	6	4.55
	Icd	6	7.7	7	6	6.6	5.55
	IH	6.3	5.8	5.9	5.6	5.8	5.42
	(a)	6.1	5.2	5.7	3.5	4.3	4.84
	t''n	4.5	3.5	2.5	5.5	4	3
	LOD	5.9	6.5	4.8	4.2	3.7	6.67
	% H	9.9	10	10	10	10	9.95
	% Pf	9.6	9.7	9.6	9.6	9.8	9.82
	(IQ)	2.6	3	1.3	1	1.1	1.49
Incidence Factor	Dimension	5.3	5.6	5.3	5.8	5.6	5.4
	Compressibility	5.2	5.7	5.5	5.1	5.3	5.03
	Flowability/ Powder flow	5.6	4.9	4.7	4.8	4.7	4.42
	Lubricity/ Stability	7.9	8.2	7.4	7.1	6.9	8.31
	Lubricity/ Dosage	6.1	6.3	5.4	5.3	5.4	5.65
Index	IPP	5.9	6	5.6	5.5	5.5	5.59
	IP	0.8	0.8	0.6	0.7	0.6	0.66
	IGC	5.7	5.7	5.3	5.3	5.2	5.32

The blend of excipients and drug was nearer to the acceptable range and dimension, compressibility lubricity, stability and compressible because it shows all values are above the acceptable limit 5. From the results, formulation F4 containing natural super disintegrants was reliable in all parameters among natural formulations (F4, F5, and F6) which show IGC, IP and IPP were 5.24, 0.66 and 5.509 respectively. Formulation F3 containing synthetic super disintegrants was good for the compression by its IGC, IP and IPP value were 5.30, 0.58 and 5.57 among all batches (figure 3). All 12 parameters of the SeDeM were obtained within limit and showed good flow property required for direct compression method.

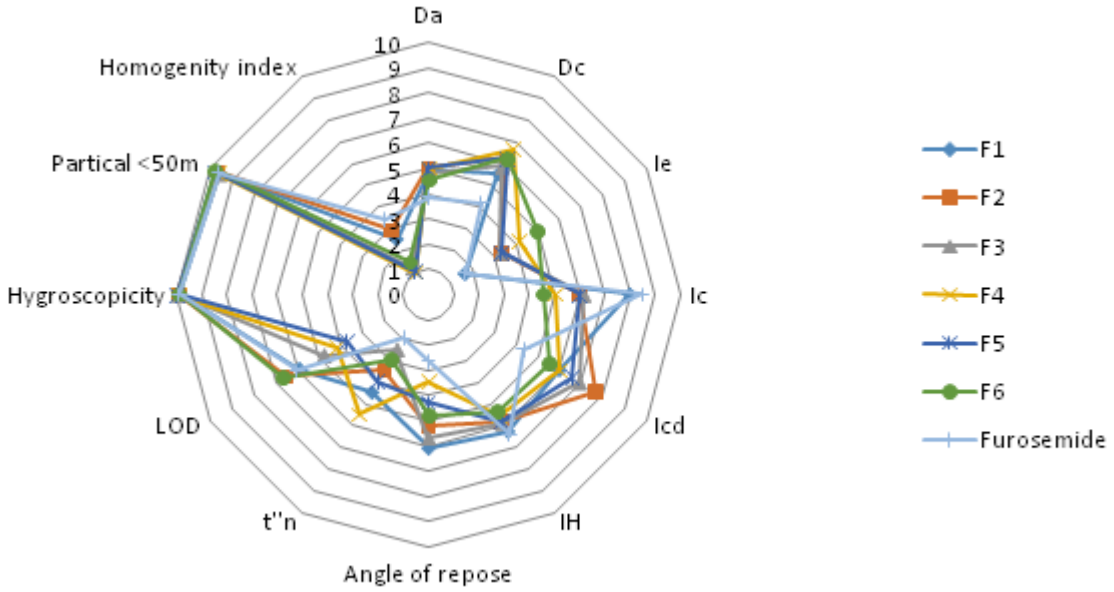

Figure 3: SeDeM diagram of furosemide ODT

Post formulation evaluation

The post compression parameter was performed and results were tabulated in Table 6.

Table 6: Evaluation of Post-compression parameters

Parameter	F1	F2	F3	F4	F5	F6
Thickness	4.4±0.12	4.5±0.14	4.3±0.07	4.5±0.04	4.5±0.13	4.4±0.10
Friability (%)	0.94±0.06	0.83±0.04	0.86±0.08	0.88±0.07	0.97±0.06	0.92±0.03
Hardness kg/cm^2)	2.3±0.08	2.4±0.15	2.5±0.18	2.4±0.16	2.5±0.19	2.3±0.09
Diameter (mm)	8	8	8	8	8	8
weight variation	199.5±0.70	200.5±0.70	201±1.41	200.5±0.70	201±0.1	200±1.41
Drug content uniformity	100.8±0.18	95.16±0.24	96.65±0.64	100.5±0.09	98.61±0.12	96.89±0.21
Disintegration time (sec)	143±2.82	157.5±2.12	173.5±0.7	16±1.41	34±2.82	129.5±2.12
wetting time (sec)	100±1.41	53±2.82	14±2.82	10±2.82	20±2.82	41±2.82
Water absorption ratio (%)	56.40±1.9	35.85±4.7	64.40±3.9	117.59±4.2	118.25±2.4	43.70±3.3

All values are expressed as mean± standard deviation

The thickness of tablets was found to be 4.3±0.07 to 4.5±0.14 mm while hardness results were in the range of 2.3±0.08 to 2.4±0.16 kg/cm^2. The drug content for all formulation was found to be in the range of 96.89±0.21-100.5±0.09% which was within the acceptable limits. All the formulations disintegrated within 173.5±0.70 second. Formulations with Banana powder as superdisintegrant showed faster disintegration than Ac-di-sol formulations. Tablets obtained were of uniform weight with acceptable variation as per IP specifications i.e. below 7.5%. From the result, formulation F4 shows 10±2.82 second, 117.59±4.22 and 16±1.41second respectively for wetting time (less), water absorption capacity (high), and disintegration time (less) having all this values in acceptable range while F1 shows very poor wetting time 100±1.41 sec, water absorption ratio 56.40±1.90 % and disintegration time 143±2.82 second (Table 6). *In-vitro* drug release studies were performed and shown in figure 4. The formulations which contain banana powder (F4) as super disintegrating agent has shown 99.41% of drug release, formulations with Ac-di-sol (F3) as super disintegrating agent has shown 91.5% of drug release at the end of 10 min. Banana powder due to its water absorption ratio (117.59±4.22%) created enough hydrodynamic pressure for quick and complete disintegration of the tablet.

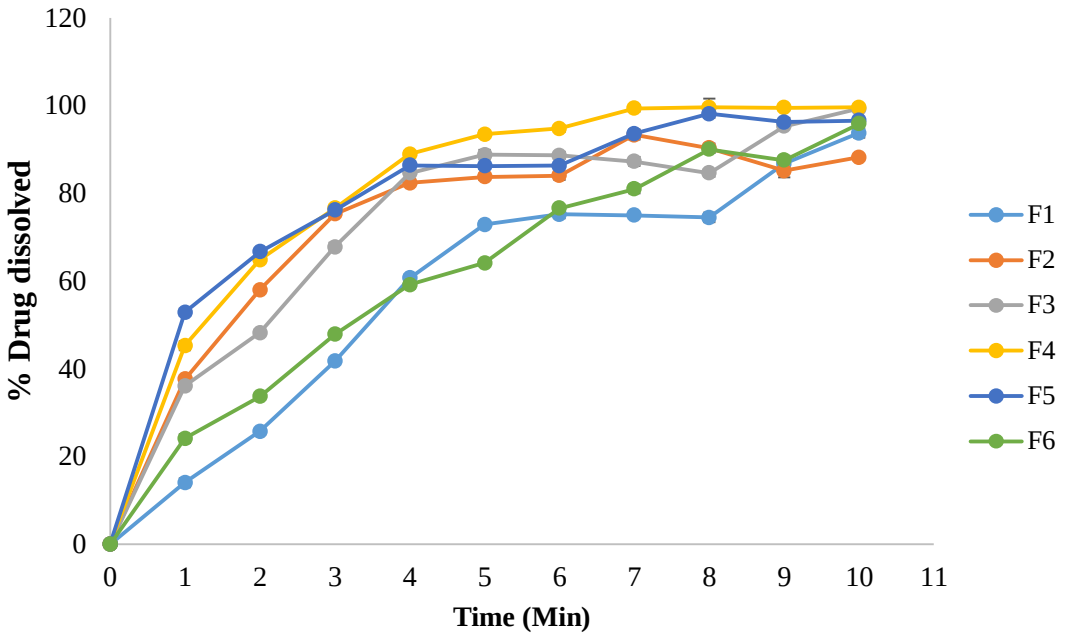

Figure 4: *In-vitro* release profile of formulation F1-F6

From the results, formulation F3 and F4 showed the good effect on fast disintegration and dissolution time period (91.5% and 99.41 % within 10 respectively). Stability studies for the optimised formulation F4 were carried out by storing the selected formulation at 40°C±2°C/75%±5% RH for three months tabulated in Table 7. For every one month interval the tablets were analyzed for the colour, friability, hardness and *in-vitro* drug release. There was no significance change in all the parameters. The F1 (dissimilarity value) and F2 (similarity value) for drug release profile at 30±2⁰C and 65±5% RH were 3.07 and 72.02 respectively while for drug release at 40±2⁰C and 75±5%RH were 2.51 and 78.51 respectively which indicated that the formulation was stable after 90 days and complies for stability test.

Time (days)	Condition	Drug Content	Hardness (kg/cm²)	*In-vitro* dissolution after 10 min
At 0 stage	--	99.5±0.09	2.46±0.05	99.58
after 30	30±2⁰C & 65±5% RH	99.33±0.045	2.43±0.11	97.95
	40±2⁰C & 75±5% RH	99.78±0.09	2.4±0.09	97.56
after 90	30±2⁰C & 65±5% RH	98.29±0.64	2.3±0.05	98.68
	40±2⁰C & 75±5%RH	98.14±0.62	2.3±0.09	98.52

CONCLUSION

SeDeM system gives accurate prediction of material of poor flow and reduces the number of batches and cost. SeDeM design system is helpful for formulation and development of Furosemide oral disintegrating tablets and formulation F4 containing natural polymer (Banana powder) are suitable and reliable super disintegrants in order to improve disintegration/dissolution of the drug in oral cavity as compared to synthetic polymer (Cross carmellose cellulose) for formulation of oral disintegrating tablets by direct compression method.

CONFLICTS OF INTERESTS

The Author(s) declare(s) that they have no conflicts of interest to disclose.

AUTHORS CONTRIBUTION

Shende Mulchand A.: Participated in its design, coordination and helped to draft the manuscript,

Chavan Kajal D.: Collected the data, and analysed the data, participated in the design of the study. All authors read and approved the final manuscript.

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