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SUSTAINED RELEASE MULTI-PARTICULATES FORMULATION OF STEREO-SELECTIVE MOLECULE OF KETOPROFEN BY FLUID BED PROCESSOR

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ABSTRACT: The aim is to prepare sustained release multi-particulates dosage form of Dexketoprofen trometamol, which is the active isomer of ketoprofen. Utilization of active moiety with minimum drug dose and administration frequency sustained-release multi-particulates dosage form is explored. Sustained release pellets of the dexketoprofen trometamol were developed by the fluidized bed technology, in which drugs along with a binder and anti-adherent agents, were loaded onto microcrystalline cellulose inert beads. These drug-loaded pellets were again coated with Kollicoat SR 30D as sustained-release coating polymer, triethyl citrate as plasticizer and talc as an anti-adherent. The formulation was further statistically optimized for agglomerates formation, process efficiency, and drug release profile using central composite design (CCD). Results show that 16.9 to 18.5% w/w sustained release coating with 9.0-14.6% w/w talc and 8.1 to 16.5% w/w triethyl citrate concentration gives desired drug product quality attributes. Sustained-release multi-particulates were successfully developed for dexketoprofen trometamol, which maybe explored to manufacture various dosage forms like capsules, compressed tablets, pellets in sachet *etc*. for ease of patient compliance.

INTRODUCTION: Chirality phenomenon has play a major role in the synthesis and development of new drug therapy to achieve better therapeutics index [1]. A molecule is referred to as chiral if it is not superimposable to its mirror image. The best example of chirality is our hand [2]. Majority molecules of importance to living systems are chiral *e.g.,* amino acids, sugars, proteins, and nucleic acids [3]. Major advantages of chiral switching include: (1) an improved therapeutic index through increased potency and selectivity and decreased side-effects; (2) a faster onset of action; (3) a reduced propensity for drug-drug interactions, and (4) exposure of the patient to a lower dosage [4].

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Dexketoprofen trometamol (DT) is a water-soluble salt of the dextrorotatory enantiomer of the NSAID ketoprofen [5]. Racemic Ketoprofen has been used since 1973 as an anti-inflammatory, analgesic and antipyretic active drug substance and is one of the most potent *in-vitro* inhibitors of prostaglandin synthesis [6, 7]. Dexketoprofen trometamol administration was found to be highly effective in treatment of moderate to severe pain when used as an analgesic in osteoarthritis, dysmenorrhea, gynecologic, orthopedic, and dental surgery [8]. This effect is because of the S (+)-enantiomer of dexketoprofen while R (-) - enantiomer is devoid of such action [9]. DT is not official in any pharmacopeia [6].

DT is well absorbed in the gastrointestinal tract when administered orally owing to its high aqueous solubility. Commercial oral DT tablets are needed to be administered 3-6 times daily due to DT's shorter elimination half-life (1.2-2.5 h) [10]. Additionally, side effects of oral immediate-release

DT tablets include gastrointestinal disturbances such as gastrointestinal discomfort, nausea, diarrhea, and gastrointestinal bleeding like other NSAIDs. A sustained-release oral formulation of DT has the potential of reducing the frequency of administration and side effects and thus improve patient compliance.

These multiple-unit doses are usually formulated in the form of suspensions, capsules, or orally disintegrating tablets, showing a number of advantages over the single-unit dosage system. The subunits of multiple-unit preparations distribute readily over a large surface area in the gastrointestinal tract, and these small particles (<2 mm) behave like liquids leaving the stomach within a short period of time. Their small size also enables them to be well distributed along the gastrointestinal tract that could improve the bioavailability, which potentially could result in a reduction in local drug concentration, risk of toxicity, and side-effects [11].

Widely used techniques to manufacture sustained-release pellets are extrusion-spheronization and bottom spray fluidized bed coating process. Amongst these two techniques, extrusion-spheronization is a shorter process compare to fluidized bed coating but produce the irregular size of pellets which leads to variation in drug product critical quality attributes (*i.e.,* drug release). Therefore to achieve narrow particle size distribution and batch to batch consistency in terms of finished product quality, a fluid bed coating technique is more preferable.

During this research work, drug loading was done on microcrystalline cellulose (MCC) spheres (Celphere CP 305) using a various drug to binder ratio to provide maximum drug loading process efficiency. Neutral, insoluble substrate without smell or odor, having high mechanical strengths, and narrow particle size distribution make these Celphere CP 203 as a good candidate for drug loading and sustained release coating in wurster coating process. This drug-loaded pellets are then coated with Kollicoat SR 30D as sustained-release coating polymer, triethyl citrate as plasticizer, and micronized talc as an anti-tacking agent to get final pellet size of 400-700 micron. During research work, sustained-release coated pellets were also optimized using statistical design *i.e.,* central composite. Sustained release pellets were evaluated for particle size by sieve analysis, coating process efficiency, and dissolution.

MATERIALS AND METHODS:

Materials: Dexketoprofen trometamol (Emcure Pharmaceuticals Ltd) was used as a model drug. MCC spheres (300-500µm, Celphere CP-305, Asahi KASEI, Japan) were selected as a substrate for coating. Polyvinyl pyrrolidone (Kollidon 30, BASF Germany) was selected as a binder during drug loading process. Triethyl citrate (Merck) was used as plasticizer during sustained release coating process. Micronized talc (Luzenac Pharma M, Imerys) was selected as anti-tacking agent during drug loading and sustained release coating process.

Manufacturing of Drug-Loaded Pellets: Drug loading of dexketoprofen trometamol was performed onto MCC sphere (300-500 µm, Celphere CP-305, Asahi KASEI, Japan) by applying drug layering suspension of dexketoprofen trometamol, which is prepared by dissolving dexketoprofen trometamol into purified water with different binder concentration. Binder concentration was selected in a range of 0-7.5% of drug. Micronized talc (2% of drug) is added to the solution to minimize static charge generation and agglomerates formation during spraying process[12]. Drug loading was done in Wurster coater (ACG Pam Glatt, Model: GPCG 1.1). The final drug-loaded pellets have 110.625 mg of dexketoprofen trometamol in 218.370 mg of drug pellets.

TABLE 1: COMPOSITION OF DEXKETOPROFEN TROMETAMOL DRUG LOADED PELLETS

Ingredients	DFBP 1 (mg)	DFBP 2 (mg)	DFBP 3 (mg)	DFBP 4 (mg)
Microcrystalline Cellulose Sphere (Celphere CP305)	100.000	100.000	100.000	100.000
Dexketoprofen Trometamol	110.625	100.625	100.625	110.625
Povidone K30	0.000	2.766	5.531	8.297
Talc (micronized)	2.214	2.214	2.214	2.214
Purified Water	q.s. to 20% w/w	q.s. to 20% w/w	q.s. to 20% w/w	q.s. to 15% w/w
Total	212.840	215.605	218.370	221.136

Manufacturing of Sustained Release Coated Pellets: Sustained release coating on drug-loaded pellets were done using liquid dispersion of Kollicoat SR30 D as sustained-release polymer which contains polyvinyl acetate (PVAc, 27%) stabilized with polyvinyl pyrrolidone (PVP, Povidone, 2.7%) and sodium lauryl sulphate (SLS, 0.3%), Triethyl citrate as a hydrophilic plasticizer and micronized talc as an anti-tacking agent. Sustained-release coating was done in a range of 10-28% with solid dispersion content of 20% w/w. Triethyl citrate was used as a plasticizer at 10% w/w concentration of dry polymer solid weight, and Talc was added as an anti-tacking agent at 5% w/w concentration of total solid material. To prepare sustained release coating dispersion (20% w/w), the Part quantity of purified water was added into the dispersion under mild stirring. TEC was added to this dispersion and stirred for 30 min to make homogeneous dispersion. Talc was dispersed into remaining purified water under continuous stirring, and this dispersion was added to previously prepared polymer dispersion. This dispersion was filtered through #60 to remove any lumps in dispersion.

This dispersion was then sprayed onto drug-loaded pellets too get final sustained-release coated micropellets of 400-700 µm. Till the completion of the spraying process, the dispersion was continuously stirred to avoid talc sedimentation.

TABLE 2: COMPOSITION OF DEXKETOPROFEN TROMETAMOL SUSTAINED RELEASE COATED PELLETS

Ingredients	SFBP1 (mg)	SFBP2 (mg)	SFBP3 (mg)	SFBP4 (mg)
Drug loaded pellets	218.374	218.374	218.374	218.374
Kollicoat SR 30D dry solid polymer	18.907	30.251	41.595	52.940
Triethyl citrate	1.891	3.097	4.160	5.294
Talc (micronized)	1.040	1.664	2.288	2.912
Purified water	q.s.	q.s.	q.s.	q.s.
Total	240.212	253.386	266.417	279.519
Concentration of sustained release dispersion	20 %	20%	20%	20%
% of sustained release coating	10%	16%	22%	28%

TABLE 3: COATING PROCESS PARAMETERS

Parameters	Drug loading	Sustained-release coating
Machine/Product Bowl	GPCG 1.1 /2.4 litre	
Air distribution plate	C	
Spray nozzle diameter (mm)	1.0	
Inlet air temperature (°C)	40-55	30-45
Product bed temperature (°C)	32-38	25-35
Fluidization air volume (cfm)	45-95	45-75
Atomization air pressure (Bar)	0.8-1.2	1.0-1.3
Spray rate (g/min)	3-15	2-10
Drying temperature (°C)	55-60	45-50
Drying time (min)	15	30

Statistical Optimization of the Sustained Release Coating: After getting satisfactory results for drug release from the feasibility trial of sustained-release coated pellet, % sustained release coating, amount of plasticizer and anti-tacking agent in sustained-release coating formulation were optimized using design of experiment tool, *i.e.*, central composite design (CCD Design). During optimization study, solid content in dispersion was kept constant at 20% w/w. As % sustained release coating weight gain, amount of plasticizer, and anti-tacking agent exhibits an important role for controlling drug release from pellets, these factors were selected as independent parameters during formulation optimization study using central composite design using three center points. The dependent responses were selected as the amount of agglomerates and drug release at 1, 4, 7, and 10 h.

TABLE 4: SUMMARY OF CCD DESIGN

Independent variable	Level	
	-1	+1
% Coating weight gain	10.00	25.00
% w/w of plasticizer with respect to dry polymer	5.00	20.00
% w/w of Talc with respect to total coating solid	5.00	20.00
Response to be studied		**Limit**
Coating Process Efficiency		NLT 90%
Agglomerates		NMT 3% w/w
Drug Release at 1 h		15 – 25%
Drug Release at 4 h		40 – 50%
Drug Release at 7 h		65 – 80%
Drug Release at 10 h		NLT 90%

Evaluation of Pellets: Drug loaded pellets and sustained-release coated pellets were evaluated for particle size distribution by using an analytical sieving method. Coating process efficiency (% w/w) was calculated for both drug loading and sustained release coating process using the following equation.

% Coating process efficiency = Wt. of Final Coated Pellets – wt. of Starter Pellets × 100 / Amount of Solid sprayed from dispersion

Assay of drug-loaded pellets was carried out to determine the actual drug content inside the drug pellets. Sustained-release coated pellets were evaluated for *in-vitro* drug release in 500 mL SGF (pH 1.2) followed by SIF (pH7.4) using paddle apparatus (USP Apparatus –II) at 50 RPM. Drug release was compared to marketed product Oruvail 150 mg (Ketoprofen Capsules) by similarity factor (f_2), mean dissolution time (MDT), and mean residence time (MRT). An *f2* value between 50-100 suggests that the two dissolution profiles are similar, and the mean dissolution profiles are assumed to differ by no more than 10% at any time point [13, 14].

$$f2 = 50.log\left\{\left[1 + (\frac{1}{n})\sum_{t=1}^{n} W(Rt - Tt)^2\right]^{-0.5} * 100\right\}$$

Where Rt and Tt are the per cent dissolved at each time point for reference (R) and test (T) products.

RESULTS:

Preliminary Trials of Drug Loaded Pellets: Process efficiency is one of the important critical quality attributes for effective drug loading process and to control the amount of drug-loaded onto pellets (*i.e.*, assay). Wurster coating process involves many dependent and independent variables which affect process efficiency. The preliminary trial drug-loaded pellets were taken to study binder amount level on drug pellets assay, process efficiency, agglomerates, and fines formation, which are summarized in **Table 5**.

Process feasibility was defined as completion of process without any agglomerates observation, and the intermittent process stops. Ranking for Process feasibility was assigned as 1 (Very poor), 2 (Poor), 3 (Good), 4 (very good).

TABLE 5: RESULTS OF DRUG LOADED PELLETS OF DT

Parameters		Concentration of Binder			
		0 %	2.5 %	5 %	7.5%
% Process Efficiency		71.3	84.0	91.2	93.4
% Agglomerates	>25#	0.35	0.75	1.1	15.6
% Fines	<40#	14.3	5.5	0.3	0.1
LOD at 105 °C		0.4	0.8	1.1	1.0
Process feasibility		Very good	Very good	Good	Poor

Preliminary Trials of Sustained Release Coating: Preliminary trials of sustained-release coated pellets were evaluated for % process efficiency, assay, particle size distribution, and drug release profile.

TABLE 6: RESULTS OF SUSTAINED RELEASE PELLETS

Parameters		% of the sustained-release coating			
		10%	16%	22%	28%
Process Efficiency		89.6	91.5	92.3	90.9
Assay		100.5	99.1	100.0	100.3
Particle Size Distribution	>25#	0.5	0.7	0.3	0.5
(by sieve analysis)	<40#	0.3	0.4	0.2	0.4

TABLE 7: DRUG RELEASE PROFILE OF SUSTAINED RELEASE PELLETS

Time (h)	Specification Limit	Marketed Product	10% SR Coated	16% SR Coated	22% SR Coated	28% SR Coated
1	15-25%	16.4 ± 2.4	47.5 ± 1.4	27.6 ± 1.7	10.5 ± 2.2	6.4 ± 1.4
2		29.2 ± 1.7	60.8 ± 2.3	40.6 ± 1.6	26.5 ± 1.7	11.5 ± 0.6
4	40-50%	43.7 ± 2.0	70.8 ± 2.0	59.2 ± 1.6	33.2 ± 1.2	20.7 ± 1.3
6		60.5 ± 2.0	90.1 ± 0.6	67.1 ± 2.5	47.7 ± 1.7	35.5 ± 1.2
7	65-80%	77.4 ± 2.0	97.1 ± 1.3	83.6 ± 3.2	61.8 ± 2.3	45.0 ± 1.7
10	NLT 90%	89.3 ± 1.9	99.2 ± 1.2	90.2 ± 0.4	81.4 ± 2.0	65.2 ± 1.6
12		93.3 ± 0.8	99.3 ± 2.2	101.0 ± 0.3	93.4 ± 1.3	78.5 ± 2.6
Similarity factor (f_2)		-	30.79	50.89	51.16	32.76
Mean Dissolution Time (MDT) (h)		4.39	2.36	4.07	5.48	6.27
Mean Residence Time (MRT) (h)		3.60	2.31	3.35	4.05	4.63

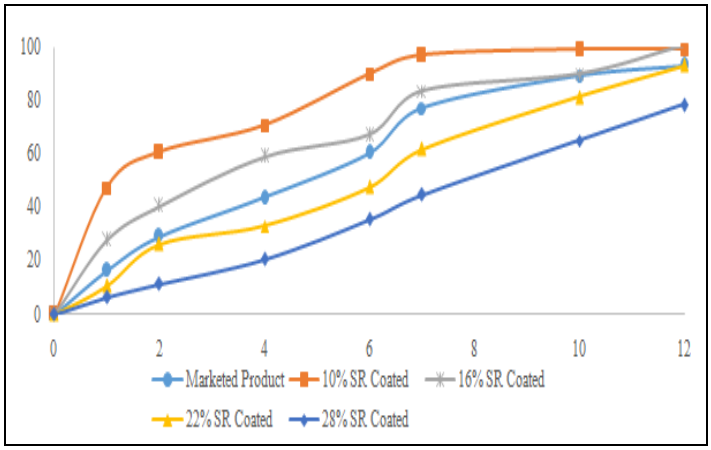

FIG. 1: COMPARATIVE DISSOLUTION PROFILE OF DIFFERENT SUSTAINED RELEASE COATING WEIGHT GAIN BATCHES

TABLE 8: RESULTS OF SUSTAINED RELEASE COATING OPTIMIZATION USING CCD DESIGN

Trials Run	1	2	3	4	5	6	7	8	9	10	11	12	13
Independent factors selected													
% Coating weight gain	10.0	17.5	6.89	17.5	17.5	17.5	17.5	25.0	10.0	17.5	25.0	28.11	17.5
TEC concentration	5.0	12.5	12.5	12.5	12.5	12.5	1.89	20.0	20.0	23.11	5.0	12.5	12.5
Talc concentration	5.0	23.11	12.5	12.5	1.89	12.5	12.5	5.0	20.0	12.5	20.0	12.5	12.5
Responses understudied													
Agglomerates	4.9	0.1	0.5	0.6	11.2	0.1	0.3	6.5	2.1	1.0	1.9	0.6	0.3
Efficiency	94.1	88.9	90.4	95.6	96.1	93.8	88.5	94.5	86.0	92.1	85.9	95	94.2
Drug release profile													
Time (h)	**% Drug release**												
1	43.2	25.9	71.9	18.3	13.2	21.0	32.4	10.1	52.9	26.8	13.1	6.0	19.2
4	75.0	54.2	94.8	44.9	39.0	47.1	54.2	40.1	87.9	57.9	30.1	20.9	45.9
7	98.1	77.8	97.1	73.8	69.8	76.0	90.1	59.2	98.7	88.1	53.2	42.0	72.4
10	96.9	100.8	99.6	96.8	98.1	97.5	96.5	75.9	99.8	98.7	66.8	66.1	99.0

DISCUSSION:

Drug Loading: Binder quantity play crucial role in adhesion of drug onto inert starter core pellets. Low binder concentration in drug layering suspension may results in powder loss during the drug loading process, which reduces assay of drug pellets. Higher binder concentration yields viscous and sticky dispersion, which results in agglomerates generation due to sticking of pellets with each other that necessitates slow spray rate and higher product bed temperature. Binder optimization trial in drug loading showed that there was an increase in process efficiency with an increase in the binder concentration. 5 & 7.5% w/w concentration of Povidone K30 with respect to drug amount gives greater than 90% process efficiency while a higher amount of agglomerates were observed for drug layering trial with 7.5%.

Based on preliminary trials for drug loading, Povidone concentration is selected as 5% of drug substance quantity. This gave good process feasibility and good adhesion of the drug onto the MCC pellets. Talc at 2% of total drug layering solid mass shows better anti-tacking property to remove unnecessary static charges as well as agglomeration generation during spraying process.

Sustained Release Coating: Sustained release coating formulation and process both play vital role in controlling drug release from the pellets. The feasibility trials for sustained release coating were taken by applying different % of weight gain. As the coating weight gain increases from 10 to 28% w/w, the drug release profile significantly decreases. 16% w/w weight gain give comparable drug release to that of the marketed product (Oruvail- Ketoprofen Extended-Release capsules) with f2 value of above 50. Even Mean dissolution time (MDT) and mean residence time (MRT) of pellets is comparable to that of a brand product. This selected 16% w/w coating weight gain was further optimized by varying levels of components to get appropriate robust formulation, which gives satisfactory quality attributes of dosage forms within narrow possible changes.

Sustained Release Coating Formulation Optimization: Sustained release coating formula optimization was done using response surface methodology *i.e.,* CCD design with three center point. Three dependent responses were investigated, which are amount of agglomerates, coating process efficiency, and drug release at 1, 4, 7, and 10 h. Fit summary of various investigated dependent responses were summarized in **Table 9**.

TABLE 9: FITS SUMMARY OF RESPONSES UNDER STUDIED

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F	Comments
Response Y_1: Agglomerates (% w/w)						
Mean *vs*. Total	69.69	1	69.69			
Linear *vs*. Mean	67.96	3	22.65	3.17	0.0779	
2FI *vs*. Linear	8.89	3	2.96	0.32	0.8104	
Quadratic *vs*. 2FI	54.73	3	18.24	88.15	0.0020	Suggested
Cubic *vs*. Quadratic	0.49	1	0.49	7.80	0.1078	Aliased
Response Y_2: Coating process efficiency						
Mean *vs*. Total	109900	1	109900			
Linear *vs*. Mean	100.03	3	33.34	5.45	0.0206	
2FI *vs*. Linear	12.76	3	4.25	0.60	0.6365	
Quadratic *vs*. 2FI	40.33	3	13.44	20.49	0.0168	Suggested
Cubic *vs*. Quadratic	0.18	1	0.18	0.20	0.6965	Aliased
Response Y_3: Drug release at 1 h						
Mean *vs*. Total	9639.69	1	9639.69			
Linear *vs*. Mean	3566.21	3	1188.74	15.38	0.0007	
2FI *vs*. Linear	81.67	3	27.22	0.27	0.8477	
Quadratic *vs*. 2FI	581.84	3	193.95	18.15	0.0199	Suggested
Cubic *vs*. Quadratic	28.27	1	28.27	14.96	0.0608	Aliased
Response Y_4: Drug release at 4 h						
Mean *vs*. Total	36835.69	1	36835.69			
Linear *vs*. Mean	**5034.82**	**3**	**1678.27**	**29.69**	**<0.0001**	
2FI *vs*. Linear	99.68	3	33.23	0.49	0.7035	
Quadratic *vs*. 2FI	405.15	3	135.05	104.90	0.0016	Suggested
Cubic *vs*. Quadratic	1.44	1	1.44	1.18	0.3904	Aliased
Response Y_5: Drug release at 7 h						
Mean *vs*. Total	76354.90	1	76354.90			
Linear *vs*. Mean	3299.75	3	1099.92	19.54	0.0003	
2FI *vs*. Linear	51.27	3	17.09	0.23	0.8756	
Quadratic *vs*. 2FI	443.73	3	147.091	38.13	0.0069	Suggested
Cubic *vs*. Quadratic	5.05	1	5.05	1.53	0.3412	Aliased
Response Y_6: Drug release at 10 h						
Mean *vs*. Total	109400	1	109400			
Linear *vs*. Mean	1313.89	3	437.96	5.84	0.0170	Suggested
2FI *vs*. Linear	27.91	3	9.30	0.086	0.9650	
Quadratic *vs*. 2FI	589.92	3	196.64	10.33	0.0433	Suggested
Cubic *vs*. Quadratic	54.56	1	54.56	43.19	0.0244	Aliased

TABLE 10: ANOVA RESULT OF DEPENDENT PARAMETERS (Y_1: AGGLOMERATES)

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Comments
Model	131.58	9	14.62	70.64	0.0025	Significant
A-% Coating	0.005	1	0.005	0.024	0.8863	
B-TEC conc.	0.25	1	0.25	1.18	0.3562	
C-Talc conc.	61.60	1	61.60	297.67	0.0004	Significant
AB	8.61	1	8.61	41.59	0.0076	Significant
AC	0.082	1	0.082	0.40	0.5737	
BC	0.20	1	0.20	0.96	0.4001	
A^2	0.54	1	0.54	2.62	0.2040	
B^2	0.75	1	0.75	3.63	0.1529	
C^2	54.55	1	54.55	263.58	0.0005	Significant
Residual	0.62	3	0.21			
Lack of Fit	0.49	1	0.49	7.80	0.1078	Not significant
Pure Error	0.13	2	0.063			
Cor Total	132.20	12				

ANOVA results for agglomerate shows that model F value is 70.64, which is more than 0.05, which shows that the selected model is significant.

Here talc concentration in sustained-release coating solution affects significantly agglomerates formation during the coating process. The value of adequate precision is 28.107, which means that model can be used to navigate the design space.

Statistical equation for the prediction of response Y_1 (Agglomerates) is: 0.1941+0.0354*A + 0.2475*B - 3.92*C-2.07*A*B - 0.2025*A*C - 0.3146*B*C + 0.2824*A^2 + 0.3324*B^2 + 2.83*C^2

TABLE 11: ANOVA RESULT OF DEPENDENT PARAMETERS (Y_2: COATING PROCESS EFFICIENCY)

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Comments
Model	153.12	9	17.01	25.94	0.0108	Significant
A-% Coating	10.58	1	10.58	16.13	0.0277	Significant
B-TEC conc.	6.48	1	6.48	9.88	0.0515	
C-Talc conc.	25.92	1	25.92	39.51	0.0081	Significant
AB	5.31	1	5.31	8.09	0.0654	
AC	2.63	1	2.63	4.02	0.1388	
BC	4.81	1	4.81	7.34	0.0732	
A^2	7.10	1	7.10	10.83	0.0461	Significant
B^2	33.58	1	33.58	51.18	0.0056	Significant
C^2	8.56	1	8.56	13.05	0.0364	Significant
Residual	1.97	3	0.6560			
Lack of Fit	0.1813	1	0.1813	0.2029	0.6965	Not significant
Pure Error	1.79	2	0.8933			
Cor Total	155.09	12				

ANOVA results for coating process efficiency show that model F value is 25.94, which is more than 0.05, which shows that the selected model is significant. Here coating weight gain and talc concentration in sustained-release coating process were significantly influence coating process efficiency. The value of adequate precision is 14.003, which means that model can be used to navigate the design space.

Statistical equation for the prediction of response Y_2 (Coating process efficiency) is: 94.62 + 1.63*A + 1.27*B - 2.55*C + 1.63*A*B + 1.15*A*C + 1.55*B*C - 1.02*A^2 - 2.22*B^2 - 1.12*C^2

TABLE 12: ANOVA RESULT OF DEPENDENT PARAMETERS (Y_3: DRUG RELEASE AT 1 h)

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Comments
Model	4229.72	9	469.97	43.99	0.0050	Significant
A-% Coating	2171.40	1	2171.40	203.24	0.0007	Significant
B-TEC conc.	15.68	1	15.68	1.47	0.3124	
C-Talc conc.	80.65	1	80.65	7.55	0.0709	
AB	3.46	1	3.46	0.3238	0.6092	
AC	26.72	1	26.72	2.50	0.2119	
BC	51.49	1	51.49	4.82	0.1157	
A^2	480.82	1	480.82	45.00	0.0068	Significant
B^2	94.80	1	94.80	8.87	0.0587	
C^2	11.34	1	11.34	1.06	0.3787	
Residual	32.05	3	10.68			
Lack of Fit	28.27	1	28.27	14.96	0.0608	Not significant
Pure Error	3.78	2	1.89			
Cor Total	4261.77	12				

ANOVA analysis results for drug release at 1 h shows that model F value is 43.99, which is more than 0.05, which shows that the selected model is significant.

Here coating weight gain plays a significant role in drug release at 1 h. The value of adequate precision is 22.988, which means that model can be used to navigate the design space.

Statistical equation for the prediction of response Y_3 (Drug release at 1 h) is: 20.55-23.30*A - 1.98*B + 4.49*C + 1.32*A*B - 3.65*A*C - 5.07*B*C + 8.41*A^2 + 3.73*B^2 - 1.29*C^2

TABLE 13: ANOVA RESULT OF DEPENDENT PARAMETERS (Y_4: DRUG RELEASE AT 4 h)

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Comments
Model	5539.65	9	615.52	478.13	0.0001	Significant
A-% Coating	2730.60	1	2730.60	2121.10	< 0.0001	Significant
B-TEC conc.	6.84	1	6.84	5.32	0.1044	
C-Talc conc.	115.52	1	115.52	89.73	0.0025	Significant
AB	43.23	1	43.23	33.58	0.0102	Significant
AC	39.02	1	39.02	30.31	0.0118	Significant
BC	17.44	1	17.44	13.54	0.0348	Significant
A^2	264.63	1	264.63	205.56	0.0007	Significant
B^2	193.78	1	193.78	150.52	0.0012	Significant
C^2	2.56	1	2.56	1.99	0.2535	
Residual	3.86	3	1.29			
Lack of Fit	1.44	1	1.44	1.18	0.3904	Not significant
Pure Error	2.43	2	1.21			
Cor Total	5543.51	12				

ANOVA results for drug release at 4 h shows that model F value is 478.13, which is more than 0.05, which shows that the selected model is significant.

Here coating weight gain and talc concentration both play a significant role in drug release at 4 h. The value of adequate precision is 74.262, which means that model can be used to navigate the design space.

Statistical equation for the prediction of response Y_4 (Drug release at 4 h) is: 45.73-26.13*A -1.31*B + 5.37*C + 4.65*A*B - 4.42*A*C - 2.95*B*C + 6.24*A^2 + 5.34*B^2 + 0.6132*C^2

TABLE 14: ANOVA RESULT OF DEPENDENT PARAMETERS (Y_5: DRUG RELEASE AT 7 h)

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Comments
Model	3794.75	9	421.64	108.68	0.0013	Significant
A-% Coating	1518.01	1	1518.01	391.29	0.0003	Significant
B-TEC conc.	2.00	1	2.00	0.5155	0.5246	
C-Talc conc.	32.00	1	32.00	8.25	0.0639	
AB	34.92	1	34.92	9.00	0.0577	
AC	11.11	1	11.11	2.86	0.1891	
BC	5.24	1	5.24	1.35	0.3291	
A^2	53.87	1	53.87	13.89	0.0337	Significant
B^2	329.43	1	329.43	84.92	0.0027	Significant
C^2	3.23	1	3.23	0.8338	0.4285	
Residual	11.64	3	3.88			
Lack of Fit	5.05	1	5.05	1.53	0.3412	Not significant
Pure Error	6.59	2	3.29			
Cor Total	3806.39	12				

For drug release at 7 h, ANOVA results show that model F value is 108.68, which is more than 0.05, which shows that the selected model is significant. Here coating weight gain imparts a significant role in drug release at 7 h. The value of adequate precision is 33.595, which means that model can be used to navigate the design space.

The statistical equation for the prediction of response Y_5 (Drug release at 7 h) is:

74.51 - 19.48*A -0.7071*B + 2.83*C + 4.18*A*B - 2.36*A*C + 1.62*B*C - 2.81*A^2 + 6.96*B^2 - 0.6897*C^2

TABLE 15: ANOVA RESULT OF DEPENDENT PARAMETERS (Y_6: DRUG RELEASE AT 10 h)

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Comments
Model	1931.72	9	214.64	11.28	0.0355	Significant
A-% Coating	561.13	1	561.13	29.49	0.0123	Significant
B-TEC conc.	2.42	1	2.42	0.1272	0.7450	
C-Talc conc.	3.64	1	3.64	0.1915	0.6912	
AB	12.55	1	12.55	0.6593	0.4762	
AC	9.88	1	9.88	0.5190	0.5233	

BC	5.48	1	5.48	0.2882	0.6286	
A^2	586.46	1	586.46	30.82	0.0115	Significant
B^2	24.85	1	24.85	1.31	0.3361	
C^2	6.62	1	6.62	0.3480	0.5968	
Residual	57.09	3	19.03			
Lack of Fit	54.56	1	54.56	43.19	0.0224	significant
Pure Error	2.53	2	1.26			
Cor Total	1988.81	12				

ANOVA results for drug release at 10 h shows that model F value is 11.28, which is more than 0.05, which shows that the selected model is significant. Here coating weight gain plays a significant role in drug release at 10 h. The value of adequate precision is 9.955, which means that model can be used to navigate the design space.

The statistical equation for the prediction of response Y_6 (Drug release at 10 h) is:

$$99.23 - 11.84*A + 0.7778*B + 0.9546*C + 2.50*A*B - 2.22*A*C + 1.66*B*C - 9.29*A^2 - 1.91*B^2 - 0.9868*C^2$$

The overall conclusion of ANOVA results was revealed that % weight gain and Talc concentration are more significant parameters that affect the responses understudied, *i.e.* (agglomerates, process efficiency, and drug release).

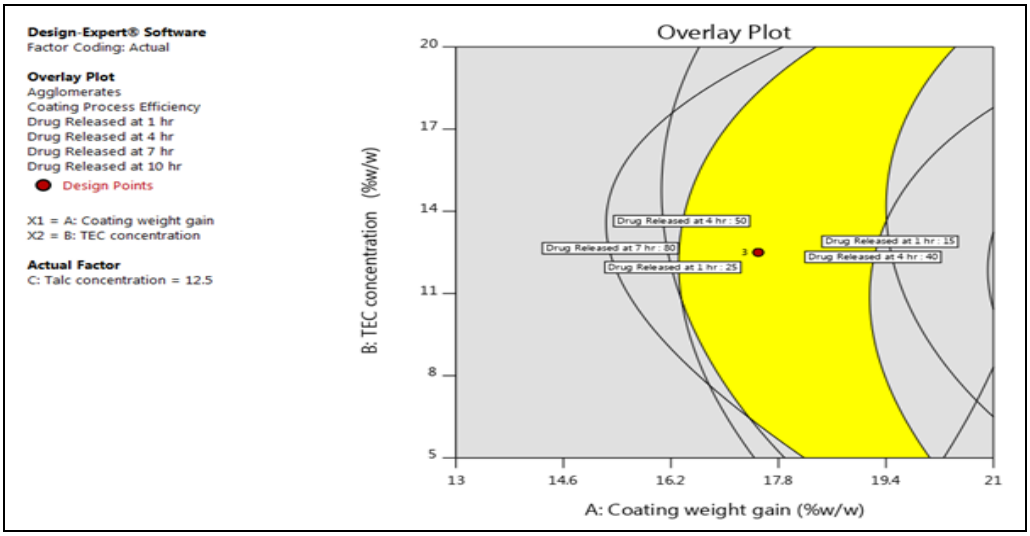

FIG. 2: OVERLAY COUNTER PLOT OF % COATING WEIGHT GAIN AND TEC CONCENTRATION RESPONSES STUDIED

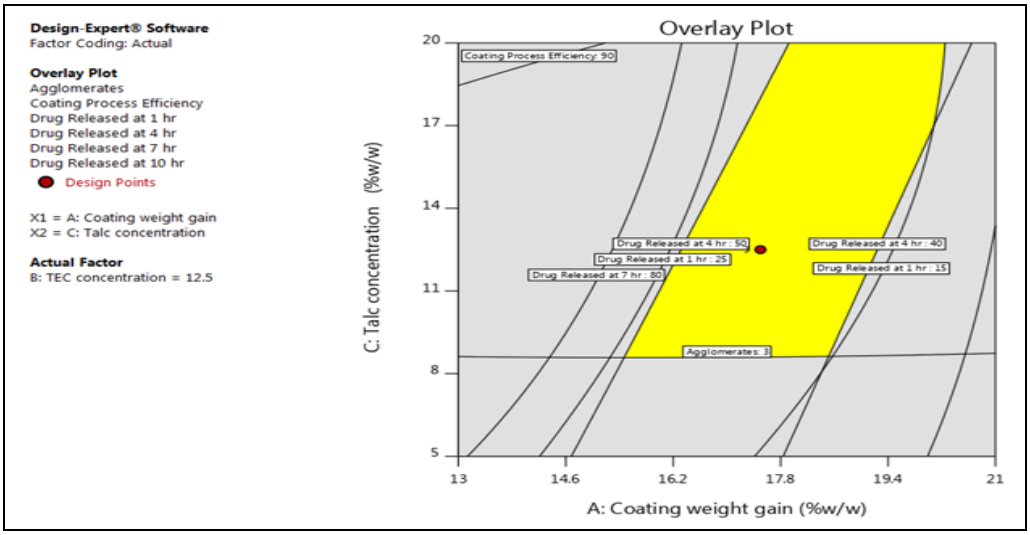

FIG. 3: OVERLAY COUNTER PLOT OF % COATING WEIGHT GAIN AND TALC CONCENTRATION ON RESPONSES STUDIED

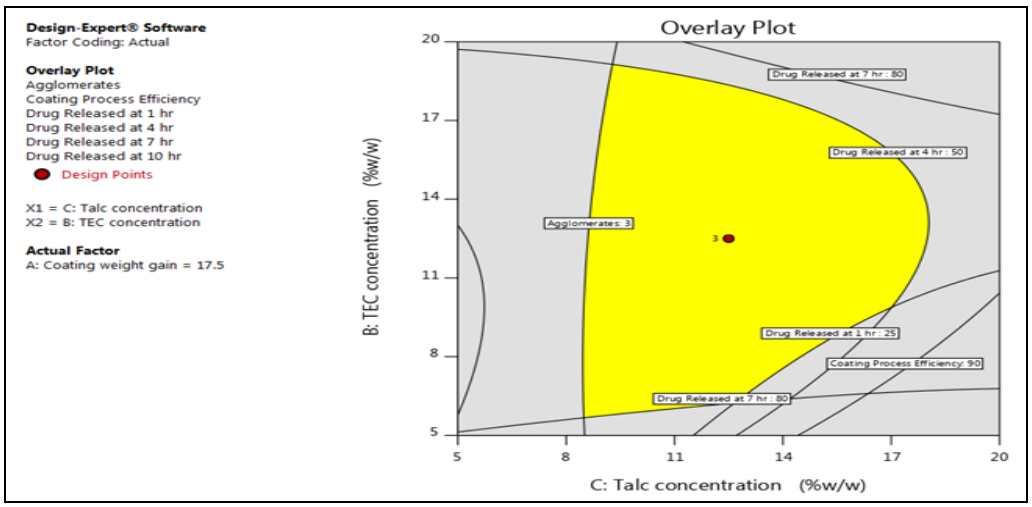

FIG. 4: OVERLAY COUNTER PLOT OF TEC AND TALC CONCENTRATION ON RESPONSES STUDIED

Yellow color area-design space in depicted overlay plot yield desired parameter settings for which all dependent responses will always be within the accepted level.

CONCLUSION: Based on this research work, it was concluded that sustained-release coated pellets were successfully developed for dexketoprofen trometamol drug-using kollicoat SR 30D as a ready-mix polymer with triethyl citrate as plasticizer and talc as an anti-tacking agent. Wurster coating process yields uniform and narrow particle size distribution range pellets. Yellow zone in overlay plot gives appropriate formulation components level setting, which will give robust pellets formulation having desired quality attributes.

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CONFLICTS OF INTEREST: We authors, the undersigned research article entitled "Sustained Release Multi-particulates Formulation of a stereo-selective molecule of Ketoprofen by fluid bed processor" confirm that we do not have any conflict of interest in connection to the proposed research work.

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