Formulation development and *in-vitro* evaluation of fast dispersible, taste masked Aceclofenac compacted pellets

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Abstract: The objective of this study was to develop Aceclofenac fast dispersible compacted pellets with improved taste and fast drug release. Pellets were prepared by extrusion-spheronization technique followed by direct compression to make compacted pellets. Formulations were comprised of sucrose, mannitol, ac-di-sol, aspartame, pine apple flavor and magnesium stearate. A mixture of distilled water and isopropyl alcohol (1:1) was used for wet massing. The effect of ac-di-sol on the drug release pattern was examined and dissolution profile comparison was established. All formulations followed First order and Weibull models and f_2 values indicated dissimilarity with the marketed immediate release product. Taste of compacted pellets was evaluated by a panel of 12 human volunteers. Formulation P5 was found to be an optimized formulation due to satisfactory quality attributes.

Keywords: Extrusion-spheronization, fast dispersible compacted pellets, Aceclofenac, direct compression.

INTRODUCTION

Pellets as the "oral dosage form" have been used to deliver the drug at required site of action for immediate release and/or sustained release since 1950's. They have multiple advantages such as excellent flow properties, content uniformity, smooth surface, wide applications etc. Pelletization is a unique technique to combine the incompatible drugs and bioactive agents (Ghorpade *et al.*, 2016). Pellets quickly dispersed in the gastrointestinal tract (GIT) and their wide distribution, minimizes irritation to the intestinal mucosa of GIT. However, pelletization is costly and time consuming method (Deb and Ahmed, 2013; Ghorpade *et al.*, 2016).

Extrusion-spheronization was introduced in early 1960's for pelletization and currently it is the most preferred method for making the pellets. It produces pellets having high density, increased drug loading, and a narrow size distribution (Akhgari *et al.*, 2011; Erkoboni, 2003). This technique has multiple stages including: blending of the powders > wet massing by granulating agent > extrusion through extruder > crushing to small sized cylindrical shapes > spheronization by spheronizer > drying of spheres. In this study pellets of the Aceclofenac (i.e. NSAID) were prepared, which is used for treating mild to moderate painful conditions like osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, dysmenorrhea, dental ache etc. It has bitter taste and practically insoluble in water (Parfitt, 2009). Therefore this study was designed with the aim of masking the bittereness of Aceclofenac and enhancing the drug release using extrusion-spheronization technique to make "*fast dispersible pellets"*. The effect of superdisintegrant used in different concentrations was examined and compared with the marketed immediate release product.

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MATERIALS AND METHOD

Materials

Aceclofenac was a gift from Sami Pharm. (Pvt.) Ltd.; sucrose, mannitol, ac-di-sol, pineapple flavor, aspartame and magnesium stearate were purchased from FMC Co., USA. Isopropyl alcohol was obtained from Merck, Germany. Remaining reagents used for analysis were procured from commercial sources bearing analytical grade quality.

Equipment and software used

Analytical balance (Sartorius: CP224S, Germany and Mettler Toledo B204-S, Switzerland), Design-Expert® version 7.0.0 (Stat-Ease, Inc, Minneapolis, MN 55413, USA), DD Solver® Add Ins program, and Minitab® (17.0). Mini Screw Extruder (Caleva Process Solution Ltd, UK), Spheronizer (Caleva Process Solution Ltd, UK), Single punch tableting machine (Erweka, Germany).

Equipments and softwares

Analytical balance (Sartorius: CP224S, Germany and Mettler Toledo B204-S, Switzerland), Mini Screw Extruder (Caleva Process Solution Ltd, UK), Spheronizer (Caleva Process Solution Ltd, UK), and single punch tableting machine (Erweka, Germany) were used. Design-Expert® version 7.0.0 (Stat-Ease, Inc, Minneapolis, MN 55413, USA), DD Solver® Add In program and Minitab® (17.0) were utilized.

Method

Formulation design

Central Composite Design was employed for formulation designing and optimization of fast dispersible Aceclofenac (100mg) compacted pellets. Sucrose (20-35 %) and ac-di-sol (2-5%) were selected as independent variables while mannitol, aspartame, pineapple flavor and

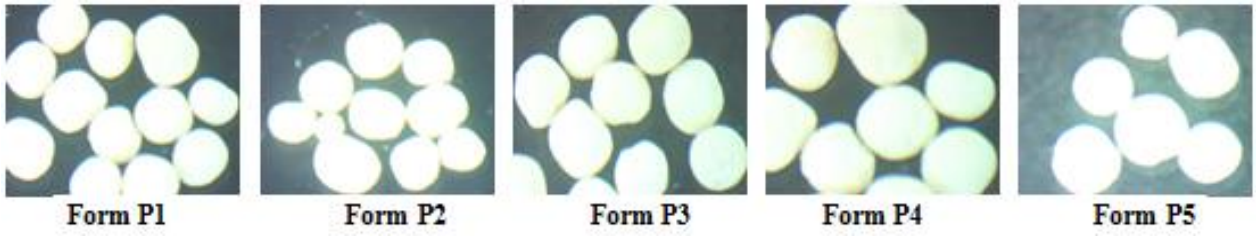

Fig. 1: Images of pelletized formulations

magnesium stearate were used in fixed amount i.e., 20%, 2%, 0.5% and 0.5% respectively. Factor levels used for formulation development are given in table 1. Disintegration time and percentage friability were taken as dependent variables. Fourteen formulations were designed using central point "1" and five best of them were pelletized by extrusion-spheronization technique (compositions are given in table 2).

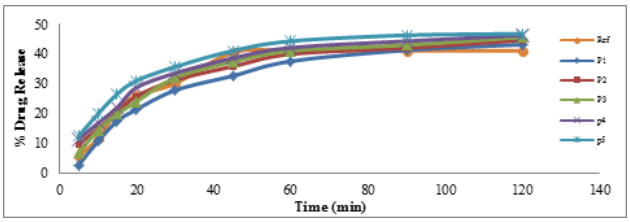

Fig. 2(a): Dissolution profile of Compacted Pellets *Vs*. Reference in 0.1N HCI solution

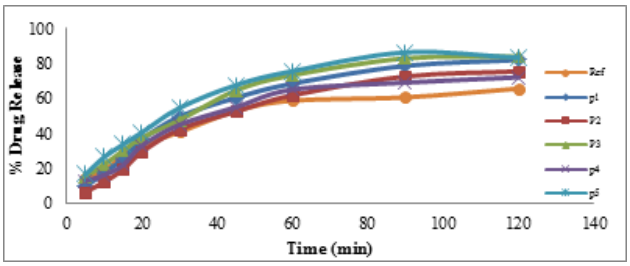

Fig. 2(b): Dissolution profile of Compacted Pellets *Vs*. Reference in buffer pH 4.5 solution

Preparation of pellets

Aceclofenac and excipients (sucrose, mannitol, aspartame and flavor) were accurately weighed and mixed to make damp mass with mixture of isopropyl alcohol and distilled water (1:1), using mortar and pestle. Approximately 2-5mL of this granulating mixture was consumed to prepare damp mass. The damp mass was passed through lab scale Mini Screw Extruder fitted with 1 mm screen; operating at 60 rpm. Next extrudates were splitted manually into sufficiently small sized cylinders (length and diameter were almost equal) and subjected to spheronization by using multi bowl bench top spheronizer at a speed 600 to 800rpm for only 10 minutes. The obtained pellets were dried at 40^{o}C for 2-hours in a conventional hot air oven (table 3). These spherical pellets were passed through sieve (18-24 mesh size) to maintain uniformity in size.

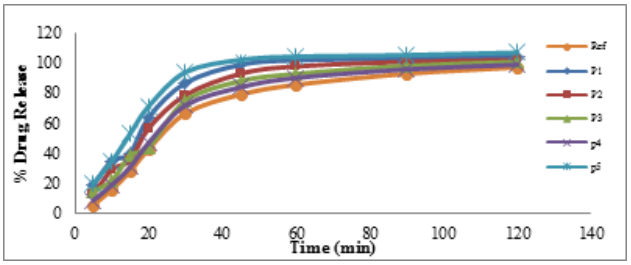

Fig. 2(c): Dissolution profile of Compacted Pellets *Vs*. Reference in buffer pH 6.8 solution

Pre-compression studies

Prior making the compacts, flow characteristics of fast dispersible Aceclofenac pellets were evaluated through bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose and image analysis.

Image analysis of pellets

For image analysis, a sample of 10-12 pellets of each formulation was spread in a petri dish and viewed under stereomicroscope (Am Scope Digital, LED-1444A, U.S.A). The Aspect ratio, Feret diameter and sphericity (roundness) of each sample was measured through a software i.e. NIH Image (J 1.47v, U.S.A). Following equations were used for this purpose:

Aspect ratio (A.R) = D_{max}/D_{min} (1)

Sphericity= $4\pi A/P^2$ (2)

Here 'A' shows the area of pellet, 'P' is the perimeter, while D_{max} and D_{min} are the max and min Feret diameters.

Compaction of fast dispersible Aceclofenac pellets

Direct compression method was adopted for compaction of pellets. After addition of ac-di-sol (2-5%), pellets were mixed for 5 minutes by tumbling method in a poly bag. Next 0.5% magnesium stearate was added in each formulation and mixed for further 5 minutes. Compression of the pellets was carried out by single punch machine of Erweka (Korsch, Germany) using disc shaped punches.

Post-compression studies

A random sample (i.e. n=20) from each formulation was collected to evaluate average weight, thickness, diameter and hardness variation. Disintegration test was conducted in basket rack assembly of USP disintegration *apparatus-II*; using 900ml distilled water at 37± 2^{o}C. The friability

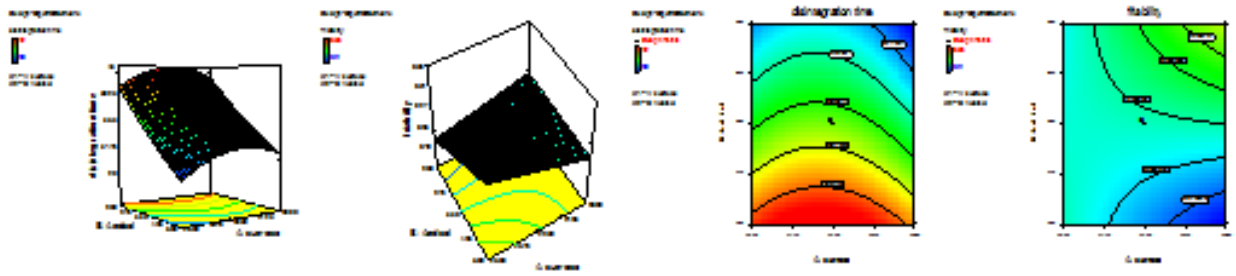

Fig. 3: 3D Surface and Contour plots exhibiting effects of excipients on disintegration time and friability of fast dispersible Aceclofenac compacted pellets

of compacts was determined on the basis of 10 compacts of each formulation using Roche friabilator (D2800, Germany).

Additional tests

Wetting time and fineness of dispersion tests were also conducted additionally as non-official tests. Dispersions of two compacts from each formulation was prepared in 100mL distilled water separately and passed through 10µm mesh steel sieve. As per European pharmacopeia; this dispersion should be smooth enough to pass through the sieve. An individual compact was placed on a tissue paper in petri dish containing 1% crystal violet solution. Stop watch was used to record the time for complete wetting of compacts.

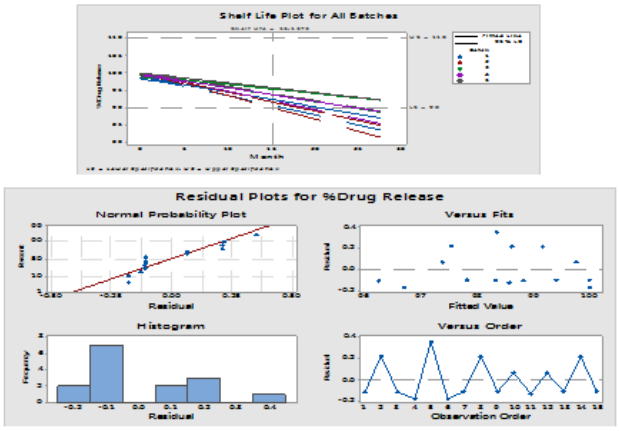

Fig. 4: Shelf-life plots of Aceclofenac compacted pellets (by Accelerated stability testing)

Drug content analysis of compacted pellets

Assay of compacted pellets was carried out using a validated reversed phase HPLC method. HPLC assembly was comprised of HPLC pump (LC 20A, Shimadzu Co., Kyoto, Japan), connected with Detector (SPD-20A, Shimadzu Co., Kyoto, Japan), communication bus Module (CBM 102, Shimadzu Co., Kyoto, Japan) attached with Software (GC 20, Shimadzu Co., Kyoto, Japan). Mobile phase was prepared by taking 0.01N potassium dihydrogen phosphate solution and acetonitrile (HPLC grade) in a ratio of 60:40. The pH of buffer was maintained to 6.8 by addition of 1molar NaOH solution. This mobile phase was filtered and sonicated before use (Yasmin *et al.*, 2017).

Sample preparation

Compacted pellets of each formulation were randomly selected for analysis. Sample was crushed in a mortar and pestle and weight equivalent to 100mg of Aceclofenac, was poured to 100mL volumetric flask. Initially 5mL absolute methanol was shaken with sample for five minutes to dissolve Aceclofenac. Mobile phase was used to make up the volume. After filtration, the solution was diluted to a suitable concentration for analytical purpose. Standard solution of Aceclofenac was also prepared in equal concentration by same procedure. By using microlitre syringe 20µL of sample was injected, keeping the flow rate of mobile phase at 1mL/min and λ=274nm (Bhardwaj *et al.*, 2010; Sharma *et al.*, 2001). C_{18} column was used for the separation of analyte.

Drug dissolution studies

Compacted pellets were subjected to *in-vitro* drug release evaluation, using the USP dissolution apparatus II (Erweka D - 63150, Germany). Samples were exposed to 900mL of three dissolution medium i.e. 0.1N HCI, phosphate buffer pH 4.5 and 6.8; maintained at 37^{o}±0.5 ^{o}C with paddle speed 50 rpm. A 10mL sample of each batch was collected at 05, 10, 15, 20, 30, 45, 60, 90 and 120 minutes with replacement of fresh 10mL of same solution, at same temperature. Collected samples were diluted, filtered and analyzed at 274nm, using UV-Visible spectrophotometer (Shimadzu Co., Japan) (Sharma *et al.*, 2001). Marketed immediate release tablets of Aceclofenac (100mg) were used for dissolution profile comparison.

Model independent approach

In the present study f_2 values were examined through dissolution data of test and reference products by DD-Solver® as previously many researchers have documented this factor (Moore and Flanner, 1996).

Model dependent approach

Different models were used to evaluate drug release kinetics for instance; First order, Higuchi, Hixson–Crowell and Weibull models (Costa and Lobo, 2001). In

the present study, dissolution data of test and reference product was evaluated by DD-Solver ® Add In (MS Excel based) program using the above stated kinetic models.

RESULTS

Pre-compression evaluation of fast dispersible pellets

In the present study, fast dispersible Aceclofenac (100mg) pellets were designed through CCD and prepared by extrusion-spheronization technique. Image analysis of pellets was performed by Stereomicroscope. Nearly all pellets were found spherical in shape and their results of aspect ratio were found to be 1.02-1.05. Feret diameter and sphericity both were found in the range of 0.94-0.97. Flow properties of pellets were evaluated and mean results of bulk density and tapped density were found to be: 0.70-0.73 and 0.73-0.77g/mL respectively. Carr's index, angle of repose and Hausner's ratio were found to be: 2.71-4.30%, 4.00-6.72^{o}, 1.02-1.07 respectively.

Post compression evaluation of pellets

The average weight of compacted pellets was found to be: 181.93±0.78-211.73±0.87mg. Mean thickness and diameter were found within the prescribed limit of ±5%. All compacted pellets disintegrated within 29-42 seconds, with average hardness 4.32±0.21 to 6.22±0.45 kg and percentage friability: 0.20-0.35%. Assay and content uniformity of all formulations were found between: 98.71 ±1.12-99.89±0.28% and 99.26±0.54% to 101.37±0.57% respectively. The f_2 values for all formulations were found less than 50 showing dissimilarity with immediate release product (as designed formulations were fast dispersible). All compacted pellets passed the dispersion test successfully with wetting time ranging from 15 - 22 sec. First order and Weibull models were found as the best fit with highest r^2 values.

DISCUSSION

Current study presents formulation development and evaluation of fast dispersible Aceclofenac (100mg) compacted pellets with the aim of designing a novel dosage form having improved palatability and quick drug release. The formulations were designed by Design-Expert® (7.0.0) using sucrose (20-35%) and ac-di-sol (2-5%) as independent variables. Mannitol, aspartame, flavor and magnesium stearate were used in fixed concentration (i.e. 20%, 2%, 0.5% and 0.5% respectively) as mentioned in table 1 and 2. Careful selection of excipients is the most important step during formulation development because they affect the physicochemical properties of the dosage form. The excipients used for making fast dispersible dosage form should produce fast disintegration, adequate mechanical strength and good compressibility (Abdelbary *et al.,* 2004; Mizumoto *et al.,* 2005). In this study sucrose was used as diluent in combination with mannitol, instead of avicel due to its rapid solubility in water and sweet taste which masks the bitterness of API. Researchers have used combinations of diluents to impart pleasant taste, improve water solubility and less moisture sensitivity to the formulations (Jacob *et al.,* 2007; Stange *et al.,* 2013). Furthermore, use of mannitol is also safe for diabetic patients because it does not raise the blood sugar level upon metabolism and its flowability and compressibility become improved (Debord *et al.,* 1987; Liu, 2002). Ac-di-sol (i.e. superdisintegrant) has been successfully utilized in many studies for quick dispersion of solid dosage form (Khairnar *et al.,* 2014; Kumar *et al.,* 2011; Mor *et al.,* 2016; Panigrahi *et al.,* 2010).

In the present study angle of repose, Carr's index, and Hausner's ratio of pellets were evaluated and their results were found within the official limits of "Excellent flow properties" according to USP, 2008. Nearly all pellets were found spherical in shape during image analysis because their aspect ratio values were found closer to 1 which is the recommended range for pharmaceutical pellets (table 4, 5 and fig. 1) (Chopra *et al.,* 2013; Dukić *et al.,* 2007; Nasiri *et al.,* 2016). Results of this study exhibited that selected excipients were capable to prepare compacts after passing through extrusion-spheronization process.

Prepared pellets were subjected to compression by single punch compression machine. The average weight and dimensions of compacted pellets were found within the prescribed limits of ±7.5% and ±5% respectively. Hardness of all fast dispersible formulations was found within recommended limit of 3-8 kg. Disintegration time is the most critical parameter which must be less than 3 minutes for fast dispersible formulations (Eur Phr, 2001). In the present study, ac-di-sol was used in the concentration range 2-5% to achieve least disintegration time. The optimized formulation P5 (containing 25% sucrose, 20% mannitol and 5% ac-di-sol) disintegrated in 29 sec only with % friability 0.22% without any splitting (table 6).

Assay and content uniformity results of all formulations were found within the specified official limit i.e. 90-110%. Formulations produced fine dispersion when passed through sieve # 710µm. The wetting time test was performed according to reported method and results were found satisfactory (Yunxia *et al.,* 1996). According to human volunteers the mouth-feel of compacted pellets was desirable and pleasant.

Dissolution profile comparison was carried out using marketed core immediate release Aceclofenac tablet (100mg) as reference. Results indicated minimum percentage of drug release in 0.1N HCl < phosphate buffer pH 4.5 < phosphate buffer pH 6.8 (fig. 2 a,b,c). Kinetic models were applied on dissolution data for evaluating the drug release pattern.

Table 1: Factor levels involved in formulation development of fast dispersible Aceclofenac pellets

Factor		Unit	Levels				
		(%)	(-α)	(-1)	0	(+1)	(+α)
Fast dispersible formulations (for manufacturing compacted pellets)							
X1	Sucrose	(%)	19.53	20	27.5	35	25.47
X2	Ac-di-sol	(%)	1.72	2	3.5	5	5.28

Table 2: Composition of selected Fast Dispersible Aceclofenac pellets

F. Code	Sucrose	Ac-di-sol	Sucrose	Ac-di-sol	Mannitol	Aspartame	Flavor	Magnesium Stearate	Drug	Compact weight
	X1 (%)	X2 (%)	X1 (mg)	X2 (mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg/tab)
P1	25.00	2.0	50.00	4.00	40.00	4.00	1.00	1.00	100	200.00
P2	25.47	3.5	52.97	7.28	41.64	4.16	1.04	1.04	100	208.13
P3	20.00	2.0	36.36	3.63	36.36	3.63	0.90	0.90	100	181.80
P4	20.00	5.0	38.46	9.60	38.46	3.84	0.96	0.96	100	192.28
P5	25.00	5.0	53.00	10.60	42.55	4.25	1.06	1.06	100	212.52

Table 3: Operational parameters for pelletization

	Extrusion	Spheronization	Drying
Speed	60rpm	600-800rpm	
Time		10min	2hours
Temperature			40^{o}C

Table 4: Image analysis of fast dispersible Aceclofenac pellets

Formulations Code.	Area	Perimeter	Feret Diameter	Aspect Ratio	Roundness
P1	10130	388.664	121.007	1.022	0.978
P2	12411	445.614	136.191	1.034	0.967
P3	8713	359.69	111.665	1.056	0.947
P4	12333	434.776	135.059	1.032	0.969
P5	12909	429.193	133.454	1.040	0.961

Table 5: Micromeritics properties of Fast Dispersible Aceclofenac pellets

Formulations Code.	Hausner's Ratio	Carr's Index (%)	Angle of Repose (θ)	Remarks
P1	1.04	4.03	4.00	Excellent
P2	1.07	4.07	4.85	Excellent
P3	1.07	4.30	6.72	Excellent
P4	1.05	4.09	4.00	Excellent
P5	1.02	2.71	4.23	Excellent

Table 6: Physicochemical evaluation of selected formulations

Tests	P1	P2	P3	P4	P5
Weight (mg)	200.56±1.08	209.12±0.77	181.93±0.78	191.85±0.90	211.73±0.87
Diameter (mm)	8.81±0.05	8.60±0.06	8.67±0.05	8.70±0.04	8.85±0.04
Thickness (mm)	2.73±0.04	2.74±0.06	2.62±0.05	2.75±0.04	2.83±0.04
Hardness (kg)	6.22±0.45	6.00±0.43	4.58±0.38	4.76±0.49	4.32±0.21
Disintegration time (sec)	42	31	42	30	29
Friability (%)	0.20	0.35	0.25	0.27	0.22
Assay (%)	98.71±1.12	99.82± 0.67	99.31±0.80	99.83±0.65	99.89±0.28
Content Uniformity	99.26±0.54	100.42± 0.51	101.37±0.57	99.72±0.99	100.44±0.74
Wetting time (sec)	17 ± 7	15 ± 6	22 ± 5	16 ± 7	16 ± 5
Dispersion Test	Ok	Ok	Ok	Ok	Ok

Table 7: Kinetic models of Fast Dispersible Aceclofenac 100mg compacted pellets in phosphate buffer pH 6.8

Formulations Code	First Order		Higuchi		Hixson-Crowell		Weibull model		
	r^2	K (hr^{-1})	r^2	K_H ($hr^{-1/2}$)	r^2	K_{HC} ($hr^{-1/3}$)	r^2	A	β
Reference	0.9483	0.044	0.7809	11.553	0.9686	0.012	0.9958	41.658	1.267
P1	0.9541	0.050	0.7497	11.316	0.9579	0.012	0.9906	21.972	1.118
P2	0.9548	0.050	0.7389	11.350	0.9558	0.012	0.9940	23.347	1.130
P3	0.9553	0.049	0.7614	11.393	0.9616	0.012	0.9924	20.941	1.079
P4	0.9522	0.052	0.7205	11.250	0.9467	0.012	0.9927	21.802	1.134
P5	0.9519	0.052	0.7211	11.260	0.9467	0.012	0.9925	21.809	1.136

Table 8: Accelerated stability testing of Aceclofenac compacted pellets at 40±5°C / 75±5% RH

TESTS	P1			P2			P3			P4			P5		
	0	3	6	0	3	6	0	3	6	0	3	6	0	3	6
Appearance	ok	ok	ok	ok	ok	ok	ok	ok	ok	ok	ok	ok	ok	ok	ok
Disintegration (Sec)	42	45	45	37	39	42	45	46	50	30	35	37	33	38	38
Dissolution (%)	98.63	98.23	98.43	102.47	101.17	98.54	100.1	99.54	98.66	100.34	98.61	97.76	100.42	99.87	98.26
Assay (%)	98.71	97.76	96.15	99.82	98.71	96.54	99.31	98.84	97.73	99.83	98.45	97.46	99.89	99.38	98.23
Shelf life (months)	16			15			24			19			25		

First order and Weibull models were found best fit for designed formulations (table 7). Results of f_2 index for all test formulations indicated dissimilarity with the reference product and f_2 values were found less than 50 (i.e. 32-41). Results of the presented study were found in close agreement with the documented results by other researchers (Bhardwaj *et al.*, 2010; Setty *et al.*, 2008; Sharma *et al.*, 2001).

3D surface and contour plots were constructed by CCD (v.7.0) to explore the effect of independent variables on dependent variables (fig. 3). An increased concentration of ac-di-sol in combination with sucrose exhibited decreased disintegration time and no prominent effect on friability. Compacted pellets were subjected to stability testing as per ICH guidelines (ICH (R_2) QIA. 2003). The estimated shelf life of formulations P1-P5 was found to be 15-25months. Formulation P5 produced best results during quality control testing and found the most stable during accelerated stability testing (i.e. 25months) and long term stability testing (i.e. 36months) (table 8, fig. 4). Thus in the light of all physicochemical tests, P5 was selected as the optimized formulation.

CONCLUSION

In this study fast dispersible Aceclofenac compacted pellets were successfully manufactured by extrusion-spheronization technique. Suitable combination of API-excipients made the formulation elegant and ac-di-sol effectively facilitated the quick dispersibility of the compacts. Bitterness of the medicament was efficiently masked by pelletization. Formulation P5 was found to be the best due to satisfactory quality attributes. It was concluded from this study that pelletization technology could be used for masking the bitterness of medicament and therefore making the dosage form patient-friendly for all ages.

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