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Studies in Formulation Development of Low Dose Content Drug Using Fluid Bed Granulation Technique

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Abstract:
During process manufacturing development of low dose Tablet, content uniformity is the main technical challenge. To achieve acceptable content uniformity, a granulation process is generally utilized. Fluid bed granulation, wet granulation, dry granulation was used for granulation purpose for formulation of sustained release tablets. Carbopol 934P solution (1 % w/v) was used as a granulating solution in the fluid bed granulator. For comparative evaluation, tablets were also prepared by direct compression and wet granulation, and subjected to dissolution. Tablets prepared by fluid bed granulation technique prolonged the release of Diclofenac Sodium better than tablets obtained by direct compression and wet granulation. Further, it complied with the requirements of ICH guidelines for stability testing. Higher temperature and humidity (40±2°C/ 75% RH, 40°C, 50°C, and 60°C) adversely affected the rate and extent of the dissolution. Diclofenac Sodium SR tablets stored in amber-colored bottles demonstrated good photo stability for 6 months at 600ft candle. The shelf-life of the formulation was predicted as 32 months.
Key Words: Stability; Carbopol 971 P; Fluid-bed granulation; Sustained release

Introduction:

There are a variety of granulation processes that can be utilized. Granulation process is grouped as either "wet" or "dry". Dry granulation is comprised of processes such as slugging or chilsonation. Wet granulation encompasses a large range of technologies including kneading; blenders with a liquid dispersion bar, and high shear mixer with an impeller and chopper blade and fluid bed granulators with top or bottom spray and possibly a rotating bottom disk[1].

Literature addresses each type of granulation process individually and in detail. However, cross comparison of different granulation technology using the same formulation not widely discussed[2]. A comparison, using sematilide hydrochloride formulation, of moisture activated dry granulation in a planetary mixer was performed vs. traditional wet granulation in planetary mixer, roller compaction and direct compression[3]. The moist granulation technique was also compared to wet granulation and dry granulation using an acetaminophen formulations[4]. The effect of manufacturing process on the initial dissolution of theophylline was also investigated using direct compression, wet granulation, extrusion spheronisation, dry granulation and spray drying[5]. A comparison of fluid bed granulation and high shear granulation related to high dose poorly water soluble low density micronized drug also performed. A comparison of low shear, high shear and fluid bed granulation during low dose Tablet process development was also investigated. Granulation comparison studies help the process engineer to choose from many available technologies in an effort to develop the most robust process for the target formulation.

The objectives of the present study were: (1) to investigate the possibility of using a Carbopol polymeric solution as granulating agent by the fluid bed granulating process; (2) to select a suitable method of tabletting for sustaining the release of Diclofenac Sodium for 12 hr; (3) to perform stability studies according to ICH guidelines and photo stability on Diclofenac Sodium SR tablets; (4) to study the influence of the storage conditions on release kinetics. The purpose of this study was to identify the robust granulation technique process for the development of sustained release tablet formulation for poorly water soluble and low dose drug content. In present investigation Diclofenac sodium is used as model drug. The wet granulation was performed by simple kneading method in a mortar and pastel. The dry granulation was

done by the high pressure slugging in a hydraulic press and by crushing it in a ball mill or in a mortar- pastel. Fluid bed granulation was performed in a top spray granulator of chronimach machineries. Granulation was done by Carbopol 934P as a binder. Prepared granules by different granulation technique were subjected for the compression. Thickness, friability, crushing strength, tensile strength, disintegration time and in vitro Tablet dissolution data.

Materials and Methods:

Diclofenac sodium was used as model drug and was gifted from Lincoln pharmaceuticals limited, India. Dicalcium phosphate and Lactose (S. D fine chemicals, Mumbai) used as diluent. Carbopol 934p (S. D fine chemicals, Mumbai) as binder, Magnesium stearate and Talc. The granulating fluid was purified water. All the chemicals and solvents used during the experiment was analytical grade.

(1) Preparation of diclofenac sodium sustained release tablets

Direct compression:

Ingredients for the preparation of tablets by direct compression are given in Table 1. Diclofenac Sodium, Carbopol 934P, and anhydrous Dicalcium phosphate were passed through sieve #25, except Ac-Di-Sol and magnesium stearate that passed through sieve #30 Diclofenac Sodium, Carbopol 934P, and Dicalcium phosphate were mixed uniformly in a V-blender and mixed with Ac-Di-Sol and magnesium stearate.

Table 1: Composition of Diclofenac sodium SR Tablets

Ingredients %	**w/w(mg)**
Diclofenac Sodium	20(75)
Carbopol 934P	10(37.5)
Dicalcium Phosphate	70(262.5)
Ac-Di-Sol	0.5(2)
Magnesium Stearate	0.5(2)

Wet granulation:

Diclofenac Sodium, Carbopol 934P, and Lactose were mixed uniformly in a V-blender and water equivalent to 0.8% w/w of the total weight was sprinkled over the powder mixture. The moist mass was passed through sieve 20# and dried at 60°C for 1 hr. The dried granules were passed through sieve #40 and mixed with magnesium stearate and Ac-Di-Sol. Composition of tablets prepared by the wet granulation is given in table 1.

Fluid bed granulation:

Diclofenac Sodium and Dicalcium phosphate were mixed uniformly in a V-blender. The granulating solution of 1 %w/v Carbopol 934P solution was sprayed at 40°C from top spray Fluid Bed Granulator. The granules were dried at 60°C. Dried granules were mixed with Ac-Di-Sol and magnesium stearate. The powder mixture prepared from direct compression, granules from wet granulation and Fluid Bed Granulation were compressed by a rotary tablet press using 3/8-inch tooling. The average weight of tablets was 379 mg, in which the Diclofenac Sodium content was 75mg.

(2) Stability studies

Diclofenac Sodium SR tablets were packed in amber colored 100-mL glass containers with polypropylene closures. Containers simulated actual packaging and the closures were secured tightly on the containers. Each container consisted of 30 Diclofenac Sodium SR tablets. They were stored in incubators maintained at 37, 40, 50, and 60°C (accelerated stability studies), 40°C/75% RH, 30°C/60% RH, and 25°C/60% RH (ICH guidelines), and in a light chamber with light intensity of 600ftcandle at 25°C. Appropriate salts were used to provide humidity in desiccators. At each time point, one container was taken out from the respective storage condition and subjected to content, dissolution, and thermal analysis. Diclofenac Sodium SR tablets were analyzed periodically for 12 months in the case of ICH guidelines and for

6 months in the case of accelerated stability studies.

(3) Dissolution studies

The drug release study was carried out using USP XXIII paddle apparatus (Veego VDA – 8D) at 37 ± 0.5^{o} C and 50 rpm using 900 ml of pH 6.8 phosphate buffer as a dissolution medium. 10 ml of sample was withdrawn at predetermined time intervals, filtered, diluted suitably and analyzed spectrophotometrically at 276 nm wavelength. Equal amount of fresh dissolution medium, maintained at the same temperature was replaced immediately. Cumulative percentage drug release at different time intervals was calculated.

Results and Discussion:

(1) Preparation of diclofenac sodium sustained-release tablets

The objectives of the study were to compare wet granulation, fluid bed granulation, and direct compression techniques in the preparation of Diclofenac Sodium SR tablets as well as to focus on one particular technique for the development of Diclofenac Sodium SR tablets. On that basis, tablets prepared from all three techniques were subjected to dissolution and the tablets prepared by fluid bed granulation were selected for stability studies. Diclofenac Sodium SR tablets prepared by wet granulation and direct compression exhibited 7- and 8-hr release (Fig. 1) and disintegrated within 2 hr. However, tablets prepared with Carbopol 934P as granulating agent exhibited 12-hr release and did not completely disintegrate even after 12 hr. A typical usage level for Carbopol resins in tablets is 10-30% as a controlled-release agent [6, 7.] However, various factors such as duration of sustained release, solubility of the drug, excipient other than Carbopol resins, and granulation technique play an important role. Presence of Carbopol 934P in granulating solution facilitated bridging during granulation and compression. Carbopol 934Phas primarily been used as a sustained-release agent. In this study it was incorporated not only as sustained-release agent, but also as granulating agent. Fluid bed granulation is far superior to wet granulation due to two basic differences. Firstly, the granulating fluid is finely atomized by the compressed air before it comes into contact with the powder, thus facilitating a more uniform and extensive distribution of granulating fluid in the powder. Secondly, the fluid bed process comprises all unit operations: spraying of granulating fluid, mixing, drying until optimum moisture content is reached.

(2) Stability studies

Several investigators identified the effect of Dicalcium phosphate dihydrate on the stability of therapeutic agents. Dulin reported that acid labile drugs such as bisoprolol degraded due to the acidic Amount of Diclofenac sodium (%) Remaining in SR Tablets Stored under Conditions Recommended by ICH environment created by the Dicalcium phosphate dihydrate[8]. However, in the present study anhydrous Dicalcium phosphate was incorporated and Diclofenac sodium is stable in acidic conditions. The amounts of Diclofenac Sodium (%) in the tablets stored under conditions according to ICH guidelines and at elevated temperature are given in Tables 2 and 3, respectively. Less than 5% of the Diclofenac Sodium was lost during 12 months in the tablets stored at 40±2°C/75% RH, 30±2°C/60% RH, and 25 ± 2°C/60% RH. The predicted shelf-life according to an Arrhenius plot for 90% Diclofenac Sodium content was 67 months, and for 95% Diclofenac Sodium 32 months. Diclofenac Sodium appeared to be stable in the storage conditions tested [9]

(3) Dissolution studies

The fit factors f_1 and f_2 are two indices that compare the dissolution profiles of a reference formulation to that of a test

Table 2: Amount of Diclofenac sodium (%) remaining in SR tablets stored under ICH guideline of stability

Time	40^0C75%RH 30°C 60% RH		25°C 60% RH
Initial	100	100	100
15 days	99.75	99.1	99.88
I month	99.55	99.1	99.82
3 months	97.39	97.57	97.9
6 months	96.08	96.94	97.46
9 months	96.64	97.36	97.72
12 months	95.35	97.38	98.45

Table 3: Amount of Diclofenac sodium (%) remaining in SR tablets stored under different storage condition

Time	60°C	50°C	40°C	37°C	Room Conditions	Light Chamber
Initial	100	100	100	100	100	100
15 days	99.5	98.74	99.12	99.69	99.9	100
I month	98.43	98.38	98.89	98.99	99.86	98.46
2 months	94.76	98.22	97.94	98.85	99.31	98.04
3 months	92.34	97.12	97.86	97.76	99.24	97.6
6 months	88.01	93.31	96.15	97.9	99.13	98.04

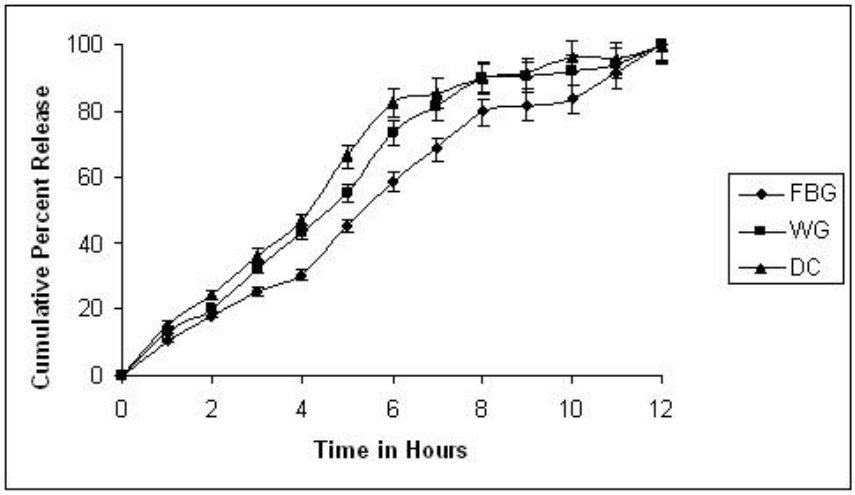

Figure 1: Dissolution profile of Diclofenac Sodium tablets prepared by Direct Compression (DC), Wet Granulation (WG), and Fluid Bed Granulation (FBG).

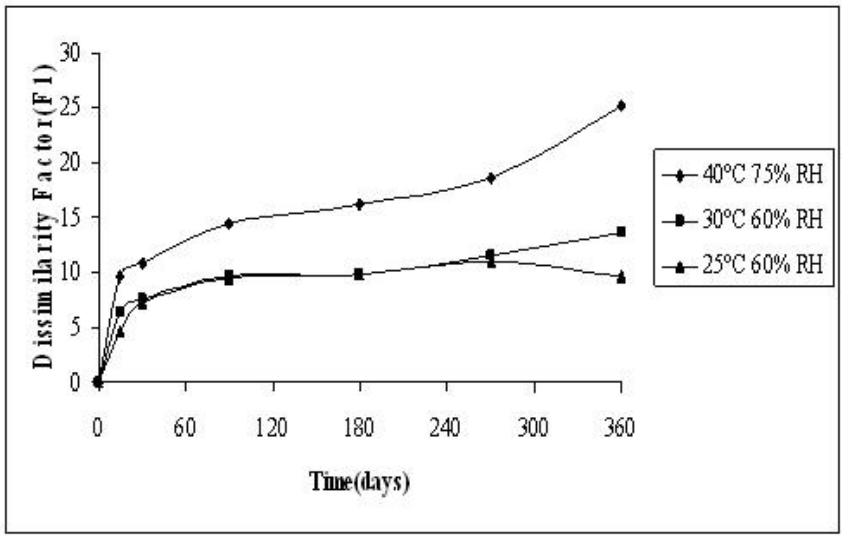

Figure 2: Comparison of f_1 factor for Diclofenac sodium SR tablets stored under ICH conditions.

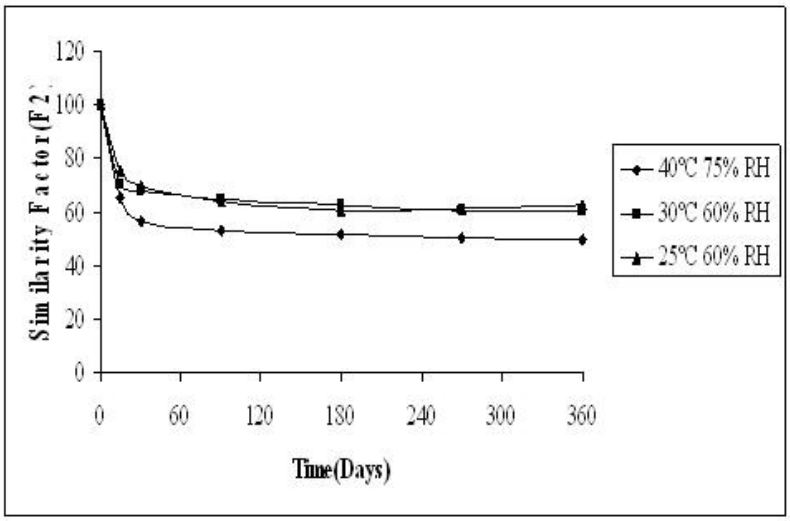

Figure 3: Comparison of f_2 factor for Diclofenac sodium SR tablets stored under ICH conditions.

formulation. These fit factors allow the systematic comparison of dissolution profiles at different time points. Based on the release kinetics, long-term stability studies and short-term accelerated stability studies were conducted only for tablets prepared by fluid bed granulation. The dissolution profile of fresh tablets was considered as a reference profile, wherein the dissolution profile of sample tablets collected periodically during the stability studies was considered as the test profile.

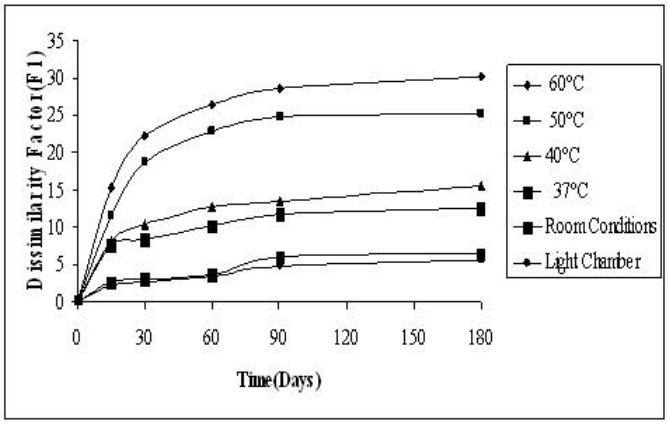

Figure 4: Comparison of f_1 factor for Diclofenac sodium SR tablets stored under different storage conditions.

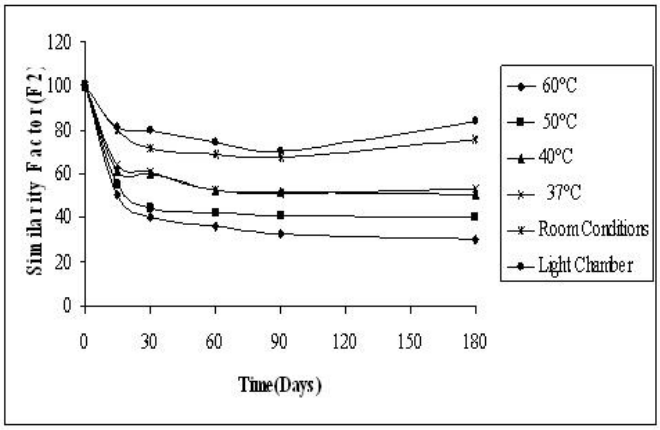

Figure 5: Comparison of f_2 factor for Diclofenac sodium SR tablets stored under different storage conditions

The f_1 and f_2 values were computed by the equations given below

$$f_1 = \frac{\sum_{t=1}^{n} R_t - T_t}{\sum_{t=1} R_t} \times 100$$

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n} W_t \left(R_t - T_t\right)^2\right]^{-0.5} \times 100\right\}$$

Where R, is the reference drug content at time point *t* and T is the test drug content at time point t, n is the number of sampling points, and W_t, is an optional weight factor. Since all the dissolution time points were treated equally, W_t was taken as 1. The average difference between the reference and test profiles is represented linearly by the test fit factor, f_1 and exponentially by the fit factor, f_2 Fit factor f_1 is 0 when the test and reference profiles are identical and increases proportionally with dissimilarity between the two profiles. Fit factor f_2 is 100 when the test and reference profiles are identical and decreases proportionally with dissimilarity between the two profiles[10]. The dissolution data points were taken at

0.5,1,2,4,6,8, and l2hr. In the calculation of 12 values, the difference between the amount of drug released by reference and test formula at a given time point is (R_t- T_t). The sum of squared difference is given as Σ Wt (R_t- T_t). The f_1 and f_2 values were calculated using Microsoft Excel. The rate and extent of dissolution of Diclofenac Sodium from tablets stored at different conditions decreased with time. Therefore, an increase in f_1 or decrease in f_2 reflects a decrease in rate and extent of dissolution

The $f_1$and f_2 values of Diclofenac Sodium SR tablets for all stability conditions are shown in Fig. 2 through 5. The rate and extent of dissolution decreased in the tablets stored at 40 ± 2°C/75% RH, 40°C, 50°C and 60°C. The FDA recommends the use of 12 values to compare the dissolution of two different products. If the value falls below 50, the dissolution profiles of the two products are considered to be significantly different from each other. The same principle was used to check at what time point the dissolution profile was significantly different from the initial dissolution profile. The dissolution profiles of the tablets stored at 50°C and 60°C differed from the fresh tablets in the first month itself. The dissolution profiles of the tablets stored at room temperature and in a light chamber remained similar to that of fresh tablets. There are several reports on the use of values in stability studies. Tablets stored under these conditions did not disintegrate during dissolution after a month of storage. During storage in these conditions, the tablets might have lost the moisture content (retained during granulation) and hardened. Therefore, during dissolution the tablets took more time for hydration, and ionic repulsion of the polymer (since the dissolution medium was phosphate buffer at pH 7.2) to manifest on a macro level as swelling. Since the tablet remained intact without any disintegration or deaggregation, the surface area did not increase to augment the dissolution as happened with the fresh tablets. Intact tablets offered a lengthy pathway for the drug to diffuse across the swollen gel. All these effects contributed to the decrease in rate and extent of dissolution. However, the dissolution profile of tablets stored under other conditions remained very close to the dissolution profile of fresh tablets.

Conclusion:

Among wet granulation, direct compression, and fluid bed granulation techniques employed for tableting the Diclofenac Sodium SR tablets, fluid bed granulation provided 12-hr Diclofenac Sodium sustained-release tablets. Tablets provided by fluid bed granulation (0.8% Carbopol 934P solution used as granulating solution) complied with the requirements of ICH guidelines for stability testing. Higher temperature and humidity (40 ± 2°C/75% RH, 40°C, 50°C, and 60°C) adversely affected the rate and extent of dissolution of drugs. Diclofenac Sodium SR tablets stored in amber-colored bottles demonstrated good photoostability for 6 months at 600 ft candle. The shelf-life of the formulation was predicted as 32 months. Therefore Carbopol 934P has been successfully used as a granulating agent to prepare Diclofenac Sodium sustained-release tablets.

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