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. Preparation and Evaluation of Directly Compressible Forms of Rifampicin and Ibuprofen

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Ibuprofen and rifampicin are high dose drugs and are known for having compression related problems. There drugs were modified to directly compressible forms by granulation and spherical crystallization technique. In granulation technique, drug was mixed with pre-gelatinized starch and sprayed with poly vinyl pyrrolidone 2% in isopropyl alcohol as binder and wet mix was passed through sieve no. 10, 16, 22 and 44 and dried. In spherical crystallization technique, a centrifuge tube containing supersaturated solution of drugs was rotated at 500-600 rpm and recrystallized by non-solvent addition along with suitable bridging liquid and formed spherical agglomerates were separated from solvent, non-solvent and bridging liquid by centrifugation and dried. The experimental parameters like effect of type of bridging liquid, concentration of bridging liquid, agitation speed, effect of temperature and mode of addition of bridging liquid on formation of spherical crystals were optimized. The resulted granules and crystals produced by respective technique were mixed with disintegrant and lubricants and compressed on running single stroke tablet compression machine by direct compression. The prepared tablets of both drugs were found to satisfy all quality control requirements of tablets mentioned in the Indian Pharmacopoeia.

Direct compression (DC) technology is receiving increasing interest in the world due to the savings in equipments, materials, labor, time and energy coupled with other advantages over conventional granulation techniques (GT). However, most of the directly compressible excipients currently available in the market are imported and hence have prohibitive cost. Compressibility and compactibility of pharmaceutical materials can be modified by crystal engineering and particle design[1-2]. Controlled or alternative crystallization technique may improve the compactibility and flow properties of active ingredients. Gorden and Chowhan[3] have modified naproxen crystals by the spherical crystallization (SC) technique. Other examples are found in an excellent review by York[2].

This investigation was prompted by this increasing emphasis on DC technology and by the need for development of indigenous technology for modifications for raw materials to directly compressible forms. Due to widespread use of ibuprofen and rifampicin and number of limitations in DC of these two drugs even by wet GT, these two drugs were selected for the present investigation. The aim of the investigation is to obtain directly compressible – modified forms of both drugs on the laboratory scale using commercially available unmodified drugs. Attempts were made to develop modified forms of drugs with properties and characteristics similar to marketed brands available internationally. For both drugs, experiments were carried out to improve flow characteristics, which will facilitate the DC tabletting.

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MATERIALS AND METHODS

Ibuprofen and rifampicin were obtained from Cadila Healthcare Ltd. Ahmedabad as gift samples. Other chemicals such as pre-gelatinized starch, polyvinyl pyrrolidone, sodium starch glycolate, microcrystalline cellulose, lactose, talc and magnesium stearate were purchased locally and confirm to LR grade standard. All solvents used in this study

were of IP grade or Analytical grade.

Preparation of directly compressible tablets by granulation technique:

In this technique[4-7], ibuprofen (80%) and pre-gelatinized starch (15%) were mixed thoroughly and transferred to a 18" coating pan rotating at 20 rpm. Polyvinyl pyrrolidone mix in isopropyl alcohol up to 2% of total mass on dry basis was sprayed on this powder mix as binder solution in coating pan. Similarly, rifampicin (75%) and pre-gelatinized starch (16%) were processed for preparing wet mass. This wet mass obtained for both drugs was passed through sieve no. 10, 16, 22 and 44 and resulting granules were dried and mixed with disintegrant and lubricant and compressed on running single stroke tablet machine (Cadmach, Ahmedabad) using 11 mm flat punches with break line on one side for ibuprofen and 8 mm flat punches with break line on one side for rifampicin, respectively. The complete manufacturing formula for both drugs by GT is shown in Table 1.

Preparation of directly compressible tablets by spherical crystallization technique:

In this technique[2-3], centrifuge tube containing supersaturated solution of drugs was rotated at 500-600 rpm and recrystallized by non-solvent addition along with suitable bridging liquid and formed spherical agglomerates were separated from solvent, non-solvent and bridging liquid by centrifugation and dried completely. The complete manufacturing formula for both drugs prepared by SC technique is shown in Table 2. The experimental parameters like effect of type of bridging liquid, effect of concentration of bridging liquid, effect of speed of agitation, effect of temperature and effect of mode of addition of bridging liquid on SC of both drugs were optimized and shown in Table 3.

Drug content analysis:

Ibuprofen and rifampicin were analyzed using a UV spectrophotometer (Hitachi U-2000, Japan) at 221 nm in phosphate buffer pH 7.2[11] and 334 nm[12] in beer's concentration range of 1-10 μg/ml, respectively.

Evaluation of flow properties of modified forms of drugs:

The modified drug forms were evaluated for flow properties[8-10] like angle of repose, compressibility, cohesion, angle of spatula, flowability index and hausner ratio and results are shown in Table 4.

Quality control tests:

All the tablets prepared by GT and SC techniques were subjected to quality control tests for tablets like weight variation, hardness, friability, disintegration, dissolution, assay and content uniformity. The dissolution profile of market preparation, product prepared by GT and product prepared by SC technique for rifampicin tablets was carried out in phosphate buffer (pH 7.2) and samples were withdrawn at regular time intervals and rifampicin content was measured spectrophotometrically at 334 nm (fig. 1).

IR-spectroscopy:

The mid-infrared region spectra of the spherical crys-

TABLE 1: FORMULA FOR DC OF DRUGS MODIFIED BY GRANULATION TECHNIQUE.

Ingredient	% Wt of ingredients	Batch size* for Ibuprofen (g)	% Wt of ingredients	Batch size* for Rifampicin (g)
Ibuprofen	80	200	-	-
Rifampicin	-	-	75	75
Pre-gelatinized starch	15	37.5	16	16
PVP in IPA (2%)	2	5	2	2
Microcrystalline cellulose	-	-	5	5
Magnesium stearate	1	2.5	1	1
Talc	1	2.5	1	1
Sodium starch glycolate	1	2.5	-	-
Total	100	250	100	100

*Batch size of 500 Tablets were prepared DC - Direct Compression.

tals of drugs were obtained using a Shimadzu IR spectrophotometer (IR-460, Shimadzu corporation, Kyoto, Japan) after making the pellets with potassium bromide.

X-ray diffraction spectroscopy:

The X-ray diffraction patterns of the pure drug and spherically crystallized drug samples were obtained using a Rigaku D max X-ray Diffractometer (Rigaku Corporation, Japan) for a 2-theta range of 5° to 50°. Fig. 2 shows X-ray diffraction patterns of pure drug and spherically crystallized forms of ibuprofen and fig. 3 shows those of rifampicin.

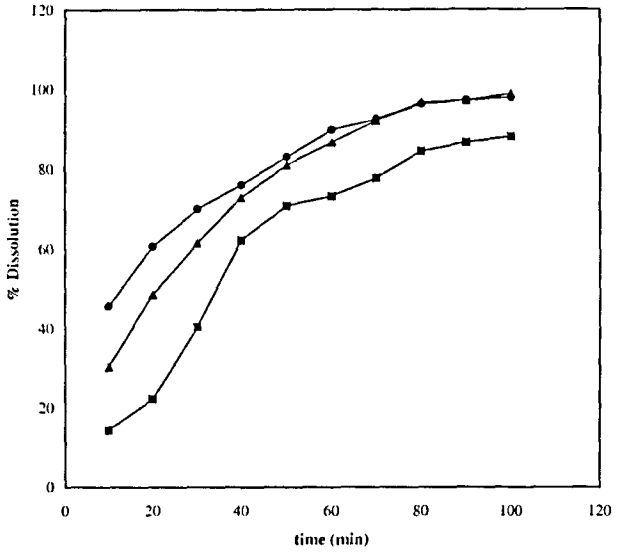

Fig.1 Dissolution profile of rifampicin tablets.

Dissolution profile of market preparation of rifampicin tablet (-▲-), Product prepared by granulation technique (-●-) and product prepared by spherical crystallization technique (-▪-) were carried out in phosphate buffer (pH 7.2), samples drawn at regular time intervals and rifampicin content was measured spectrophotometrically at 334 nm.

Differential scanning calorimetry:

The pure drug and spherically crystallized drug samples were subjected to differential scanning calorimetric studies using a Shimadzu Thermal Analyzer Model SC-30 (Shimadzu Corporation Kyoto, Japan). The heating rate was kept at 10°/min and chart speed of 5 mm/min. The test was carried out in an atmosphere of air with a flow rate of 30m/min.

Particle morphology:

Particle shapes, structure, crystalline format, agglomerated form of both drugs were observed from photomicrographs taken through a Wild M32 Stereomicroscope (Wild, Heerburgg, Switzerland) at magnification of 25 X using a neutral filter. Surface characteristics of the samples were also studied.

RESULTS AND DISCUSSION

In GT, drug was mixed thoroughly with pre-gelatinized starch and transferred to an 18" coating pan rotating at 20 rpm. Polyvinyl pyrrolidone mix in isopropyl alcohol up to 2% of total mass on dry basis was sprayed on to this powder mix as binder solution in coating pan. The drug itself has limited binding property; so pre-gelatinized starch was added to promote agglomeration of drug particles and increasing the compactibility of the drug mixture[4-6].

TABLE 2: FORMULA FOR DC OF DRUGS MODIFIED BY SPHERICAL CRYSTALLIZATION TECHNIQUE.

Ingredient	% Wt of ingredients	Batch size* for Ibuprofen (g)	% Wt of ingredients	Batch size* for Rifampicin (g)
Ibuprofen	97	200	-	-
Rifampicin	-	-	98.6	75
Magnesium stearate	1	2.0	0.17	0.13
Talc	1	2.0	0.17	0.13
Microcrystalline cellulose	-	-	0.82	0.63
Sodium starch glycolate	1	2.0	-	-
Total	100	206.0	100	75.9

*Batch size of 500 Tablets was prepared. DC - Direct Compression.

In SC technique, a centrifuge tube containing supersaturated solution of drugs was rotated at 500-600 rpm and recrystallized by non-solvent addition along with suitable bridging liquid and the so formed spherical agglomerates were separated from solvent, non-solvent and bridging liquid by centrifugation[2-3]. Various experimental parameters such as type of bridging liquid, concentration of bridging liquid, effect of agitation speed, effect of temperature and mode of addition of bridging liquid are optimized.

Out of different bridging liquids like hexane, benzene, chloroform and toluene, hexane was found to be suitable for both the drugs as both drugs have almost the same ratio of solubility. Hexane is immiscible in water and will give proper orientation of agglomerated particles within the suitable size range. When hexane was used in concentration range of 0.2-0.3 ml ranges, it gave best agglomeration of the drugs. Reducing the concentration of the bridging liquid gave no or very less agglomeration as very less amount of bridging liquid was available for solubility of the drug while higher concentration of bridging liquid resulted in compacted agglomerates, which may be due to over solubilization of drug in bridging liquid. Agitation speed of 500-600 rpm was found to be suitable for the production of SC of drug agglomer-

TABLE 3: EFFECT OF VARIOUS PARAMETERS ON SPHERICAL CRYSTALLIZATION OF THE DRUGS

Type of bridging liquid		
Bridging Liquid	**Observation**	
	Ibuprofen	**Rifampicin**
Hexane	Spherical Crystals	Spherical Crystals
Toluene	Clumps	Clumps
Benzene	Clumps	Clumps
Chloroform	Clumps	Clumps
Concentration of bridging liquid (Hexane) (ml)		
0.1	No agglomeration	Partial agglomeration
0.2	SC - Moderate agglomeration	Partial agglomeration
0.3	Partial agglomeration	SC - Moderate agglomeration
0.4	Large agglomeration	Clumps
0.5	Large agglomeration	Clumps
Agitation speed (rpm)		
300	Irregular shape	Very huge agglomerates
500 - 600	Spherical agglomerates	Spherical agglomerates
900	Small compacted agglomerates	Small compacted agglomerates
Temperature (°)		
4 ± 2	No agglomeration	No agglomeration
Room Temp. (30)	Spherical crystals	Spherical crystals
50 ± 2	Large agglomerates	Large agglomerates
Mode of addition of bridging liquid		
Whole amount at once	Irregular Spherical crystals	Irregular Spherical crystals
Drop wise	Spherical crystals	Spherical crystals

TABLE 4: EVALUATION OF FLOW PROPERTIES OF PURE DRUGS AND MODIFIED FORM OF DRUGS.

Flow properties	Pure Drug		Granulated Form of drug		Spherical crystalline form of drug	
	ibuprofen	rifampicin	ibuprofen	rifampicin	ibuprofen	rifampicin
Angle of Repose (°)	51.3	49.1	25.8	23.8	26.1	24.8
Compressibility (%)	32.2	29.8	17.3	19.2	19.3	17.4
Cohesion	52.0	51.0	10.0	7.6	12.0	8.0
Angle of Spatula (°)	61.4	61.4	24.1	26.3	26.3	25.0
Flowability Index	37.0	41.0	81.9	83.2	80.0	83.0
Hausner Ratio	1.52	1.53	1.21	1.19	1.23	1.21

ates. By decreasing the agitation speed, the agglomerated crystals were irregular in shape while by increasing speed; the agglomerated crystals were with randomly broken edges due to high force of agitation. Temperature was also important factor for the formation of spherical agglomerates of the crystalline drugs. At low temperature (4±2°) and high temperature (50±2°) it resulted in no agglomeration of the crystals only because of the solubility of the drug in the solvent system while at room temperature (30±2°) gave proper drug agglomerates. Drop wise addition of the bridging liquid has resulted in more regular shape the spherical crystals, as even distribution of the bridging liquid was available surrounding the primary drug crystals.

Flow property of the modified forms of the drugs was evaluated in terms of angle of repose, compressibility, cohesion, angle of spatula, flowability index and Hausner ratio. Flow properties behavior of the drug alone along with its modified forms has been shown in the Table 4 for ibuprofen and rifampicin. The angle of repose value for pure Ibuprofen (51.3°), its granulated form (25.8°) and spherically crystallized form (26.1°) indicated improvement in the flow property. Similarly for pure rifampicin (49.1°), its granulated form (23.8°) and spherically crystallized form (24.8°) also these values suggest improvement in the flow properties. This may be due to regular shape and smooth surface of the spherical agglomerates. The compressibility indices for pure ibuprofen (32.2%), its granulated form (17.3%) and spherically crystallized form (19.3%) and for pure rifampicin (29.8%), its granulated form (19.2%) and spherically crystallized form (19.3%) reconfirmed the good flow properties of the modified forms of these drugs. Cohesion, angle of spatula and flowability values also confirmed the improved flowability of the modified drugs (Table 4). Hausner ratio was found to be <1.25, which indicated that the addition of more amount of glidant may improve the flow of the modified drugs.

Findings of the quality control tests performed on the prepared tablets of both the drugs demonstrate that these tablets confirm to the pharmacopoeial limits, however, rifampicin tablets prepared by SC technique showed lower drug release in the dissolution experiment (fig.1). This may be due to conservation of more energy required to form crystalline lattice of the spherical crystals, which requires more time to dissolve the drug crystals. The comparative dissolution profile of market preparation, product prepared by GT and product prepared by SC technique are shown in fig. 1. From the graph it is evident that the product manufactured by GT is superior to market formulation in terms of initial drug release and product prepared from the spherical crystals of drug shows slow drug release.

IR spectra of the spherically crystallized drug and the pure drug are showing the prominent characterizing peaks for ibuprofen (1728, 1420, 1231.5, 1184.2 and 780 cm^{-1}) and for rifampicin (2355, 2850, 1375, 1240 and 975 cm^{-1}), which confirms that no chemical modification of the drugs has been taken place.

X-Ray diffraction pattern of pure drug and spherically crystallized drug were compared. In ibuprofen, pure drug shows 56 major peaks with comparatively low intensity of amplitude while spherically crystallized form shows 77 major peaks with comparatively high intensity of amplitude, which clearly indicates that the crystal structure of the drug has been modified by SC of the drug (figs. 2a, 2b). In rifampicin, pure drug shows 7 major peaks with low amplitude while the spherical crystallized modified form shows 44 major peaks with comparatively high amplitude, which indicate the

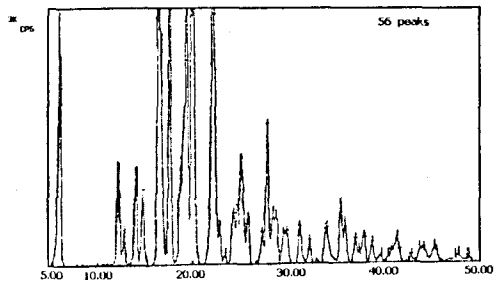

Fig. 2a: XRD of pure ibuprofen.

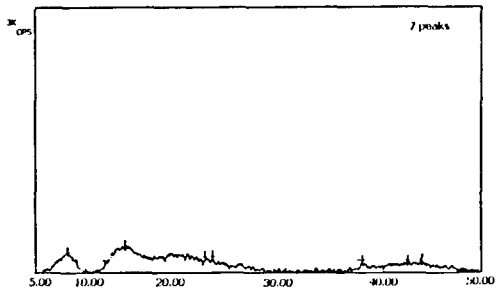

Fig. 3a: XRD of pure rifampicin.

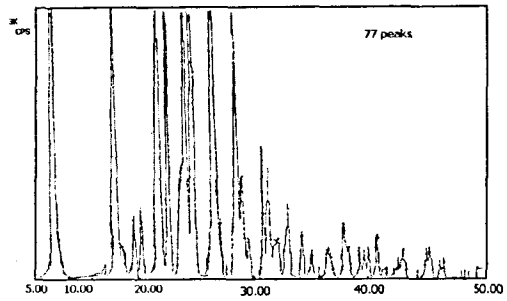

Fig. 2b: XRD of spherically crystallized ibuprofen.

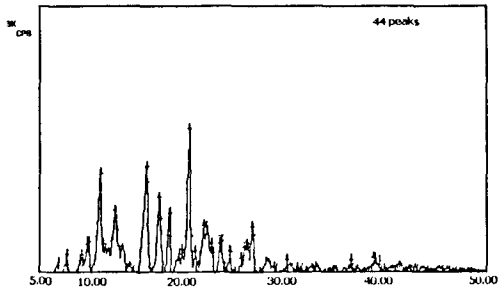

Fig. 3b: XRD of spherically crystallized rifampicin.

amorphous drug has been converted to the crystalline form (figs. 3a, 3b).

Examination of the DSC thermograms of ibuprofen pure drug and modified drug form shows that the melting point of pure drug was 79.2°, which is matching with the reported value of 76-79°. The melting point of spherically crystallized drug was found to be 78.2°, which is near the m.p. of pure drug. Similarly in the case of rifampicin, the melting endotherm was having the same pattern for the pure drug and spherically crystallized drug form (i.e. 183-188°).

From the photomicrographs of the modified forms, it is evident that there is a change in the physical form of the drugs, which possess good compressibility and good flowability. The SC technique has offered the loose agglomeration of crystallized form of drug, which will get converted into spherical nature, which gave better flow characteristics. The GT has offered deposition of the drug particles on the binder solution, which gave spherical granules that, gave better flow characteristics.

Finally, it may be concluded that there is a physical modification in the crystalline nature of drugs without any chemical modification. These modified forms show better flow characteristics then the original drug powder form, which ultimately is responsible for ease in DC. These flow properties could be correlated with the observed particle morphology. It may be beneficial to use glidant to improve the flow properties of the modified form. Thus findings of this investigation conclusively demonstrate that modified crystalline form of selected drugs can be used for DC. Rifampicin crystalline form modified by SC resulted in the formation of a different polymorphic form, which appears to be responsible for the slower dissolution observed with the tablet prepared by SC technique.

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