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EFFECT OF LACTOSE, L-HPC GRADES ON FLOW PROPERTIES OF MICRONIZED TADALAFIL FORMULATED AS SOLID DOSAGE FORM

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ABSTRACT: Tadalafil belongs to BCS class IV and recommended for treatment of erectile dysfunction. Micronization technique is used by researchers to improve its solubilization and dissolution rate. The conventional tabletting excipients pose challenge especially with micronized drug particles. The current research work aimed to study the effect of some speciality excipients on flow properties of micronized Tadalafil formulated wet granulation approach. Different grades of L-HPC and Lactose were studied. L-HPC grades included L-HPC NBD 21, L-HPC 21 and HPC – LM. The lactose grades included Milled lactose (Pharmatose 200M) and Granulated lactose (Supertab GR and Supertab SD 11). Milled lactose was used in formulation using wet granulation process whereas granulated lactose was used as directly compressible excipient. PVP k-30 added intra-granularly in concentration range of 1 - 3% w/w. All the formulation batches were evaluated for its micromeritics and dissolution. The batch with L-HPC NBD 21 showed 'Excellent' flow properties as compared to L-HPC LM and L-HPC 21. Both grades of granulated lactose showed 'Excellent' flow of granules but slightly greater angle of repose values (30 - 35°) indicating 'Good to Fair flow'. Batches with PVP k-30 gave compressibility index in range of 17 - 20% indicating fair flow of granules. These intra - granular excipient improved granule characteristics, in wet granulation process for formulation using micronized Tadalafil.

INTRODUCTION: Pharmaceutical powder technology has undergone rapid transformation with respect to its utilization for solubilization of poorly soluble drugs. The better understanding of particle characteristics of excipients such as particle size, morphology, density, wettability and drug characteristics such as micronizing technique, crystal structure and polymorphic form are resulting in formulation of novel drug product with improved solubility and permeability characteristics [1].

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The excipients added to formulation are just not added to give the dosage form its characteristics. These are scrutinized and its individual impact on release characteristics and on overall dosage form is studied. With this viewpoint, the current research work focussed on understanding the effect of different grades of excipients in microenvironment of micronized Tadalafil.

Tadalafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP); a specific phosphor-diesterase inhibitor type 5 (PDE5). The inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function by increasing the amount of cGMP which in turn results in smooth muscle relaxation and increased blood flow to the corpus cavernosum. It is widely prescribed for treatment of erectile dysfunction.

It is available in US in strengths of 2.5 mg, 5 mg, 10 mg and as 20 mg tablets to be taken once in a day. 10 mg is recommended dose and depending on individual tolerability, the dose is either decreased to 5 mg or increased to 20 mg [2]. In India, it is available in strengths of 10 mg and 20 mg as immediate release tablet and as film coated immediate release tablets by some pharmaceutical manufacturers [3]. Tadalafil is characterized by lower aqueous solubility of less than 2 µg/ml [4]. It takes 2 hours to reach maximum concentration. Although, onset of action is observed in first 15 min, the therapeutic response is observed only after 2 hours. Delayed onset of action for drug like Tadalafil may result in development of "Performance anxiety" in patients suffering from erectile dysfunction [5].

Several researchers have reported the enhancement of solubility of Tadalafil using solubilizers, solid dispersion, hot melt granulation techniques [6, 7]. However, these dosage forms are not commercialized. Considering, the therapeutic requirement for Tadalafil molecule, the research work was directed to achieve comparable release profile. Attempts were made to understand the impact of some of the speciality excipients on flow properties and release characteristics of Tadalafil. Micronization is simple process for improvising solubilization of Tadalafil. The selection of intra-granular excipients play a key role in order to achieve uniform drug distribution at granulation stage. The selection of micronized Tadalafil based on its dissolution was studied in earlier research work. As per that Tadalafil having particle size; wherein 90% of particles are lying the range of 60 - 90 microns was found to be suitable [8].

In current research work, micronized Tadalafil having d (0.9) in range of 60 - 90 microns was used for all the formulation batches. The study involved the selection of suitable intra-granular excipients for this micronized API and its suitability for tabletting processes. The micromeritics and moisture content of granules were studied for each excipient grade. These were studied for assay and dissolution and effect of selected excipient on release characteristics of Tadalafil are discussed.

MATERIALS AND METHODS:

Materials: Tadalafil, SMS pharmaceuticals, (Lot No. TDF/06) [d(0.9) in range of 60 - 90 microns], Milled lactose (DFE Pharma), Croscarmellose Sodium (Ac-di-sol), Microcrystalline cellulose (Avicel PH 102) (DFE Pharma), L-HPC NBD 21, L-HPC 21 (Shin-Etsu) and HPC LM (Nippon Soda), Polyvinylpyrollidone (PVP K 30) (Ashland Pharmaceuticals), Sodium lauryl Sulphate (Kolliphor SLS, BASF).

Chemicals: Sodium lauryl sulfate (AR grade) (S.D. Fine chemicals).

Instruments: Electronic Weighing Balance (Contech Pvt. Ltd., Model No: CA-224), UV-Vis Spectro-photometer (UV-1800) (Schimadzu), pH meter (Toshicon, Model No: 13/I/1684). Purified water for preparation of binder solution was generated in-house using water purification system of Siemens (Model No: Lobastar 7TWF).

Methods:

Preparation of Tadalafil Tablets: The amount of Tadalafil, Croscarmellose sodium as super disintegrant and Magnesium stearate as lubricant were kept constant while excipients such as L-HPC NBD 21, L-HPC, HPC- LM, Milled Lactose and PVP k-30 were varied. Quantity in terms of mg/tablet of trial formulation batches are given in **Table 1**. The batches were manufactured at laboratory scale, batch size comprising of lubricated blend equivalent to 100 tablets. L–HPC NBD 21, L-HPC LM and L-HPC 21 studied as intra-granular excipient to aid in uniform mixing of micronized drug. All the batches were formulated using wet granulation approach except B5 and B6. In all the batches, micronized Tadalafil was mixed with speciality excipient and lactose (one-third quantity) to achieve uniform distribution of micronized drug before wet granulation.

Pharmatose 200 M, a one-third quantity (Approximately 82 mg/tablet) was mixed with micronized Tadalafil and L-HPC NBD 21 (B1 and B2), L-HPC 21 (B3), L-HPC LM and L-HPC 21(B4) at stage of dry mixing. B5 and B6 involved mixing of Tadalafil with one-third quantity of Super tab GR and Supertab SD 11 respectively. HPC LM and L-HPC 21 were used as carrier along with Supertab GR for B5. Whereas, L-HPC 21 was used in B6. B5 and B6 were processed using direct compression. L-HPC and SLS was used as binder for all batches except B5 and B6.

In B7-B9, PVP K-30 in different concentrations was mixed with Pharmatose 200 M and micronized drug. Concentration of Croscarmellose sodium was kept constant at 3.7% w/w (intra-granular) and 2.85% w/w (extra-granular) for all the batches. In order to maintain constant weight to 350 mg, the quantity of Avicel PH 102 was varied. The Concentration used in batch, as a diluent, ranges from 13% w/w to 16% w/w.

Drug and excipients for each batch were weighed accurately and sifted using # 60 sieves (ASTM 250 microns). Drug was co-blended with carrier and part quantity of lactose monohydrate (Pharmatose 200 M) (82 mg/tablet) as explained in earlier paragraph. Granules obtained were wet-sifted through # 8 sieves (ASTM, 2.36 mm) and then dried in hot air oven (Expo Hitech) at temperature of 60 °C.

LOD was monitored at intervals of 5, 15 and 30 minutes (Set Limit: Below 2% w/w). Drying time of 30 minutes was required to achieve drying of granules. These granules were lubricated using pre-sifted Magnesium stearate (# 60 ASTM sieve, 125 microns) and compressed using 11 mm (circular punches) on single station compression machine at target weight of 350 mg ± 5%.

Micromeritics Properties of Powder Blends: The powder blends were evaluated for parameters like bulk density, tapped density, Carr's index, Angle of repose and Hausner's ratio.

Loss on Drying (LOD): 1 g of dried granules was weighed and crushed using mortar pestle and subject to LOD study using Moisture IR balance. The LOD was carried out at 105 °C in triplicates.

Pharmaceutical Evaluation of Tablets: Compressed tablets of each batch were studied for in-process tests such as Hardness, Thickness, Disintegration time and Dissolution studies.

***In vitro* Dissolution Studies:** The dissolution medium reported in USP monograph for Tadalafil Tablets was chosen as medium of choice due to poor solubility of drug in pH range of 1 - 7. It was modified to include time point of 5 min and 60 min along with Q time points. Dissolution testing was carried out using 1000 ml of purified water containing 0.1% Sodium Lauryl Sulfate (SLS), USP Type II (Paddle apparatus) at 50 RPM. The temperature maintained at 37 ± 0.5 °C. (Dissolution Apparatus: DBK Instruments). 5 ml of aliquot was withdrawn at each time intervals and filtered using 0.45 µ whatmann filter paper and replaced with 5 ml of fresh dissolution medium. The filtered dissolution samples were suitably diluted using dissolution medium and analysed using UV spectrophotometer at λ_{max} of 284 nm [9].

RESULTS AND DISCUSSION: Different batches of Tadalafil tablets 20 mg were formulated as described above in Methods section. The **Table 1** gives the formulation composition in terms of mg/tablet (B1 to B9).

TABLE 1: FORMULATION COMPOSITION FOR B1 TO B9

Composition	B1	B2	B3	B4	B5	B6	B7	B8	B9
Tadalafil (particle size 60-120 microns)	20	20	20	20	20	20	20	20	20
Lactose Monohydrate (Pharmatose 200 M)	245	245	245	245	-	-	245	245	245
Polyvinyl Pyrrolidone (PVP K 30)	-	-	-	-	-	-	5.6	7.0	10.5
L-HPC NBD 21	6	6	-	-	-	-	-	-	-
HPC LM	-	-	-	6	6	-	-	-	-
L-HPC 21	-	-	6	6	6	6	-	-	-
Croscarmellose Sodium (Ac-DI-Sol)	13	13	13	13	13	13	13	13	13
Sodium Lauryl Sulfate (as solution)	1.0	5.0	1.0	1.0	-	-	1.0	1.0	1.0
L-HPC (Binder solution)	2.5	-	2.5	2.5	-	-	2.5	2.5	2.5
Extra granular excipients									
Microcrystalline cellulose (Avicel PH 102)	48.5	51.0	48.5	48.5	46.0	48.5	48.9	47.5	44.0
Granulated Lactose (Supertab GR)	-	-	-	-	-	245	-	-	-
Spray dried lactose (Super tab SD 11)	-	-	-	-	245	-	-	-	-
Croscarmellose Sodium (Ac-DI-Sol)	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5
Magnesium Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total Tablet Weight	350	350	350	350	350	350	350	350	350

Effect of L-HPC Grades: L-HPC is low-substituted hydroxypropyl ether of cellulose. It is insoluble in water and swells in water by holding water molecules around hydroxypropyl groups. L-HPC is widely used as a dual-functionality excipient with properties as binder and disintegrant thus helping tablet to disintegrate quickly and forming fine dispersion which may enhance dissolution rate [10]. L-HPC NBD grades were introduced by Shin-Etsu, having different particle morphology and are designed to improve the binding properties [11]. L-HPC LM from Nippon soda grade is fine particle size grade for L-HPC. It is finer than other grades used here. L-HPC NBD 21, HPC-LM and L- HPC 21 grades were used along with micronized drug in batches B1, B4, B3 respectively. Rest of the composition was kept same. B2 also comprising of L-HPC NBD 21, was granulated using SLS aqueous solution as binder. Granule properties are presented in **Table 2**.

TABLE 2: MICROMERITICS STUDY OF B1-B9

Granule Properties	B1	B2	B3	B4	B5	B6	B7	B8	B9
Bulk density g /cm^3	0.49	0.49	0.551	0.53	0.57	0.55	0.526	0.53	0.44
Tapped density g /cm^3	0.54	0.52	0.66	0.68	0.64	0.65	0.64	0.64	0.55
Angle of repose (θ)	24^o	25^o	23^o	21^o	34.4^o	32.0^o	29^o	23^o	33^o
% compressibility	9.28%	5.77%	16.33%	22.06%	10.94%	15.38%	17.81%	21%	20.88%
Loss on Drying (% w/w)	0.90%	0.68%	0.03%	0.05%	0.53%	0.65%	0.04%	0.03%	0.01%

Overall, except B5 and B6, rest all the batches indicated 'Excellent flow properties' considering Angle of Repose values. Whereas, based on compressibility values, B1, B2 showed excellent flow characteristics followed by B5 and B6.

Remaining batches showed fair to passable flow of granules. B5 and B6 were based on direct compression approach and remaining batches by wet granulation technique. B1-B6 comprised of L-HPC grades.

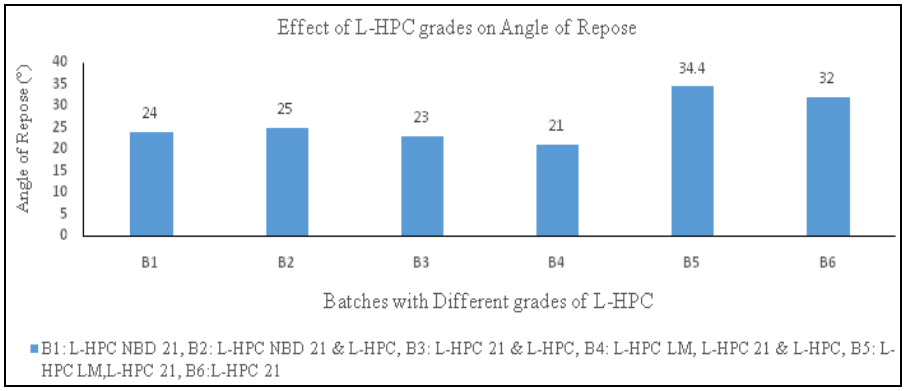

FIG. 1: EFFECT OF L-HPC GRADES ON ANGLE OF REPOSE VALUES

It was observed in **Fig. 1** that batches B1 to B6, comprising of LHPC grades; showed 'Excellent' flow properties as per Angle of Repose values for B1- B4 batches. Whereas B5, B6 showed "Good" flow properties as Angle of Repose values were in range of 30° - 35° [12]. Thus, B1 - B4 formulated with wet granulation approach was having slightly improved flow properties as compared to B5 and B6. L-HPC LM and L-HPC 21 combination (B4) was found to be suitable for improvement in flow properties for granulation using micronized Tadalafil as compared to other L-HPC grades.

Effect of Lactose: Lactose is widely used as diluent in tabletting process. Pharmaceutical α lactose monohydrate is available in several grades. The grades used were granulated lactose (B6), milled lactose and spray dried lactose. Milled lactose is manufactured to create a slight damage to crystal structure of lactose and allow formation of amorphous lactose. It is kept below 2% for Pharmatose 200 M. Milled lactose has less flowability as compared to sieved lactose and spray dried grades, however it provides good compactibility during compression but may hamper flow property. So as to improve flowability, milled lactose is available as granulated (milled) lactose [13, 14]. Supertab GR and Supertab SD 11 were used extra-granularlyin B6 and B5 respectively to improve flow property of granules during compression.

The granule properties (**Table 2**) showed excellent flow properties for Pharmatose 200 M over Supertab SD 11 and GR grades. However, Angle of repose was higher for Supertab grades (**Fig. 2**).

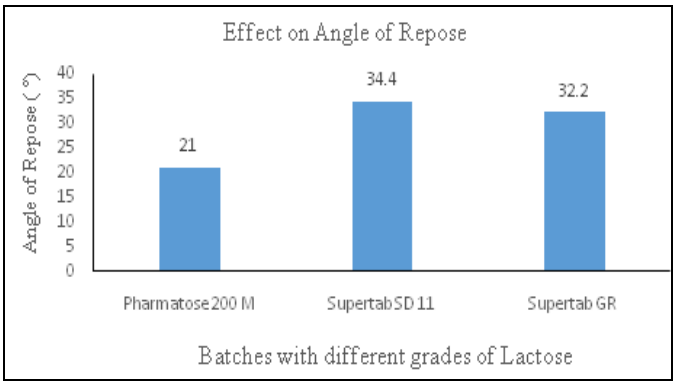

FIG. 2: EFFECT OF LACTOSE GRADES ON ANGLE OF REPOSE

Effect of PVP k-30: Povidone is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights [15]. The different types of Povidone are characterized by their viscosity in aqueous solution, relative to that of water, expressed as a K-value. PVP K 30 is typically used as binder for wet granulation process [16]. Here, it is used intra-granularly at dry mixing stage along with micronized drug. This is granulated using aqueous solution of SLS and L-HPC solution (Batch No. B7, B8 and B9). The concentrations of PVP k-30 added at step of dry mixing were studied in range of 1.6, 2% and 3% w/w with respect to tablet's weight. The micromeritics study revealed fair to passable flow based on percent compressibility index and angle of repose (**Table 2**, **Fig. 3**).

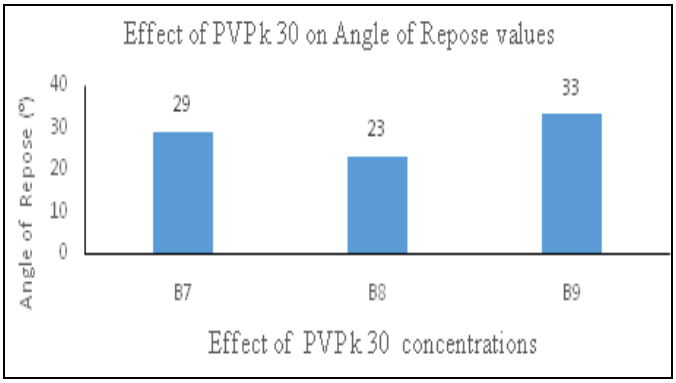

FIG. 3: EFFECT OF PVP K - 30 ON ANGLE OF REPOSE VALUES

Effect of flow properties can also have an impact during compression process and on tablet characteristics. Batch B5 containing HPC LM and L – HPC 21 showed comparatively improved release as compared to other HPC grades used as binder. However, B5 had higher Angle of Repose values and batch showed 'rat-holing' during compression. B9 containing PVP k-30 at concentration of 3% w/w showed slightly improved release as compared to 1.6% and 2 % w/w of PVP K 30. Although, B9 had angle of Repose of 33%, it did not show the compression problems. Dissolution Profile of all the batches showed release of less than 70% (**Fig. 4**).

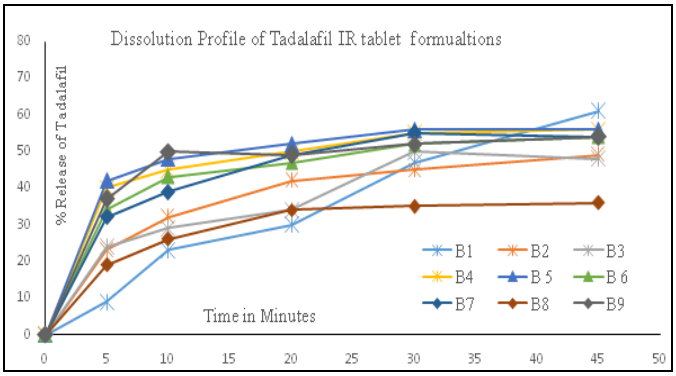

FIG. 4: EFFECT OF VARIOUS GRADES OF EXCIPIENTS ON RELEASE OF TADALAFIL

CONCLUSION: Micronized Tadalafil having d (0.9) in range of 60 - 90 microns requires intra-granular carrier along with lactose to achieve uniform drug distribution. Granules and its flow characteristics obtained with HPC LM and L-HPC 21 using wet granulation approach was better as compared to direct compression process. HPC LM and L-HPC 21 were suitable carrier for micronized Tadalafil. Also, the similar findings were observed with Lactose grades such as Supertab grade GR. Milled lactose, Pharmatose 200 M was suitable as intra-granular carrier for micronized Tadalafil as compared to Supertab grades of Lactose. PVP K-30 at concentration of 2 - 3% w/w was found to be suitable as carrier for uniform mixing of drug with Pharmatose 200 M over L - HPC and Lactose grades.

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CONFLICT OF INTEREST: There are no conflicts of Interest.

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