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Original Research Paper

IMPROVED PERFORMANCE OF CELECOXIB TABLETS USING NANOPARTICLE APPROACH

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ABSTRACT

Oral route has been the most convenient mode for the drug delivery. It has been received more attention in the pharmaceutical field because of more flexibility in developing of dosage form than any other route of drug delivery. The present research work was aimed to enhance the performance of existing water insoluble drug molecule with suitable technique. Particle size of water insoluble molecule (Celecoxib) was reduced to nanometer range using Dyno Mill. The suspension was dried to powder blend using fluidized bed granulator and spray drier. The tablets were manufactured by wet granulation and direct compression technique. The blend and tablets were characterized for particle size, micromeritic data, quality control parameters and *in vitro* drug release. The applied technique was successful in enhancing the dissolution behavior of celecoxib.

Keywords: Nanotechnology, BCS, Spray drying, Drug release kinetics.

INTRODUCTION

The number of poorly soluble drugs is steadily increasing. About 40% of the drugs in the development pipelines and approximately 60% of the drugs coming directly from chemical synthesis are poorly soluble.[1] Consequently most of them exhibit a poor oral bioavailability because in general low saturation solubility correlated with low dissolution velocity. When considering oral administration, drug release from its pharmaceutical form and its dissolution into gastrointestinal fluids generally precedes absorption and systemic availability. If the dissolution velocity is too low, a sufficiently high blood level cannot be achieved (Biopharmaceutical Classification System (BCS) class II drugs). The solubility-dissolution behaviour of a drug is frequently the rate-limiting step to absorption of drugs from the gastrointestinal tract (BCS class II drugs). Poor aqueous solubility has always been a very challenging obstacle as it is together with membrane permeability, an essential factor in the limitation of a drug's bioavailability following oral administration.[2] Since an increasing number of newly developed drug candidates in pre-clinical development phases present poor water-solubility characteristics, there is a great need for formulation approaches to overcome this factor. One of the major advancements in the areas of pharmaceutics and drug delivery in the last

decade has been the recognition of the benefits that can be gained by formulating poorly-water soluble actives as nanometer-sized drug particles, frequently referred to as nanosuspensions and/or nanoparticles.[3] Poorly-water soluble compounds are known to comprise a significant and growing percentage of the industries drug development pipeline and historically they have been viewed as highly risky development candidates.[4,5] In the past, the overwhelming consensus was that poorly-water soluble drug candidates would be difficult to develop, there would be numerous post launch issues prompting clinicians to prescribe such medications cautiously, and when available, alternative therapies to improve compliance, efficacy and safety would be prescribed. To address this need, a significant amount of attention over the years has been focused on formulation strategies for this class of molecule, which includes molecules in BCS classification II (poorly soluble and permeable), and Class IV (poorly soluble and impermeable). Out of the many ways to increase a product's solubility/dissolution rate characteristics with the aim of enhancing its oral bioavailability, drug formulation as nanoparticles has received much-increased interest over the last decade. The hypothesis behind dissolution rate enhancement, considering drug particle size reduction to nanometer range, lies primarily in a much-increased effective surface area (Noyes-Whitney) presented by the resulting drug nanoparticles. Nanoparticles are defined as particulate dispersion or solid particles with size range of 10-1000 nm. The drug is dissolved, entrapped, encapsulated or attached to nanoparticle matrix.[6] Depending upon method of preparation nanoparticles, nanosphere, nanocapsule can be obtained. Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene-1-sulfonamide) is a non-steroidal anti-inflammatory drug (NSAID) of BCS class II drug used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms, and to reduce numbers of colon and rectum polyps in patients with familial adenomatous polyposis. The objective of present investigation was to evaluate the potential of wet milling/ media milling process in the development of crystalline nanoparticle formulations of Celecoxib and to compare the dissolution profile of nano-sized and micronized oral formulation.

MATERIALS AND METHODS

Materials

The Celecoxib API was available in formulation laboratory. Aerosil 200 was purchased from M/S Evonik, Degussa, Germany. Avicel PH 102 was purchased from M/S FMC Biopolymers, U.S.A. The HPMC E5 PREMIUM LV, propylene glycol and glycerin were purchased from Dow Chemicals, U.S.A. Povidone (polyvinyl pyrollidone K30) was purchased from BASF, U.S.A. Lactose Monohydrate and Lactose DCL11 were supplied by DMV International, Netherlands. Sodium lauryl sulphate was procured from Stephan,U.S.A. Cross povidone (PP XL10) was purchased from ISP, U.S.A. HPC-L was supplied from Herculus,U.S.A. Magnesium Stearate was purchased from Covidien,U.S.A.

Methods

Development of Celecoxib Nanoparticles Using Dyno Mill

Dyno milling process is ideal for the smallest possible applications in research and development and for small-scale productions. Nanoparticle of Celecoxib using HPC-L as a stabilizer were prepared as described. Batch No. (Formulation1).Solution of SLS and HPC-L was prepared in purified water to produce 20% dispersion under continuos stirring To the solution of SLS and HPC-L, Celecoxib was dispersed under stirring for 30 minutes to get homogenous dispersion (described as Table 1). The above dispersion was milled through Dyno Mill KDLA to get desired particle size of Celecoxib using zirconium beads as grinding media (described as Table 2). Parameters recorded during media milling of Celecoxib dispersion (described as Table 3).

Manufacture of Celecoxib Granules Using Spray Drying Process

600 gm of nanosuspension (HPC-L as stabalizer) was dried using BUCHI Mini Spray Dryer. 200 gm of water was added to decrease viscosity of suspension for easy passage through spray nozzle. The operating parameters are listed in Table 4.Spray drying was continued up to 4 hours.

% Yield

The yield of granules was calculated using equation as under:

$$\% \text{ yield} = \left(\frac{\text{amount obtained after drying}}{\text{amount present before drying}}\right) \times 100$$

Amount obtained after spray drying = 46 gm
Amount of solid present before spray drying in 600 gm of suspension = (241×600) / 1112
= 130.03 gm
% yield = (46÷130.03) × 100
= 35.37%

Assay

$$practical\ yield = \left(\frac{absorbance\ of\ test}{absorbance\ of\ standard}\right) \times (standard\ \frac{dilution}{test}\ diution) \times 100$$

= (0.5/0.493) × (0.008/0.0096)×100

= 84.17 mg of Celecoxib
Hence, 100mg of spray dried product contains = 84.17 mg of Celecoxib
Theoretically, 120.5 mg of spray dried product contains = 100 mg Celecoxib
Therefore 100 mg spray dried product contains = 82.99 mg Celecoxib

$$\%Assay = \left(\frac{practical\ yeild}{theoretiaclyeild}\right) \times 100$$

= (84.17/82.99)×100
= 101.2%

Manufacture of Celecoxib Granules Using Fluid Bed Process

Celecoxib drug loaded granules were fabricated using milled suspension of the drug sprayed on Fluidized Bed Dryer (Top spray arrangement of GLATT GPCG 1.1).Lactose was used as inert carrier in GLATT chamber GPCG 1.1. Celecoxib milled suspension was sprayed by using Top spray arrangement of GLATT GPCG 1.1. The operating parameters are listed in Table 5. Granules were dried for 2 hours at product temperature 40±5 °C.

% Yield

The yield of granules was calculated using equation as under

Assay was done Phosphate buffer pH 12 as the media.

Standard Preparation

The Celecoxib (100 mg) dissolved in 50 ml of methanol and volume was made up to 500ml using phosphate buffer pH 12 as media in 500 ml volumetric flask.

Sample preparation

Spray dried product (120.5 mg) is equivalent to 100 mg of Celecoxib was dissolved in 50ml methanol and made up to 500 ml using phosphate buffer pH 12 as media in 500 ml volumetric flask (V.F.). 4 ml from each V.F was taken and made up to 100 ml using media in separate V.F. This dilution was observed for its absorbance by U.V method at 255 nm.

Weight of the powder post granulation/ Total weight (carrier + Suspension)= (333.6/344.5)×100
=96.8%

Assay

Standard Preparation

The Celecoxib (100 mg) dissolved in 50 ml of methanol and volume was made upto 500 ml using phosphate buffer pH 12 as media in 500 ml volumetric flask.

Sample Preparation

Dried Celecoxib granules (241.43 mg) is equivalent to 100mg Celecoxib, were dissolved in 50 ml of methanol and volume was made up to 500 ml using phosphate buffer pH 12 as media in

500 ml volumetric flask.4 ml from each V.F was taken and made up to 100 ml using media in separate V.F. (100 ml each). This dilution was observed for its absorbance by U.V method at 255nm.

$$practical\ yield = \left(\frac{absorbance\ of\ test}{absorbance\ of\ standard}\right) \times (standard\ \frac{dilution}{test}\ diution) \times 100$$

= (0.469/0.433) × (.008/0.0193)×100
= 45.4mg of Celecoxib

Hence, 100mg dried Celecoxib granules contains = 45.4 mg of Celecoxib
Theoretically, 241.43 mg of spray dried product contains = 100 mg Celecoxib
Therefore 100 mg spray dried product contains = 41.41 mg Celecoxib

$$\%Assay = \left(\frac{practical\ yeild}{theoretiaclyeild}\right) \times 100$$

= (45.4/41.4)×100
%Assay = 108.8%

Manufacturing of Celecoxib Tablet

Preparation of Celecoxib Blend

100 mg celecoxib (micronized) along with other excipients i.e. Fillers (lactose DCL 11 and Avicel 102), Disintegrants (crosspovidone); Glidant (Aerosil); Lubricant (Talc). The fillers Lactose DCL 111 and Avicel 102 were chosen because of good compressibility and flow ability of these excipients. The talc and Aerosil were used to produce good lubricating and flow ability of the powder blend.

Fabrication of Celecoxib Tablets Using Micron Sized Celecoxib Powder-Batch F1

Tablets were formulated using wet granulation method. HPC-L (1.2 gm) was mixed with with 75 ml of purified water to produce a binder solution. Celecoxib (2.10 gm), 12.05 gm of Lactose MH, 5 gm of Avicel 102,2 gm of Crosspovidone and 0.2 gm of Aerosil were mixed (refer Table 6) and passed through sieve BSS 22. This blend was mixed for 10 minutes in Rapid Mixer Granulator with gradual addition of binder. High kneading was done for 30 seconds. After mixing in RMG, blend was dried in Fluidized Bed Dryer for 1 hour at 60 °C and passed through sieve no. 22 (BSS). Material was mixed in an octagonal blender for 15 minutes and evaluated. Tablets were compressed using single rotatary compression machine and evaluated.

Fabrication of Celecoxib Tablets Using Spray Dried Celecoxib Powder-Batch F2

Tablets were formulated using direct compression method**.** All ingredients were weighed (refer Table 7) and passed through sieve no.30 (BSS) and magnesium stearate through sieve no. 60 (BSS). Blend was then mixed in an octagonal blender for 15 minutes and evaluated. Tablets were then compressed using single rotatory compression machine.

Fabrication Of Celecoxib Tablets Using Celecoxib Loaded Granules (FBP Process)-Batch F3

Tablets were formulated using direct compression method**.** All ingredients were weighed and (refer Table 8) passed through sieve no.30 (BSS). The magnesium stearate through sieve no. 60 (BSS). Blend was then mixed in an octagonal blender for 15 minutes. Tablets were then compressed using single rotatory compression machine.

Evaluation of Formulations

Evaluation for Blend of F1, F2, F3

Size of particles

Particle Size Distribution (PSD) was determined by Sieving Method: The sieves were weighed separately before starting the experiment and were arranged in ascending order of their mesh size (BSS No.) in a particular order i.e.22, 30, 44, 60, 85, 100 and pan. The assembled set of sieves

was placed in test sieve apparatus and 100 g of blend of formula F1, F2, F3 was added on the top of the sieve. After 30 min of shaking, the assembly was opened & each sieve along with the retained sample was reweighed. The weights of the individual sieves were subtracted from the initial weight of the empty sieves. Wt of the sample taken for analysis = 100 g (refer Table 9).

Micromeritic properties

The blend was analyzed for flowability and compressibility parameters such as angle of repose, Carr's compressibility index, Hausner Ratio and density studies (refer Table 10).

Evaluation for Tablets of Formula F1, F2, F3

Quality control parameters

These quick release part tablets were also subjected to various parameters i.e. weight variation, hardness and disintegration (refer Table 11)

- *Weight variation*

  The weight variation was determined by taking 20 tablets. Each tablet was taken and then weight of each tablet was determined accurately using electronic balance. The % deviation from average weight was calculated accordingly.

- *Hardness*

  Hardness of tablets was determined by Monsanto Hardness Tester on 10 tablets of each batch.

- *Thickness*

  Thickness of these three batches was determined using Verniere Calliper. Test was done on 10 tablets of each batch.

- *Diameter*

  Diameter of these three batches was determined using Verniere Calliper. Test was done on 10 tablets of each batch.

- *Disintegration Time*

  Disintegration was done using USP device having 6 glass tubes, 3 inches long open at the top held against a 10 mesh screen at the bottom end of basket rack assembly. Six tablets ,one in each tube were placed from each batch and basket rack is positioned in 1-l beaker of simulated gastric fluid at 37±2 °C such that tablets remain 2.5 cm below the surface of liquid on their upward movements and descend not closer than 2.5 cm from the bottom of the beaker. A standard motor driven device is used to move the basket assembly containing the tablets up and down through a distance of 5 to 6 cm at a frequency of 28 to 38 cycles per minute. Time was calculated for tablets to disintegrate completely.

In Vitro Drug Release

The *in vitro* characterization of the formulation of F1, F2, F3 was done under different dissolution conditions. The dissolution of formulations was determined using different dissolution media. For dissolution studies USP-1 (paddle) type of apparatus was used. The tablet was immersed in a flask containing 1000 ml of appropriate medium maintained at 37±0.5°C and paddle was rotated at 75 rpm. At appropriate time intervals the samples were withdrawn and analysed for drug content by UV spectrophotometric analysis at λ max 255 nm. The concentration of drug was determined from the standard curves and cumulative % release of drug was calculated. The graphs were plotted between the cumulative percent of drug released vs. time. The media used for dissolution studies are as under:

A. 0.1N HCl+0.25% SLS
B. 0.1N HCl+0.5% SLS
C. Acetate buffer pH 4.5 + 0.25% SLS
D. Acetate buffer pH 4.5 + 0.5% SLS

Release Kinetics

The data obtained from in vitro drug release studies was subjected to fitness of best model for drug release such as Zero order, Higuchi, First order and KorsMeyer- Peppas in order to explain its release mechanism.[7-9]

RESULTS AND DISCUSSION

Nanoparticle formulations were prepared with HPC-L as a stabilizer using Dyno mill. Particle size distribution d (0.5) and d (0.9) 0.133 µm and 0.761 µm respectively was achieved. It is one of the critical parameter impacting the quality of formulation. Different surface stabilizers were evaluated. HPC as stabilizer has produced better results in terms particle size reduction, dispersion

stability post milling and suspension characteristics. The generated suspension was processed using spray drying and fluid bed processor to produce suitable granules for tabeltting (Table 1-5). Celecoxib (micronized) tablets were manufactured by wet granulation method (batch F1) and direct compression method (batch F2 and F3) was adopted for nano particle formulations. Table 6-8 presents the composition of these formulations. The blends as well as tablet formulations were then subjected to evaluation for various parameters. The blend was characterized for particle size distribution, flow properties, density studies and compressibility behaviour (Table 9-11). The formulated batches of tablets were evaluated for quality control parameters and dissolution studies. The *in vitro* drug release profiles of Celecoxib tablets manufactured by using micronized and nanosized/Nanoparticle drug were obtained (Figure1 to Figure 2). A reasonable faster drug release was observed in case of Nanoparticle formulation due to decrease in particle size of drug. Rate of drug release was significantly improved using Celecoxib in nano particle formulation in comparison to micronized Celecoxib. The extent of drug release was also significantly improved using nano particle formulation. Complete drug release was observed using nanoparticle formulation approach whereas drug release was in complete using micronized formulation.

CONCLUSION

The inferences drawn from present investigation suggest that nanoparticles of Celecoxib (BCS class II) were successfully prepared using Dyno mill (wet milling techniques). Dispersion was stabilised using HPC-L stabilizers. Nanoparticle dispersion was converted to powder form using spray drying and fluid bed processor with suitable carrier. Subsequently the tablet formulation was developed and evaluated. Significant increase in dissolution profile was observed using nanoparticle formulation as compared to micronized formulation. The dissolution profile indicates enhanced performance of existing molecule using nanoparticle formulation.

Table 1: Composition of Celecoxib formulation using HPC-L as a stabilizer

Material	Gm/Batch	Percentage (%)
Celecoxib	200	18
SLS	2	0.18
HPC-L	20	1.8
Demineralized water	888	80
Total	1110	100

Table 2: Process Parameters of Dyno Mill (KDL-A)

Media	Zirconium beads
Size	0.4-0.6 mm
Density	2.3 kg/ltr
Volume of milling chamber	600ml
Volume of bead	480ml
Lubricant used	PEG400
Time per cycle (min)	15
Total milling cycles performed	24

Table 3: Parameters recorded during media milling

Milling Time (min)	Flow Rate (gm/min)	Product Temperature (ºC)	Temperature of Cooled water (ºC)	Pressure of mill (Bar)	Speed (RPM)	Milling mode
30	82	32	7	0	2500	Continuous
60	83	32	7	0	2500	Continuous
90	79	32	8	0	2500	Continuous
120	76	34	8	0	2500	Continuous
150	85	34	10	0	2500	Continuous
180	82	32	10	0	2500	Continuous
240	76	34	10	0	2500	Continuous
300	83	32	10	0	2500	Continuous
360	83	32	10	0	2500	Continuous

Table 4: Parameters of spray dryer during drying

Inlet temperature	220	°C
Aspirator	50	%
Pump	13	%
Nozzel Clearance	1	
Actual Inlet temperature	224	°C
Outlet temperature	58	°C
Nitrozen Gas	40	PSI

Table 5 : Parameters of GLATT during drying

Parameters	Set	Actual	Min	Max	Unit
Inlet temperature	50	42	20	120	ºC
Product temperature	70	40	20	85	ºC
Exhaust temperature	60	32	20	85	ºC
Drive speed	60	60			%
Spray pump speed	15	15			
Atomization Air	1.6	1.5			Bar
Air Flow		78			Cfm
Operating Air		7.8		4.5	Bar
Actual weight		0.00			Kg
Spray Rate	10	00			Gm/min

Table 6: Composition of Batch F1

Material	Quantity (mg/tab)	Quantity (100 tab in gm)
Celecoxib (micronized)	100	10
Lactose MH	120.5	12.05
HPC-L	12	1.2
Aerosil 200	2	0.2
Avicel 102	50	5.0
Crosspovidone(PPXL-10)	20	2.0
Extragranular Material		
Avicel 102	6.3	0.63
Crosspovidone(PPXL-10)	20	2.0
Magnesium stearate	4	0.4
Lactose MH	13	1.3
Total	400	34.73

Table 7: Composition of Batch F2

Material	Quantity(mg/tab)	Quantity(50 tab in gm)
Spray Dried Celecoxib powder + lactose DCL	241	12
Lactose MH	13	0.65
Avicel102	100	5
Crosspovidone (PPXL-10)	40	2
Magnesium stearate	4	0.2
Aerosil 200	2	0.1
Total	400	20

Table 8: Composition of Batch F3

Material	Quantity(mg/tab)	Quantity(50 tab in gm)
Celecoxib loaded Granules	230	11.5
Crosspovidone(PPXL-10)	40	2
Avicel 102	124	6.2
Magnesium Stearate	4	0.2
Aerosil	2	0.1
Total	400	20

Table 9: particle size distribution for different formulations

S. No.	Sieve No.	F1(g)		F2(g)		F3(g)	
		Qty. Retain	Cumulative	Qty. retain	Cumulative	Qty. Retain	Cumulative
1	22	0	0	0	0	0	0
2	30	6	6	0	0	0	0
3	44	12	18	0	0	0	0
4	60	23	41	0	0	8	8
5	85	17	58	0	0	17	25
6	100	19	77	0	0	26	51
7	Pan	23	23	100	100	49	49

Table 10: Micromeritic data of the blend

S. No.	Angle of repose (°)	Bulk density gm/ml	Tap density gm/ml	Carr´s index	HR	Loss on drying
F1	28	0.5061	0.6858	26.20%	1.355	1.89%
F2	27	0.417	0.689	39%	1.652	1.56%
F3	25	0.5	0.625	20%	1.25	1.39%

Table 11: Quality Control Parameters for Tablet Formulations

S. No.	Hardness (Kph)	Thickness (mm)	Diameter (mm)	Disintegration time (min)	Weight variation (%)
F1	8.19	4.94	10.02	2.85	0.028
F2	8.61	5.92	10.03	3.08	0.073
F3	8.87	5.92	10.03	1.81	0.04

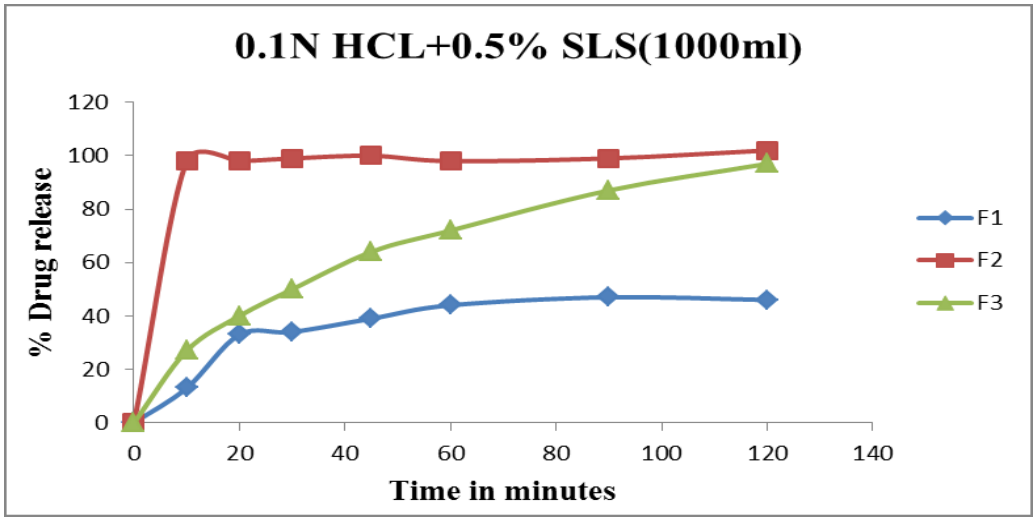

Figure1: Drug release profile of immediate release tablets in 0.1N HCl+0.5% SLS

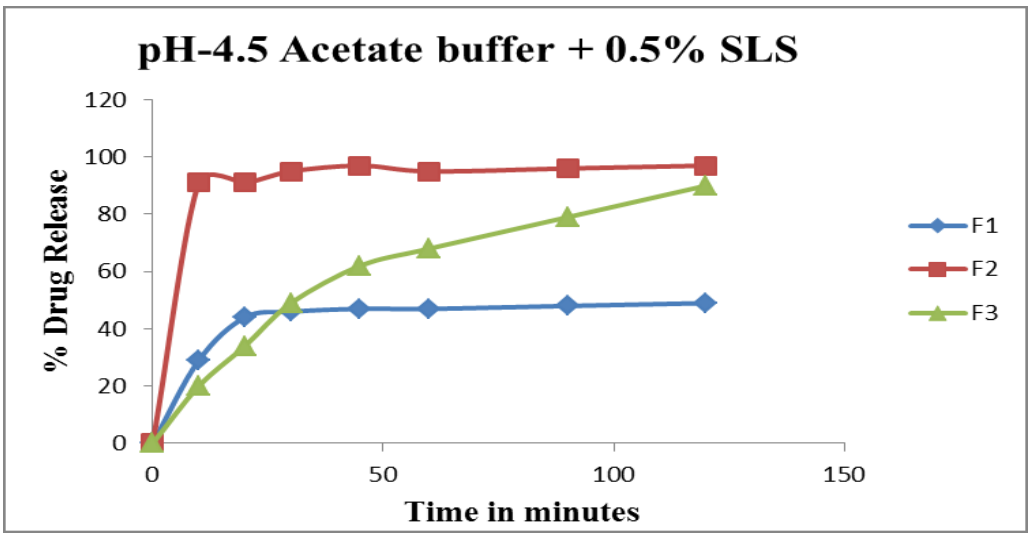

Figure 2: Drug release profile of immediate release tablets in Acetate buffer pH 4.5 + 0.5% SLS

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