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Formulation of different polymer coated spherules from granules

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Abstract

A novel spheronisation technique is reported here for forming spherules from granules using FDA approved excipients and common pharmaceutical unit operations. The aspirin is used as a model drug to check stability during the process. For that, spherules are prepared by "bed coating during sliding" (BCDS) of granules. Spherules with two size range (sieve no 22 and 44) are compared. These spherules are further coated with polymers to show the versatility of the process. They are characterised by microscopical evaluation, flow property determination, drug content evaluation and *in vitro* drug release studies. Microscopical evaluation reveal that number of edges (90° and 45°) are less for spherules compared to granules. Angle of Repose sand packing parameters appeared excellent. Different polymer coating gives different release profile as per the properties of the polymer. However, the drug content is lower for 44 as compared to 22 while drug release profile appears similar. This is a robust and versatile platform delivery system for developing advanced drug delivery systems (ADDS). However, the stability of aspirin is affected by the wet process may be because aspirin is a hydrolytically labile drug.

Keywords- Spherules, Granulation, Spheronization, Bed coating during sliding (BCDS), Advanced drug delivery systems (ADDS), fluidised bed drying (FBD)

INTRODUCTION

Spheronization is the most widely used method of manufacturing spherules (spherical shaped particles) [1, 2]. Which produces spherules with high drug loading capacity and better flow properties as compared to granules and pellets [3, 4]. This is because in granules and pellets the shape is not necessarily spherical in nature [5, 6]. The spherules in addition provides an opportunity to modify its surface properties by polymer film coating [7]. Surface coatings improve the functional properties such as appearance, drug release and integrity of particles during processing of spherules [8, 9]. As compared to granules, spherules have low surface area to volume ratio so less amount of coating solution is required [10, 11]. Spheronization is generally done with fluidised bed drying (FBD) [12], where the droplets are dried in air under circulation produce spherules with irregular shape and surface roughness due to rapid drying. Thus, alternative methods are required that can be adopted in small and large process to produce uniform spherules.

Low cost production of spherules can be achieved by wet granulation followed by "bed coating during sliding (BCDS)" as these processes can be engineered to regular pharmaceutical unit operations and scaled up [1]. Granulation can be done by sieving followed by sizing [13]. The spheronization by BCDS can lead to uniform sized particles as polishing of coated starch particles to granules are happening during sliding, that can lead to conversion of granules to spherules. The spherules can be surface modified by polymer film coating [14]. Polymers with different physical properties can be used for that purpose. Ethyl cellulose (EC), is a cellulose derived polymer, widely used in sustained release formulations [15]. Hydroxypropyl methyl cellulose (HPMC) absorbs gastric fluid and swells to form a gel, hydration of this gel leads to erosion and release of the drug into external environment [16]. HPMC is used to modify drug release properties from particles [17, 18]. Eudragit is a PH sensitive anionic copolymer of methacrylic acid and methyl acrylate [19]. Eudragit S 100 is soluble at pH above 7 and is used for colon targeting. Eudragit coating provides pH dependent drug release [20]. During coating color and appearance of the spherules are being changed using appropriate colors and excipients [21].While this process appears affordable and accessible for small and large scale processes, it can lead to disadvantages as well. For example, the wet process can affect the stability of drug molecule.

In the current study, the effect of wet granulation, BCDS and polymer coating on stability of aspirin is analysed. The granules, spherules and coated spherules are successfully prepared, however, the stability of aspirin is affected.

MATERIALS AND METHODS

Materials

Aspirin, lactose, and acetone were purchased from Spectrum chemicals Pvt Ltd, Cochin, Kerala. Starch and ethanol was obtained from Nice chemicals. Ethyl cellulose (EC) and Hydroxy Propyl Methyl cellulose (HPMC) were procured from Loba Chemie Pvt Ltd, Mumbai, India. Eudragit S 100 was bought from Research lab fine chem industries, Mumbai, India. All the chemicals and reagents used were of laboratory grade. All the reagents and buffers were prepared as per standard protocol.

For drug content analysis UV/Visible spectrum (SHIMADZU UV-1800 UV Visible spectrophotometer) were used and for drug release studies, dissolution test apparatus (Veego instruments, Mumbai, India) have been used, the physical properties and surface appearance of spherules were analysed using Projection Microscope (Medimeas instruments, Haryana) and Tap density apparatus (VTAP Matic-2, Veego instruments, Mumbai, India).

Methodology

Wet granulation of aspirin granules was done by an established procedure [22]. For that, aspirin (12gm), lactose

(6mg) and starch powder (80mg) were taken in a mortar and pestle, ground it into fine powder. Then starch paste (5% w/v) was added and mixed well to form coherent mass. The coherent mass were passed through sieve no.12 to get wet granules [13, 23].

Preparation of polymer coated spherules

Wet granules (10gm) was accurately weighed and taken into 250ml beaker and rotated in clockwise direction at 45° angle. While rotating ethanol: water (50:50 v/v) mixture were sprayed to granule bed for maintaining the wetness. Small amount of starch powder was added while rotating, to improve the flow properties and 6-7 drops of starch solution (prepared by adding 3 drops of 5% starch paste in 7ml distilled water) are also added or sprayed to this rotating granule bed for improving the binding of small fines of starch powder to get the spherules. The prepared spherules were then sieved (sieve no 22 and 44) to get uniform sized spherules. Coating solution were prepared by dissolving polymer (500 mg), dye (100 mg), and talc (400 mg) dissolved in acetone (25 ml). Coating solution were sprayed to the spherule bed with constant rotation. After coating the spherules were spread on petridish and kept at 60□C in hot air oven for 20 min to prepare dried polymer coated spherules.

Microscopical evaluation of spherules and granules

The shape and surface properties of granules and spherules were examined using a projection microscope. The prepared spherules and granules were separately taken in a glass slide and kept under projection microscope (10x) to observe the shape and edges of particles. Randomly selected 15 particles were studied for its shape. Particles were analysed by counting the number of edges 45^0, 90^0, 120^0 in each particles were collected and analysed using projection microscope.

Flow property determination

The parameters such as Angle of repose, Carr's index, Hausner's ratio of spherules (retained in sieve no: 22 and 44) were measured.

Angle of Repose:

Angle of repose reflects the free flow of solids reflected in terms of maximum angle between the cone of the pile of solid material and horizontal plane.

Spherules were allowed to flow through a funnel freely into a graph paper to form a pile. The Angle of repose calculated using the following formula

Angle of Repose (tan θ) = h/r

Where 'h' is the height and 'r' is the radius of pile

The flow pattern of different AR is as follows; excellent (25-30), good (31-35), fair (36-40), passable (41-45), poor (46-55), very poor (56-65) and >66 represents very very poor flow property [24, 25, 26, 27].

Particle packing parameters:

Bulk density is mainly used to find out the uniformity of spherules. That helps to conform size of container, closures, capsules, selection of production apparatus and equipment's.

For that, spherules (20gm) were taken in a 10 ml measuring cylinder were used to find out the bulk density and tapped density. Bulk density was determined by noting down the volume occupied by spherules after tapping manually 2 times on the flat surface. The measuring cylinder containing spherules was attached with a tapped density apparatus and the tapped volume was determined by noting the volume occupied by spherules after 100 tappings on a flat table top. Bulk and tapped density were calculated from bulk and tapped volume by the following formula.

Bulk density = Spherule weight/ Bulk volume

Tapped density = Spherule weight/ tapped volume

Compressibility Index or Carr′s Index is the measure of tendency of spherules to consolidate, based on interparticulate interactions. It is estimated by below formula,

Carr′s index = [Tapped density-Bulk density/Tapped density] 100

Carr′s index control values are excellent flow (<10), good (11-15), fair(16-20), passable(21-25), poor(26-31), very poor (32-37), and very very poor (>38).

Hausner′s Ratio is the ratio of tapped and bulk density. Low values indicate good flow property of spherules.

Hausner′s ratio = Tapped density/Bulk density

Hausner′s ratio control values are excellent (1.0 – 1.11), good (1.12-1.18), fair (1.19-1.25), passable (1.26-1.34), poor(1.35-1.45), very poor(1.46-1.59) and very very poor (>1.60) [25, 26, 27].

Drug content evaluation

Aspirin spherules (50mg) were weighed accurately and dissolved in 50ml of suitable phosphate buffer (6.8 or 7.4) which was chosen according to the polymer used for coating stirred for 30 minutes and filtered. Absorbance measured at 265nm by UV spectrophotometer using phosphate buffer as blank [27].

***In vitro* dissolution study**

Amount of drug released from spherules with respect to time were determined by USP type 2 basket apparatus. Suitable phosphate buffer of pH 6.8 or 7.4 were taken in dissolution basket and 1500mg spherules were added. The apparatus was maintained the temperature of 37 ± 0.5°C and basket rotated (75 rpm) to maintain sink condition. At various interval 5ml samples were withdrawn (1, 2, 3, 4, 5 and 6 hours) and the same amount of buffer was replaced after each interval. Absorbance measured at 265nm using UV spectrophotometer [27, 28].

Kinetic Modelling

The kinetics and mechanism of drug release from spherules were determined by fitting the *in vitro* drug release data into Zero order, First order, Higuchi and Korsmeyer Peppas model. The best fitted model conformed using R^2 and n value [29].

Zero order release:

In Zero order release of the drug is at constant rate. The obtained drug release data is represented as cumulative percentage drug released against time [30, 31].

$$\mathbf{Q_t = Q_0 + K_0 t}$$

Where, Q_t = Drug released in time't'

Q_0 = initial drug content

K_0 = Rate constant of zero order release

First order release:

According to first order release, the release depends upon the concentration. The release data plotted as log cumulative percentage drug remaining against time.

Log Q_t = log Q_0 - K_1t/ 2.303

Where, Q_t = Drug release at time't'

Q_0 = initial drug content

K_1 = Rate constant of first order release

Higuchi model:

The drug release data plotted as cumulative percentage drug release against square root of time.

$Qt = K_H t^{½}$

Where, Q_t = amount of drug release at time't'

K_H = Higuchi release rate constant

Korsmeyer-Peppas model:

Drug release data plotted as log cumulative percentage drug release v/s log time.

$Q_t/ Q_0 = K_k p\ t^n$

Where, Q_t/ Q_0 = fraction of drug release at time't'

$K_{K\ p}$ = Korsmeyer- Peppas release rate constant

Release mechanism determined based upon the release exponent (diffusion constant 'n') from Korsmeyer- Peppas model. According to that fickian (n=0.5), non-fickian Transport (0.45 < n), case -2 transport (n < 0.89), super case- 2 transport (n>0.89) [32].

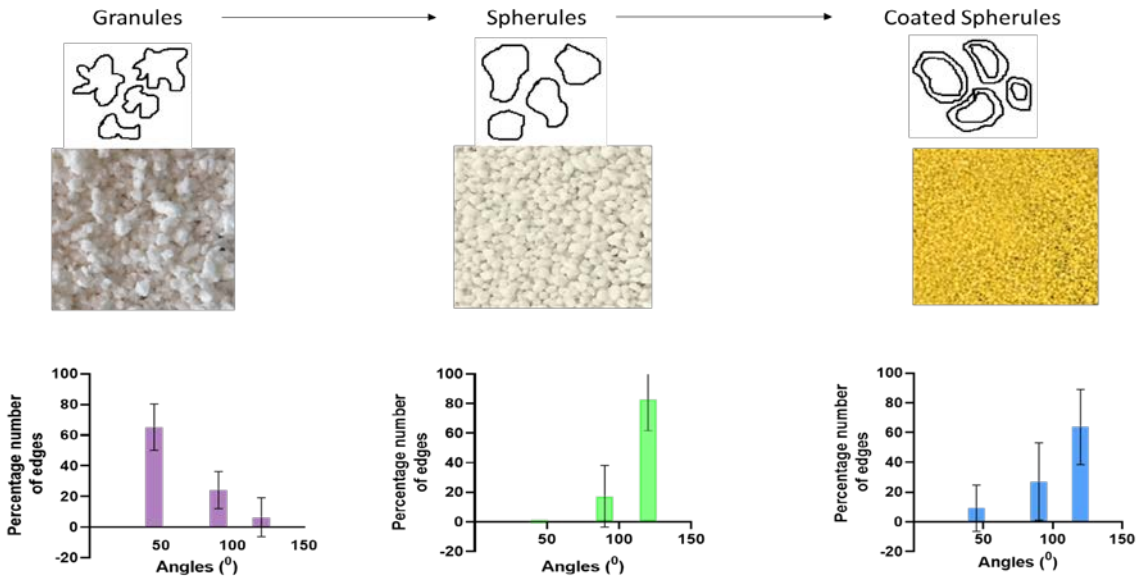

Figure: 1 Morphological comparison between granules, spherules and coated Spherules

Table: 1 Angle of Repose, Bulk density, Tapped density, Carr's Index and Hausner's Ratio of Spherules

Spherules	Angle of Repose (°)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner's Ratio
Ethyl cellulose *--*coated spherules retained in sieve No.22	27.32°±0.52	0.542±0	0.583±0.02	0.069±0.03	1.07±0.03
Ethyl cellulose coated spherules retained in sieve No.44	26.56°±0	0.582±0.01	0.603±0.01	0.035±0.03	0.703±0.61
HPMC coated spherules retained in sieve no.22	24.69°±0.48	0.572±0	0.572±0	0	1±0
HPMC coated spherules retained in sieve no.44	25.63°±0.47	0.6±0	0.613±0.01	0.021±0.02	1.02±0.02
Eudragit coated spherules retained in sieve no.22	23.12°±0.34	0.561±0	0.575±0.01	0.024±0.01	1.01±0.01
Eudragit coated spherules retained in sieve no.44	26.86°±0.25	0.553±0.00	0.572±0.011	0.031±0.03	1.03±0.03

Table: 2 Drug content evaluation of Spherules

Spherules	Percentage Drug content (%)
Ethyl cellulose coated spherules retained in sieve No.22	25.30±0.39
Ethyl cellulose coated spherules retained in sieve No.44	21.61±0.45
HPMC coated spherules retained in no.22	26.90±0.70
HPMC coated spherules retained in sieve no.44	21.21±0.42
Eudragit coated spherules retained in sieve no.22	27.49±0.66
Eudragit coated spherules retained in sieve no.44	24.51±0.78

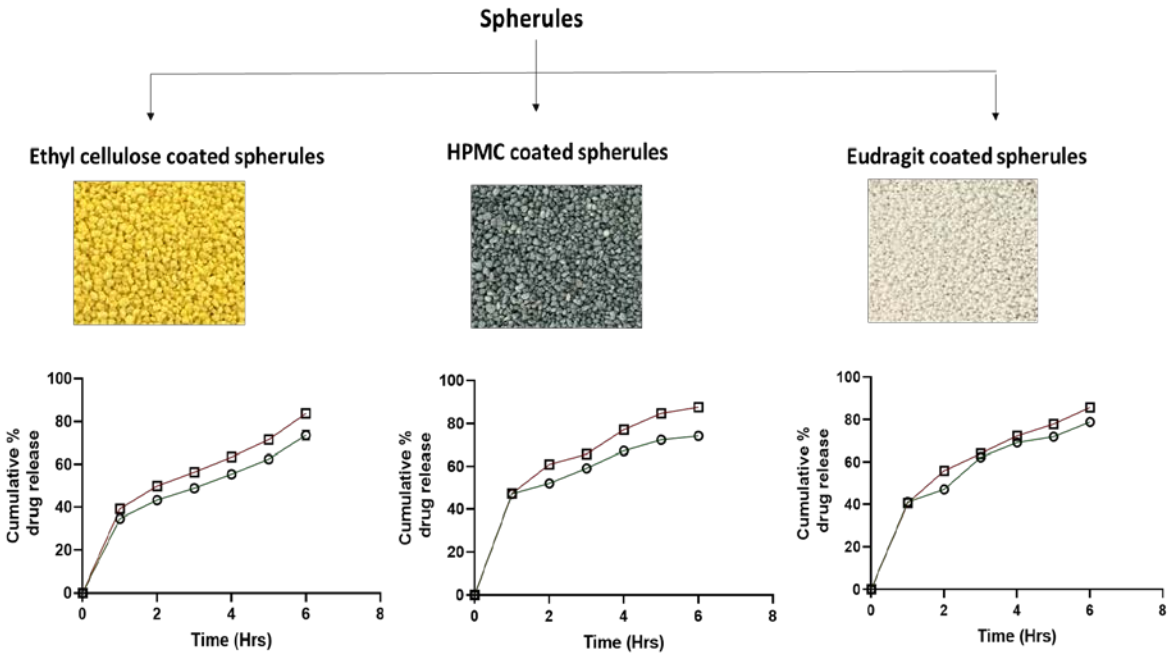

Figure:2 Different polymer coated Spherules and its Drug release profile.

Table: 3 R^2 and n values based on Drug release profile.

Kinetic Models	EC Coated Spherules retained in Sieve No.44		HPMC Coated Spherules retained in Sieve No.44		Eudragit Coated Spherules retained in Sieve No.44	
	R^2	n	R^2	n	R^2	n
Zero Order	0.88	11.78	0.82	12.66	0.86	12.45
First Order	0.95	-0.11	0.98	-0.15	0.98	-0.13
Higuchi Model	0.99	32.07	0.98	35.52	0.99	34.43
Korsmeyer-Peppas Model	0.97	0.40	0.99	0.35	0.99	0.41

RESULT AND DISCUSSION

The granulation followed by bed coating during sliding (BCDS) with starch leads to the formulation of spherules which is further coated with functional polymers. The spherules are then sieved to obtain 2 different population of uniformly sized spherules (sieve no 22 and 44). In this study the effect of spherionization on flow properties, net aspirin content and kinetics of drug release from the spherules (sieve no 22 and 44) are analysed.

The spherical shape of the granules, spherules and coated spherules retained in sieve no 22 and 44 are compared based on the number of sharp edges present. For this, the surface angle at the corner or edge regions of randomly selected particles are observed under a projection microscope and the data is represented in fig: 1. An acute (45^0) or right angle (90^0) is regarded as indicator of sharp edges while obtuse angle (120^0) as indicator of smooth spherical shape. The percentage number of edges making an acute or right angle is highest in granules (>80%) and decrease in case of spherules (<20%) and polymer coated spherules (<30%) while the percentage number of edges making an obtuse angle is highest in spherules (appr. 80%). This indicates BCDS process reduce the sharp edges of the granules and bring a smooth spherical morphology in spherules.

The flow properties in terms of angle of repose and packing parameters in terms of bulk and tapped density, Carr's index as well as Hausner's ratio of 2 differently sized spherules (sieve no 22 and 44) prepared by coating with different polymers (EC, HPMC and Eudragit) are given in Table no: 1. The different sized spherules coated with all the 3 polymers exhibited angle of repose (24.6- 27.3), Carr's index (0- 0.069), Hausner's ratio (0.7- 1.11) indicating excellent flow properties.

The table 2 shows the drug content comparison between different spherules retained in sieve no 22 and 44. In all the spherules, the drug content has significantly reduced to less than 30% showing more than 70% of the drug is lost during the granulation to coating process. Among this the percentage drug content is least with EC coated smaller sized spherules (sieve no 44) while maximum with eudragit coated large sized spherules (sieve no 22) showing polymer type and the particle size dependency in drug content of spherules.

Figure 2 shows cumulative percentage drug release from different polymer coated spherules during dissolution in phosphate buffer and the release kinetics as in table 3. The drug release profile of all the three polymer coated spherules found to follow a 1^{st} order release kinetics with maximum release of 87% within 6 hour duration.

CONCLUSION

Aspirin loaded spherules and coated spherules are successfully prepared from granules by bed coating during sliding (BCDS) process and the flow properties, surface angles, drug content, drug release are optimized. The resulting spherules and the coated spherules are having smooth spherical shape with maximum obtuse angle indicating the spherionization process is successful. The spherules exhibited excellent flow property useful for its manufacturing fidelity. The drug content studies shows 70% of the drug was lost during processing possibly due to degradation triggered by wet granulation process because aspirin is a labile drug. Therefore, protective measures and optimisation of process parameters are required for preparing the spherules of labile drugs like aspirin. Spherules retained in sieve no 44 (smaller spherules) shows more controlled release than larger spherules. The spherules retained in sieve no 44 releases maximum amount of drug within 6 hrs. and exhibited a 1^{st} order release kinetics may be because of higher surface to volume ratio. The coated spherules developed and demonstrated here is a versatile platform for developing different coated spherule based pharmaceutical formulation using drugs.

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REFERENCE

[1] Muley S., Nandgude T., Poddar S., Extrusion–spheronization a promising pelletization technique: in-depth review, *Asian Journal of Pharmaceutical Sciences*. 2016, *11 (6),* 684-699.

[2] Sinha V.R., Agarwal M.K., Agarwal A., Singh G., Ghai D., Extrusion-spheronization: process variables and characterization, *critical reviews in therapeutic drug carrier systems*. 2009, *26 (3),* 275-331.

[3] Soltanbeigi B., Podlozhnyuk A., Jin Y. Ooi., Kloss C., Papanicolopulos S.A., Comparison of multi-sphere and superquadric particle representation for modelling shearing and flow characteristics of granular assemblies, *EPJ Web Conf*. 2017, *140*, 1-4.

[4] Zoubari G., Ali R., Dashevaskiy A., Water soluble and insoluble polymers as binder for pellet preparation by extrusion/ spherionization, *JDDST*. 2019, *49*, 1-5.

[5] Lau C.L.S., Yu Q., Lister V.Y., Rough S.L., Wilson D.I, Zhang M, The evolution of pellet size and shape during spheronisation of an extruded microcrystalline cellulose paste, *Chemical Engineering Research and Design*. 2014, *92*, 413–424.

[6] Parkin J., Widjaja K.S., Bryan M.P., Rough S.L., Wilson D.I., Experimental validation of a dimensional analysis of spheronisation of cylindrical extrudates, *Powder Technology*. 2016, *298*, 73-83.

[7] Basak S. C., Kaladhar K., Doxycycline hyclate delayed release capsules with sodium starch glycolate as a pH- dependent pore forming agent, *Indian J. Pharm. Sci*. 2004, *66*, 704–707.

[8] Kablitz C. D., Urbanetz N.A., Characterization of the film formation of the dry coating process, *Eur. J. Pharm. Biopharm*. 2007, *67*, 449–457.

[9] Ramlakhan M., Wu C.Y., Watano S., Dave R.N., Pfeffer R., Dry particle coating using magnetically assisted impaction coating: Modification of surface properties and optimization of system and operating parameters, *Powder Technol*. 2000, *112*, 137–148.

[10] Bhaskaran S., Lakshmi P. K., Extrusion spheronization –a review, *Int.J. PharmTech Res*. 2010, *2 (4),* 2429-2433.

[11] Kamata T., Wada K., Ichikawa H., Dry pre-coating of active pharmaceutical ingredient with submicron-sized hydroxypropylcellulose in dry granulation using roller compactor improves granule properties, *JDDST*. 2017, *453*, 1-24.

[12] Pisek R., Sirca J., Svanjak G., Srcic S., Comparison of rotor pelletization (fluid bed) and extrusion/spherionization method for pellet production, *drugs made in Germany*. 2011, *63 (11),* 1202-1209.

[13] D'cruz D., Ajith A., Subburaj T., Kamalasanan K., Magnesium stearate is an incompatible excipient for aspirin in wet granulation producing non-linear degradation, *Int J Pharm Sci Res*. 2018, *10 (2),* 240-242.

[14] Link K. C., Schlunder E. U., Fluidized bed spray granulation investigation of the coating process on a single sphere, *Chemical Engineering and Processing*. 1997, *36*, 443–457.

[15] Goswami K., Khurana G., Marwaha R.K., Gupta M., Development and evaluation of extended release ethylcellulose based matrix tablet of diclofenac sodium, *Int J Pharm .Pharm Sci*.2014, *6 (6),* 296-301.

[16] Barba A. A., Amore M., Chirico S., Lamberti G., Swelling of cellulose derivative (HPMC) matrix systems for drug delivery, *carbopol*. 2009, *78*, 469-474.

[17] Basak S. C., Kaladhar K., Subburaj T., Studies in formulation of delayed release capsules of doxycycline hyclate, *Acta Pharmaceutica Sciencia*. 2006, *48*, 121-128.

[18] Tung N. T., Pham T. M. H. , Nguyenc T. H., Pham T. T., Nguyen T. Q., Pectin/HPMC dry powder coating formulations for colon specific targeting tablets of metronidazole, *JDDST*. 2016, *177*, 1-30.

[19] Kumar R., Majumdar D.K., Panda A. K., Pathak D. P., Eudragit polymers in colon targeted oral delivery of insulin, *IJPCBS*. 2014, *4 (4),* 968-979.

[20] Vikas Jain R. S., Jain D., Factors effecting the morphology of eudragit S-100 based Microsponges bearing dicyclomine for colonic delivery, *J. Pharm. Sci*. 2011, *100*, 1545–1552.

[21] P. Avinash S., B. Deepak V., K. Vineeta V, K. Vilasrao J, Advances in pharmaceutical coatings, *Int.J. ChemTech Res.* 2010, *2 (1),* 733-737.

[22] Singh P., Kumar P., Prasad N., Formulation and evaluation of aspirin tablets by using different lubricants in combination for better kinetic drug release study by PCP, *Research Journal of Pharmacy and Technology*. 2017, *10 (9),* 2934-2938.

[23] Hu L., Hu Q., Kong D., Formulation and *in vitro* evaluation of aspirin and isosorbide 5-mono-nitrate sustained bilayer tablets, *Int J Pharm Sci Res*. 2014, *5 (3),* 799-804.

[24] Avbunudiogba J. A., Cash-Torunarigha O.E., Onah I., Effect of humidity on the physical properties of aspirin tablets produced by melt granulation and slugging methods, *J Pharm Biol Sci*. 2013, *7 (5),* 20-25.

[25] Sharma V., Bhowmick M., Rathi V., Rathi J., Preformulation, precompression and post compression evaluation of bilayer tablet of aspirin as immediate release and nicotinic acid as sustained release, *IJPCBS*. 2017, *7 (1),* 55-70.

[26] Kalvimoorthi V., Narasimhan N., Formulation development and evaluation of aspirin delayed release tablets, *Int J Pharm Sci Rev Res*. 2011, *7 (1),* 27-32.

[27] Sahoo C. K., Satyanarayana K., Ramana D. V., Panda K. C., Formulation and evaluation of controlled release tablets of aspirin, *AJPTech*. 2017, *7 (4),* 229-233.

[28] Gattu D. K., Nagaraju K., Eswaraiah M.C., Formulation and evaluation of immediate release tablets containing antiplatelet drugs, *Int. Res J Pharm. App Sci*. 2012, *2 (5),* 170-179.

[29] Dash V., Mishra S.K., Singh M., Goyal A.K., Rath G., Release kinetic studies of aspirin microcapsules from ethyl cellulose, cellulose acetate phthalate and their mixtures by emulsion solvent evaporation method, *Sci Pharm*. 2010, *78 (1),* 93-101.

[30] Miastkowska M., Sikora E., Ogonowski J., Zielina M., Ludzik A., The kinetic study of isotretinoin release from nanoemulsion, *Colloids Surfaces A Physicochem. Eng. Asp*. 2016, *510,* 63–68.

[31] Zhang L., Alfano J., Race D., Davé R. N., Zero-order release of poorly water-soluble drug from polymeric films made via aqueous slurry casting, *Eur J Pharm Sci*. 2018, *117*, 245-254.

[32] Siswanto A., Fudholi A., Nugroho A. K., Martono S., *In vitro* release modeling of aspirin floating tablets using DDSolver, *Indonesian J. Pharm.* 2015, *26 (2),* 94-102.