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ORIGINAL ARTICLE

Formulation And Evaluation of Pioglitazone Solid Dispersion Microcapsules: A Microparticulate Drug Delivery Approach

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ABSTRACT
*The purpose of this study was to prepare pioglitazone microcapsules prepared by 3-different methods and to evaluate the same. Specifically, Selection of optimum microcapsule polymer and formulation method. Effect of type of polymer on the microcapsule preparation, were examined. Ethyl cellulose microcapsules of Pioglitazone were prepared by modified coacervation technique. Ethyl-cellulose (Ethocel10 cps) was used as the coating material which was added to a solution of cyclohexane containing 30%w/w triacetin. EudragitRLl00and Eudragit RSlOO in ratio of 4:2 and 3:3, were used for the coating of microcapsules. The physical characteristics like particle size, drug entrapment, FTIR, SEM, DSC, in vitro drug release profiles were studied. Preformulation includes active characterization, drug-polymer compatibility, drug solubility, thermal property was also tested. Surface characteristics were studied using SEM which revealed that the microcapsules were prepared successfully but merely fused with each other owing to sticky properties of the polymers. The coacervation technique with ethylcellulose as coating material gave the higher yield (92%) of microcapsules. The release **of** Pioglitazone from ethyl-cellulose coated microcapsules was slow whilst the release from those **of** acrylate-methacrylate copolymer was faster. According to the results obtained in this study, solid dispersion techniques could be successfully used for the enhancement of aqueous solubility and dissolution rate of Pioglitazone.*
Keywords: *Pioglitazone, FTIR, SEM, DSC*

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INTRODUCTION

Diabetes mellitus is reported as chronic metabolic disease caused by either by lack of insulin production as a result of pancreatic islet cell destruction, or insensitivity of host cells to endogenous insulin [1,2]. In developed countries, diabetes mellitus is one of main causes of mortality. The objective of diabetes treatment is to decrease rate of disease development, and avoid its life-threatening impediments [3,4,5]. Insulin is widely used to manage blood sugar level (BSL) in a significant proportion of type I diabetes mellitus (T1DM) and type II diabetes mellitus (T2DM) patients [6].

Insulin is a 5790 Da peptide hormone [7] consisting of 51 amino acids its monomer composed of 2 polypeptide chains, chain A of 21 amino acids and chain B of 30 amino acids [8]. These amino acids are connected by 2 disulfide bonds. Insulin is considered as a first line treatment in DM [9]. however, Insulin has been administered by multiple daily subcutaneous injections, and lead to a various shortcomings like patient uneasiness, pricking pain, trauma, local infection, stress, non-compliance, and needle phobia [10,11,12,13].

Therefore, oral delivery of various antidiabetic drugs are highly preferred by the physicians for the treatment of DM. Number of approaches have been recognized to attain the control on DM [14, 15]. these approaches include use of polymeric carriers, nanoparticles and microparticles development, use of permeation enhancer, enteric coating or sustained or controlled drug delivery, liposomes, enzyme inhibitors etc. Out of said approaches, microparticulate drug delivery has attracted attention of several pharmaceutical scientists. In most of the modern literature, the term "microparticles" and "nanoparticle"

refer to particles where the dimension of particle is measured in micrometer and nanometer respectively. Particles with size larger than 1000µm are considered as microparticle and less than are nanoparticle [16]. Characteristics of nanoparticle and microparticle offer numerous advantages like adequate drug loading efficiency, drug release manipulations, permeability improvement across the biological membrane and tissue or organ targeting [17,18,19].

Sustained drug delivery system represents one of the leading edge areas of pharmaceutical science, which involve exploitation of multidisciplinary scientific knowledge for the improvement of biopharmaceutical characteristics of BCS class II drugs. Pioglitazone is one of the poorly soluble drugs. Its narrow half life leads to the rapid elimination from the body, this reason, consequently enforces prescriber for frequent dosing and ultimately leads to poor patient compliance [20,21]. It has also been reviewed that the Pioglitazone may cause several side effects if it is developed in any conventional drug delivery.

Present investigation has aimed to ameliorate the problems associated with the Pioglitazone in context of its short half life and side effects. In order to curtail the probles associated with the Pioglitazone, Microparticulate drug delivery was explored in present investigation because of core benefits offered by this system.

Microparticulate delivery systems in pharma tender numerous benefits over conventional dosage forms. These benefits include improve defectiveness of drug, reduced toxicity, and better patient compliance and convenience.

The terms used to describe micro-particulate formulations may sometimes be inconsistent and confusing to readers. Fundamentally, the term “microparticle” refer to particle with a diameter between 1 to 1000µm, irrespective of precise interior or exterior configuration of these microparticles. Within the broad category of microparticles, “microspheres” specifically refers to spherical microparticles and the subcategory of “micro-capsules” applies to micro particle which have core surrounded by material which is markedly different from that of core. The core may be solid, liquid, or even gas. The 3 D view of the system was shown in following figure.

The term “microcapsule” was defined, as spherical particle having size between 50 nm to 2 mm and contains a core substance. Microspheres are in exacting sense are spherically unfilled particles. Still, the terms microcapsule and microsphere are frequently used synonymously. In addition, some related terms like “microbeads” and “beads” are also used alternatively. Sphere and spherical particles are also employed for a large size and rigid morphology. Due to striking properties and wider utility of microcapsules and microspheres, pharmaceutical researchers have focused microencapsulation and its applications in sustained or modified drug delivery [22,23,24,25].

Development of microparticulate (precisely, microcapsules) drug delivery systems often needs macromolecules (polymers) as coating or covering agents. The core would be of the drug or API/s.

Oral drug delivery of drug is most preferable route of drug delivery due to ease of administration, patient compliance and formulation flexibility. Development of oral sustained-release system has been a challenge to formulation scientist since their inability to restrain and localize system in targeted area of the gastrointestinal tract. Sustained release preparation using other routes has been formulated, but oral route still remains preferable.

Sustained drug delivery system permit for well-defined release pattern. Effective drug level can be maintained without inducing toxic effect. Formulated sustained drug delivery system should be such that it releases the drug, according to physiological needs and also pass through the GI barrier in order to obtain optimal therapeutic action. Hence it was thought that microcapsules could be used as an ideal drug delivery.

Pharmaceutical invention and research are increasingly offering attention on delivery system which improves desirable therapeutic objectives and at the same time minimizes side effects. Current trend indicate that microcapsule drug delivery system is especially suitable for achieving controlled or sustained release oral formulation with low risk of dose dumping, flexibility of processing to attain different release pattern as well as reproducible and short gastric residence time. Pioglitazone as an API has to be explored in context of its side effects and narrow half life. The release of Pioglitazone from microcapsule can sufficiently diminish the problems. Consequently, microcapsule drug delivery system provide tremendous opportunities for designing newer sustained or controlled release oral formulations, thus extending the frontier of prospect pharmaceutical development.

The purpose of this study was to prepare pioglitazone microcapsules prepared by 3-different methods and to evaluate the same. Specifically, Selection of optimum microcapsule polymer and formulation method. Effect of type of polymer on the microcapsule preparation, were examined.

MATERIAL AND METHODS

Chemicals & reagents

Following API and other excipients, reagents, chemicals were used of analytical, pharmaceutical or extra pure grade.

TABLE 1:MATERIALS

Material	Supplier
Pioglitazone	Dr. Reddy's Laboratories, Hyderabad.
Ethyl Cellulose	S.D. Fine-Chemicals Ltd.,
EudragitRS100	S.D. Fine-Chemicals Ltd.,
Cellulose Acetate	S.D. Fine-Chemicals Ltd.,
Polyvinyl alcohol	S.D Fine Chemicals Pvt. Ltd., Mumbai.
Polyethylene glycol	
Hydrochloric Acid	
Sodium hydroxide	
Sodium Chloride	Loba cheme
Potassium dihydrogen Orthophosphate	Qualigens fine chemicals
Alcohol	Loba cheme
Acetone	
Dichloromethane	Loba cheme
Methanol	Loba cheme

EQUIPMENT AND INSTRUMENTS

Table 2: Instruments

EQUIPMENT	MANUFACTURER
Single Pan electrical balance	Lab India.
Hot air oven	Lab India.
Diffusion cell	Neutron Scientific Corporation,
Stirrer (Magnetic)	Remi equipment
pH meter	Pen type pH meter.
U.V. Spectrophotometer (Double Beam)	JascoV-530
Differential scanning calorimetry	Shimadzu,Kyoto,Japan.
ATR FTIR	PerkinElmer,PerkinElmerInst.USA
Scanning electron microscope	HITACHISU 3700
Dissolution apparatus	Lab India
Particle size analyzer	MicrotracS350
Rotary Evaporator	SENCOTechnologyCo., Ltd.,

Methods:

Drug and excipients compatibility [31, 32]:

The objective of drug/excipients compatibility study was to demarcate, as quickly as possible, possible interaction between API and excipients. Compatibility study was an important risk lessening exercise early in formulation development. Homogenous mixtures of drug and excipients were prepared and filled in glass vials. Chemical compatibility was tested by FTIR spectroscopy, which was one of most widely used techniques to identify functional interaction of the API with polymer or excipient used if any.

Development of Pioglitazone Microcapsules using coacervation Method:

Ethyl cellulose microcapsules of Pioglitazone were prepared by modified coacervation technique defined by Tirkonen et al. (1993). Ethyl-cellulose (Ethocel10 cps) was used as the coating material with stirring rate of1000 rpm. Ethyl-cellulose was added to a solution of cyclohexane containing 30%w/w triacetin as a percentage of ethyl-cellulose weight. The mixture was heated to75°C. required amount of Pioglitazone was suspended in the solution. The ratios of Pioglitazone :ethyl-cellulose were 2:1,1:1 and 1:2. The suspension was homogenized at a speed of 4000 rpm for 4 min. Suspension was allowed to cool down slowly, at a controlled stirring speed of 1000rpm, to 40°C for 1h. The mixture was then further cooled down to 25°Con an ice bath. Stirring was continued for more 20min.Prepared microcapsules were then separated from solution by sedimentation and then filtration on a Buchner funnel. The filtered microcapsules were then washed thrice using 25 ml portions of fresh cyclohexane. The microcapsules were subsequently collected and dried at room temperature for 10h. Microcapsules were stored in desiccator for further studies [33].

Combination of Eudragit RLlOO with EudragitRSl00:

EudragitRLl00and Eudragit RSlOO in ratio of 4:2 and 3:3, were used for the coating of microcapsules. Microencapsulation of Pioglitazone was carried out by modifying the coacervation technique described by Watts et al.(1991). Microcapsules were produced by using an emulsification-solvent evaporation method. Accurate quantities of EudragitRLl00in combination with Eudragit RS lOO were dissolved in methylene chloride containing 25% w/w triacetin as a percentage of Eudragit RLlOO and EudragitRSl00 weight. 2gm of Pioglitazone (considering dose of Pio, 45mg/day) was added to the polymer solution: the ratio of drug:polymer were 2:1, 1:l and 1:2 and the dispersion was aided by sonication for 25min. The drug-polymer-solvent phase was poured into 200ml of an aqueous solution with agitation using a controlled stirring rate at 1200 rpm. Stirring was continued at 38°C until the methylene chloride was completely evaporate. The resulting microcapsules were collected by centrifugation at 3500rpm for 20 min and dried at room temperature for 16 h and stored in a desiccator for more studies.

Evaluation of Microcapsules:

Scanning electron microscopy (SEM).

Scanning electron microscope was used to examine the morphological characteristics of the surface of the microcapsules [34].

UV Spectrophotometric Assay:

The absorption maximum was found to be at 269 nm. The absorbance of the solutions was measured at 269 nm against the blank and the calibration curve was constructed.

Preparation of Standard Solution

Standard solution of Pioglitazone was made by dissolving 100mg of API in 100ml of 0.1N hydrochloric acid (Solution A, 1000 µg/ml). Further, 10ml of solution 1 was diluted to 100ml with 0.1N hydrochloric acid (Solution B, 100µg/ml). Solution 2 was used as the standard stock [35].

Preparation of Calibration Curve:

Aliquots of 1ml to 7ml of std. solution 2 were transferred in to series of calibrated 10ml std volumetric flasks and final volume was made up using 0.1N HCl. The solutions were scanned in the range of 200-400nm using blank as a reference (0.1N HCL).

Dissolution studies:

Dissolution studies of pure and microencapsulated API were performed out in a 6-station dissolution tester: 50mg of the API or an amount of the microencapsulated drug equivalent to 50mg of pure API were placed in 900 ml of water. Dissolution apparatus was maintained at 36°C and the paddle method was used in these studies with a constant paddle stirring rate of *60*rpm. Samples of ***5***ml were withdrawn at appropriate time intervals and immediately replaced with fresh dissolution medium over a period of 10h. The samples were then filtered through a 0.22 pm membrane filter unit and diluted with water to get an appropriate concentration before determining the pioglitazone concentration using a spectrophotometer at a wavelength of 262 nm. After each time interval, the average value and standard deviation were computed and finally the mean release of pioglitazone was plotted versus time to obtain dissolution profiles.

RESULT AND DISCUSSION

Compatibility studies:

Pioglitazone and excipients were subjected to FTIR spectral study. The drug was found to be compatible with the excipients since no significant changes were observed in intensity and position of the peaks in the spectra. FTIR spectrum were shown in following figures and it was confirmed that there were no any significant interactions between the drug and polymer.

Scanning electron microscopy:

Microcapsules of API prepared by coacervation method showed accumulation of particles because of drying at room temperature. During cooling, some polymer may have segregated from solution. During drying the microcapsules may get fused together to produce aggregated particles. This effect was detected both in ethyl cellulose and Eudragit microcapsule. The surface morphological properties of microcapsule using ethylcellulose as coating material were shown in following figures. The increase of coating polymer gave larger particle sizes along with thickened walled microcapsule. The drug content for ethyl cellulose microcapsule was typically 95-98%. For Eudragit microcapsule it ranged from 72-93 %.

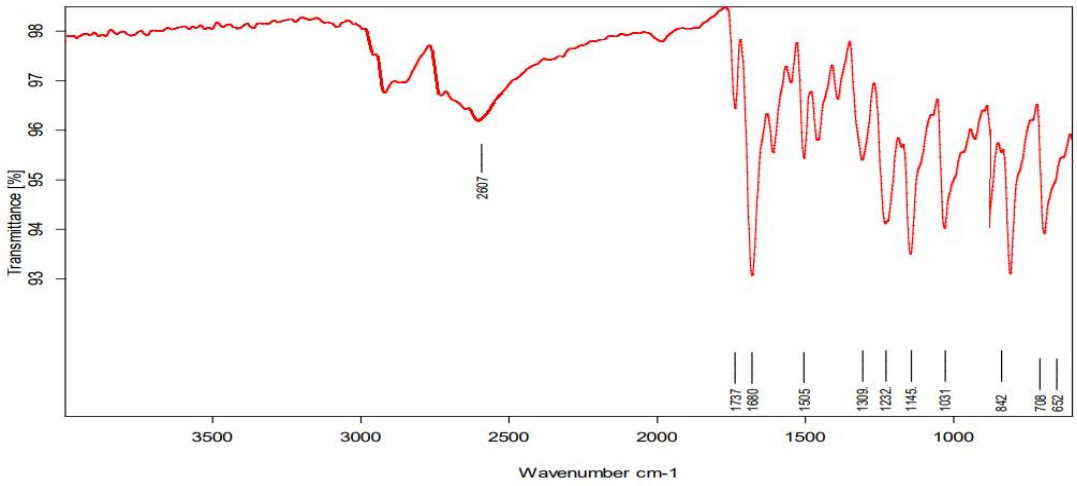

Fig 1: FTIR of Pioglitazone

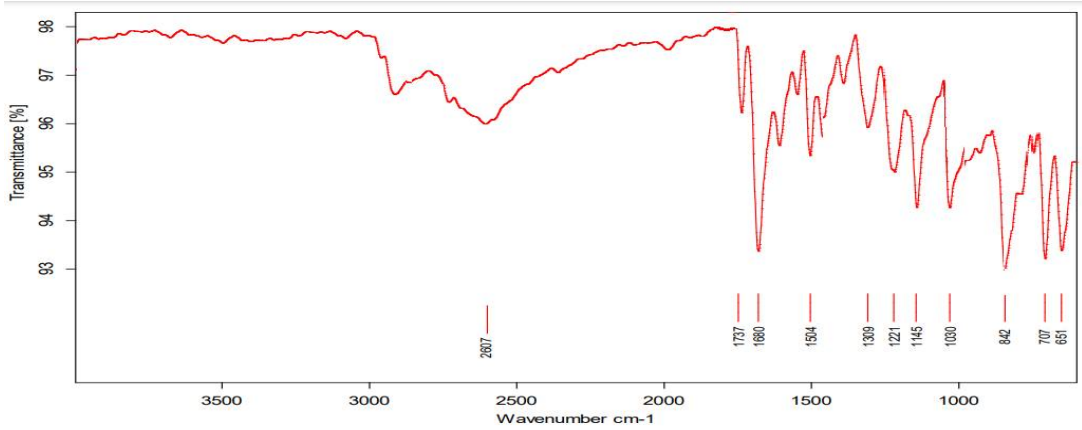

Fig 2: FTIR of Pioglitazone with excipients

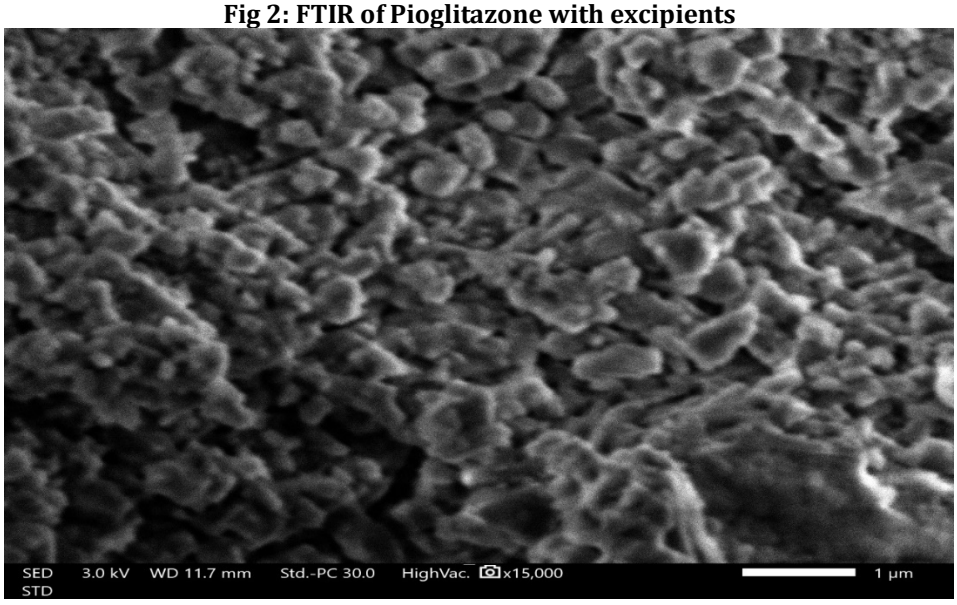

Fig3: Surface morphology microcapsule prepared by coacervation technique, using ethyl cellulose as coating material, the core to coating ratio is 2:1, Magnification15000 x

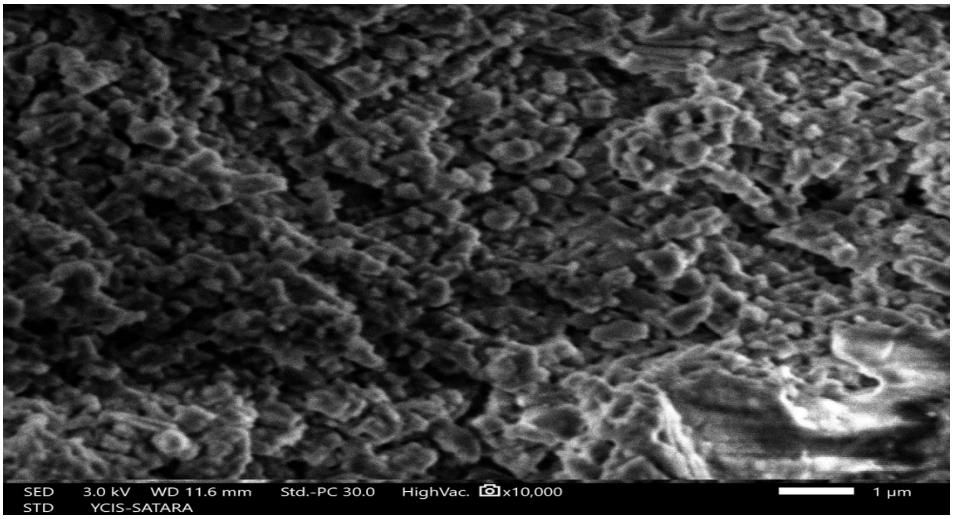

Fig 4: Surface morphology of microcapsule prepared by coacervation technique, using ethyl-cellulose as coating material, core coating ratio was 1:1, Magnification10000 x

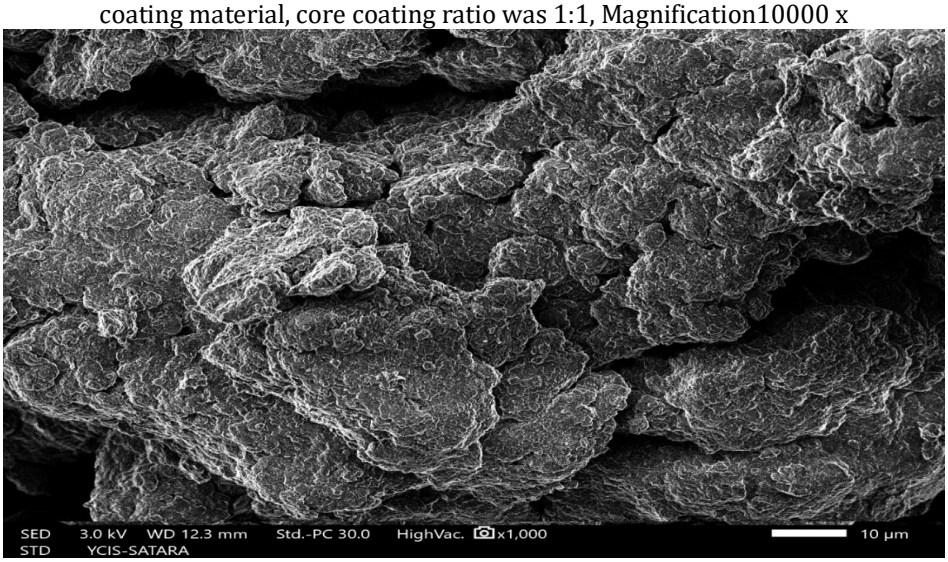

Fig 57: Surface morphology of microcapsule prepared by coacervationmethod, using ethylcellulose as coating material, the core to coating ratio is 1 :2, Magnification1000 x

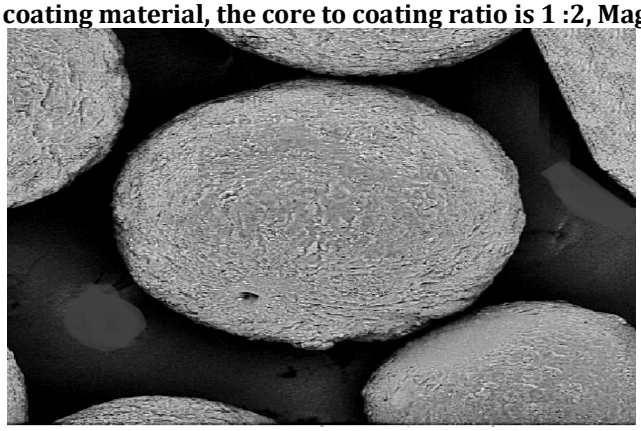

Fig 6: SEM of the microcapsules

Standard Calibration curve:

UV visible spectroscopy was successfully performed to study the calibration curve of API. The objective of the study was to confirm the identity of the API as well as to explore the study during drug dissolution investigations. Uv visible spectroscopy revealed that the API used in the investigation was Pioglitazone. Calibration curve was built successfully. The lambda max and calibration curve was shown in following figure.

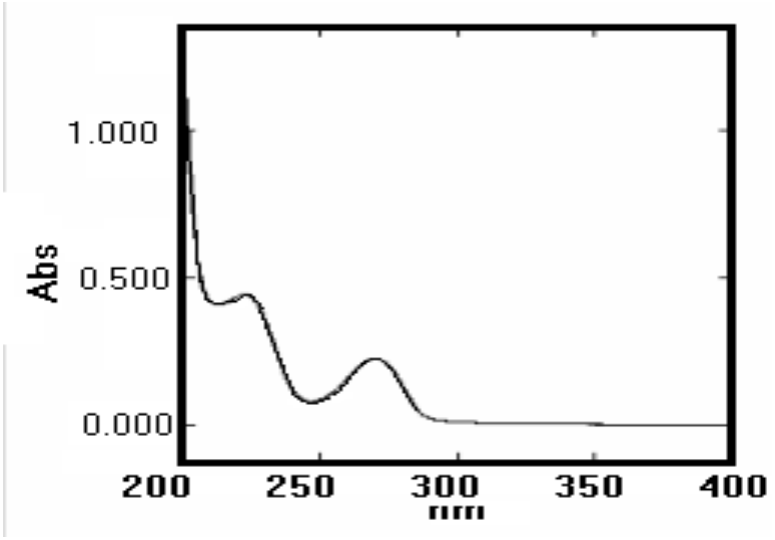

Fig 7: Pioglitazone absorbance maxima at 269nm

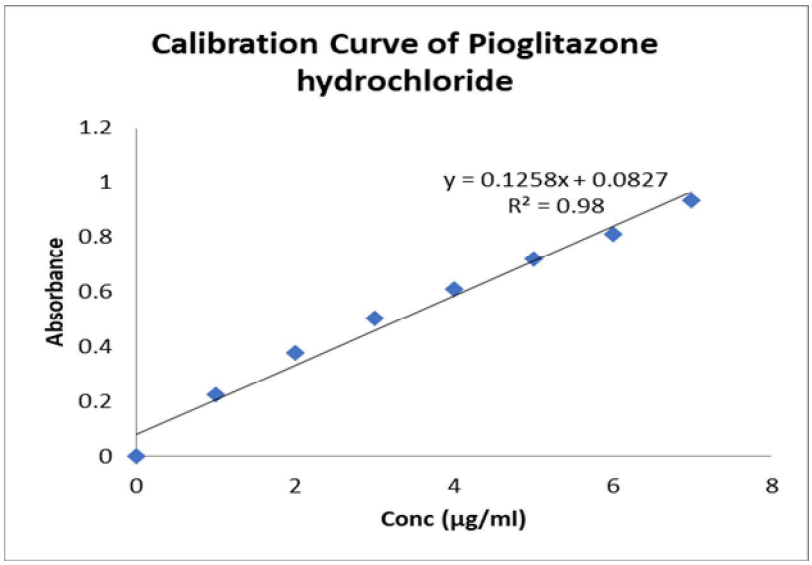

Fig 8: Calibration Curve; Pioglitazone

Table 3: Calibration Curve; Pioglitazone

Sr. no	Concentration (µg/ml)	Absorbance
1	0	0±0
2	1	0.228±002
3	2	0.378±001
4	3	0.505±002
5	4	0.609±003
6	5	0.722±002
7	6	0.812±001
8	7	0.93±0003

Yield:

The yield was higher with ethyl-cellulose microcapsule (86-91%) than Eudragit microcapsule (53-69%)

Dissolution studies

Figure shows that the API, pioglitazone got released successfully from microcapsules. Drug release with a core to coating ratio of API: ethyl cellulose, 1:2 gave a lower release rate than for 1 :1 and 2:l ratios. The variation of the core to coating ratios on the release of pioglitazone from Eudragit RL:RS coated microcapsule also gave a similar effect as shown in following figure. Being hydrophobic, ethyl cellulose

microcapsules showed slower penetration rate of dissolution medium in to microcapsule. In case of Eudragit microcapsule, Eudragit is reported as 'a polymer which although insoluble in water allows water to permeate through it' and hence, it showed, faster rate of water penetration through the polymer and gave higher drug release rate from microcapsules.

Table 4: % Drug release profiles

Time (h)	% DR			
	API: EC 2:1	API: EC 1:1	API: EC 1:2	Pure API
0	0	0	0	0
1	36	33	22	72
2	45	34	29	87
3	54	35	32	91
4	65	37	36	92
5	72	40	40	92
6	78	43	42	91
7	83	45	43	91
8	88	58	44	91
9	90	64	45	90
10	91	72	46	90

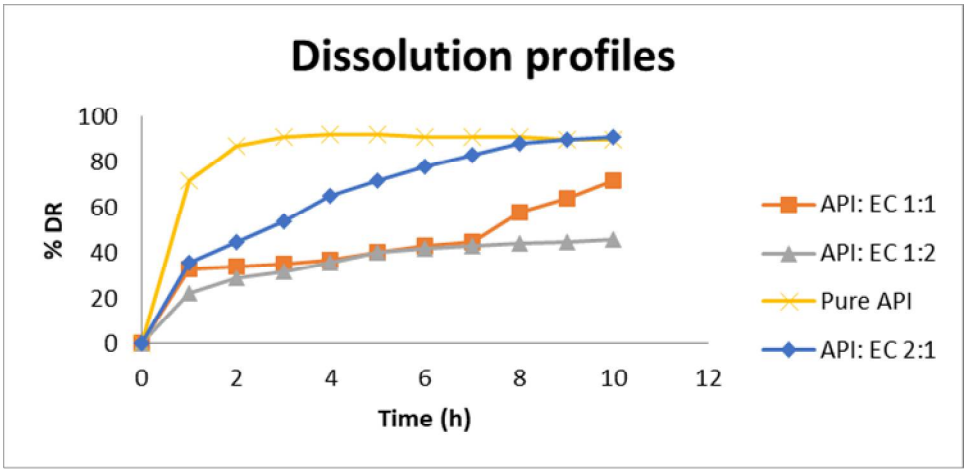

Fig 9: In vitro % Drug release Profiles from Pioglitazone microcapsules

Time (h)	% DR			
	EudRLRS-3:2/ 2:1	EudRLRS-3:2/ 1:1	EudRLRS-3.2/1.2	Pure API
0	0	0	0	0
1	39	38	19	71
2	63	62	29	88
3	76	74	39	92
4	79	76	51	92
5	83	79	60	93
6	89	81	64	91
7	92	81	71	91
8	93	82	82	90
9	93	83	87	89
10	92	82	89	90

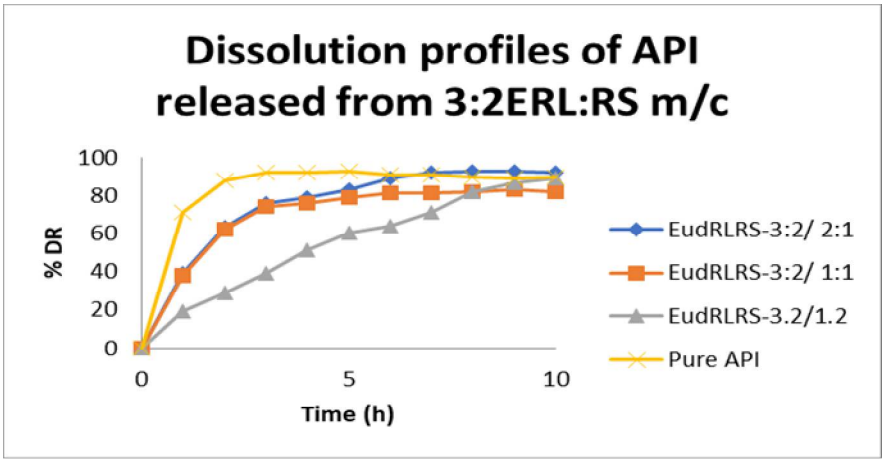

Fig 10: In vitro % Drug release Profiles of API Released from 3:2 ERL:RS m/c

CONCLUSION

In present investigation, ethyl-cellulose and another polymer, acrylate-methacrylate copolymer Eudragit RL100, EudragitRSl00) coatings were prepared successfully by using suitable amounts of plasticizers. 30% and **20%** of triacetin based on polymer weight were found to be appropriate plasticizer for ethyl-cellulose coatings and acrylate-methacrylate copolymer coatings, respectively. Pioglitazone was chosen as a model API. The coacervation technique was used successfully for the development of microcapsules. Ethyl-cellulose and acrylate-methacrylate copolymer corresponding to the mentioned ratios were selected as coating materials of the microcapsule. The effect of core-to-coating ratio on the surface characteristics and dissolution of the microcapsule were also studied. Surface characteristics were studied using SEM which revealed that the microcapsules were prepared successfully but merely fused with each other owing to sticky properties of the polymers. The coacervation technique with ethylcellulose as coating material gave the higher yield (92%) of microcapsules. The release **of** Pioglitazone from ethyl-cellulose coated microcapsules was slow whilst the release from those **of** acrylate-methacrylate copolymer was faster.

REFERENCES

1. Robertson, R. P. (2004). Chronic oxidative stress as a central mechanism for glucose toxicity in pancreatic islet beta cells in diabetes. *Journal of Biological Chemistry*, *279*(41), 42351-42354.
2. Samaha, M. M., Said, E., & Salem, H. A. (2019). A comparative study of the role of crocin and sitagliptin in attenuation of STZ-induced diabetes mellitus and the associated inflammatory and apoptotic changes in pancreatic β-islets. *Environmental toxicology and pharmacology*, *72*, 103238.
3. Meza-Palacios, R., Aguilar-Lasserre, A. A., Ureña-Bogarín, E. L., Vázquez-Rodríguez, C. F., Posada-Gómez, R., & Trujillo-Mata, A. (2017). Development of a fuzzy expert system for the nephropathy control assessment in patients with type 2 diabetes mellitus. *Expert Systems with Applications*, *72*, 335-343.
4. Wu, Y., Ding, Y., Tanaka, Y., & Zhang, W. (2014). Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. *International journal of medical sciences*, *11*(11), 1185.
5. Kawahito, S., Kitahata, H., & Oshita, S. (2009). Problems associated with glucose toxicity: role of hyperglycemia-induced oxidative stress. *World journal of gastroenterology: WJG*, *15*(33), 4137.
6. Worthley, M. I., Holmes, A. S., Willoughby, S. R., Kucia, A. M., Heresztyn, T., Stewart, S., ... & Horowitz, J. D. (2007). The deleterious effects of hyperglycemia on platelet function in diabetic patients with acute coronary syndromes: mediation by superoxide production, resolution with intensive insulin administration. *Journal of the American College of Cardiology*, *49*(3), 304-310.
7. Hu, Q., & Luo, Y. (2018). Recent advances of polysaccharide-based nanoparticles for oral insulin delivery. *International journal of biological macromolecules*, *120*, 775-782.
8. Tager, H., Given, B., Baldwin, D., Mako, M., Markese, J., Rubenstein, A., ... & Poucher, R. (1979). A structurally abnormal insulin causing human diabetes. *Nature*, *281*(5727), 122-125.
9. Casado, J. L. (2014). Prevalence of insulin resistance and risk of diabetes mellitus in HIV-infected patients receiving current antiretroviral drugs. *Endocrinology*, *171*, 545-554.
10. Im, G. J., Chae, S. Y., Lee, K. C., & Lee, D. S. (2009). Controlled release of insulin from pH/temperature-sensitive injectable pentablock copolymer hydrogel. *Journal of Controlled Release*, *137*(1), 20-24.
11. Shah, R. B., Patel, M., Maahs, D. M., & Shah, V. N. (2016). Insulin delivery methods: past, present and future. *International journal of pharmaceutical investigation*, *6*(1), 1.
12. Wadher, K., Kalsait, R., & Umekar, M. (2011). Pulmonary insulin delivery: Challenges and current status. J. *Pharma Sciences and Research*, *3*(2), 1052.

13. Mo, R., Jiang, T., Di, J., Tai, W., & Gu, Z. (2014). Emerging micro-and nanotechnology based synthetic approaches for insulin delivery. *Chemical society reviews*, *43*(10), 3595-3629.
14. Rodbard, H. W., Jellinger, P. S., Davidson, J. A., Einhorn, D., Garber, A. J., Grunberger, G., ... & Bloomgarden, Z. T. (2009). Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocrine practice*, *15*(6), 540-559.
15. Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., ... & Matthews, D. R. (2012). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes care*, *35*(6), 1364-1379.
16. Davidov-Pardo, G., Joye, I. J., & McClements, D. J. (2015). Food-grade protein-based nanoparticles and microparticles for bioactive delivery: fabrication, characterization, and utilization. *Advances in protein chemistry and structural biology*, *98*, 293-325.
17. Raj, S., Khurana, S., Choudhari, R., Kesari, K. K., Kamal, M. A., Garg, N., ... & Kumar, D. (2021, February). Specific targeting cancer cells with nanoparticles and drug delivery in cancer therapy. In *Seminars in cancer biology* (Vol. 69, pp. 166-177). Academic Press.
18. Muhamad12, I. I., Selvakumaran, S., & Lazim, N. A. M. (2014). Designing polymeric nanoparticles for targeted drug delivery system. *Nanomed*, *287*, 287.
19. Goldberg, M., Langer, R., & Jia, X. (2007). Nanostructured materials for applications in drug delivery and tissue engineering. *Journal of Biomaterials Science, Polymer Edition*, *18*(3), 241-268.
20. Chhater, S., & Praveen, K. (2013). Solid Dispersion Incorporated Microcapsules: Predictive Tools for Improve the Half Life and Dissolution Rate of Pioglitazone Hydrochloride. *A Journal of Biomedical Research*, *1*(3), 57-70.
21. Türk, D., Hanke, N., Wolf, S., Frechen, S., Eissing, T., Wendl, T., ... & Lehr, T. (2019). Physiologically based pharmacokinetic models for prediction of complex CYP2C8 and OATP1B1 (SLCO1B1) drug–drug–gene interactions: a modeling network of gemfibrozil, repaglinide, pioglitazone, rifampicin, clarithromycin and itraconazole. *Clinical pharmacokinetics*, *58*(12), 1595-1607.
22. Peanparkdee, M., Iwamoto, S., & Yamauchi, R. (2016). Microencapsulation: a review of applications in the food and pharmaceutical industries. *Reviews in Agricultural Science*, *4*, 56-65.
23. Chang, T. M. S. (1998). Pharmaceutical and therapeutic applications of artificial cells including microencapsulation. *European journal of pharmaceutics and biopharmaceutics*, *45*(1), 3-8.
24. Dubey, R. (2009). Microencapsulation technology and applications. *Defence Science Journal*, *59*(1), 82.
25. Huang, H. J., Yuan, W. K., & Chen, X. D. (2006). Microencapsulation based on emulsification for producing pharmaceutical products: A literature review. *Developments in Chemical Engineering and Mineral Processing*, *14*(3-4), 515-544.
26. Jyothi, S. S., Seethadevi, A., Prabha, K. S., Muthuprasanna, P., & Pavitra, P. (2012). Microencapsulation: a review. *Int. J. Pharm. Biol. Sci*, *3*, 509-531.
27. Yang, X., Liu, Y., Lv, Z., Hua, Q., Liu, L., Wang, B., & Tang, J. (2021). Synthesis of high latent heat lauric acid/silica microcapsules by interfacial polymerization method for thermal energy storage. *Journal of Energy Storage*, *33*, 102059.
28. Du, W., Yu, J., Gu, Y., Li, Y., Han, X., & Liu, Q. (2019). Preparation and application of microcapsules containing toluene-di-isocyanate for self-healing of concrete. *Construction and Building Materials*, *202*, 762-769.
29. Singh, M. N., Hemant, K. S. Y., Ram, M., & Shivakumar, H. G. (2010). Microencapsulation: A promising technique for controlled drug delivery. *Research in pharmaceutical sciences*, *5*(2), 65.
30. Lachman, L., Lieberman, H. A., & Kanig, J. L. (1976). *The theory and practice of industrial pharmacy*. Philadelphia: Lea & Febiger.
31. Pani, N. R., Nath, L. K., Acharya, S., & Bhuniya, B. (2012). Application of DSC, IST, and FTIR study in the compatibility testing of nateglinide with different pharmaceutical excipients. *Journal of Thermal analysis and Calorimetry*, *108*(1), 219-226.
32. Rojek, B., & Wesolowski, M. (2019). FTIR and TG analyses coupled with factor analysis in a compatibility study of acetazolamide with excipients. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *208*, 285-293.
33. Nimmannit, U., & Suwanpatra, N. (1996). Microencapsulation of drugs by the coacervation technique using ethylcellulose and acrylate-methacrylate copolymer as wall materials. *Journal of Microencapsulation*, *13*(6), 643-649.
34. Vos, K., Vandenberghe, N., & Elsen, J. (2014). Surface textural analysis of quartz grains by scanning electron microscopy (SEM): From sample preparation to environmental interpretation. *Earth-Science Reviews*, *128*, 93-104.
35. Yekta, R., Dehghan, G., Rashtbari, S., Sheibani, N., & Moosavi-Movahedi, A. A. (2017). Activation of catalase by pioglitazone: Multiple spectroscopic methods combined with molecular docking studies. *Journal of Molecular Recognition*, *30*(12), e2648.