Original Article

Development of Solid Dispersions of Clopidogrel using Innate Excipient: Synergistic Antiplatelet Activity

Chander Pal Singh Verma[1], Santosh Verma[2], Mahendra Singh Ashawat[3], Vinay Pandit[3]

[1]Department of Pharmacognosy, Motherhood University, Rorkee, Uttarakhand, INDIA.
[2]Department of Pharmacology, Motherhood University, Rorkee, Uttarakhand, INDIA.
[3]Department of Pharmaceutics, Laureate Institute of Pharmacy, Kathog, Jawlamukhi, Himachal Pradesh, INDIA.

ABSTRACT

Aim: The present study encompasses on formulation and evaluation of solid dispersion of Clopidogrel, Class II drug-using pectin extracted from mango peel. **Materials and Methods:** Pectin was extracted from full-grown mango peel grown in the Kangra region. Solid dispersions were prepared using kneading, hot fusion method and solvent wetting method and the solvent wetting method were gauged and optimized. The prepared solid dispersions were subjected to solubility analysis and selected optimized formulation was further subjected to DSC, PXRD, *in-vitro* Dissolution and *in-vitro* antiplatelet activity. The *in-vitro* release studies are subjected to mathematical data analysis using DD Solver 1.0 version. **Results:** Extracted pectin from mango peel was light brown in color and soluble in water. The screened carriers PVPK30 and extracted pectin showed the enhanced solubility of pure drug. The pectin was further selected for the formulation of solid dispersions by three different methods. The solvent wetting method has given expected results and the formulation SD6 containing drug: pectin ratio 1:2 was selected and evaluated. The *in-vitro* release has shown 91.2 % in 60 min with a mean dissolution time of 14.64 min and dissolution efficiency of 0.691%. The formulation SD6 has shown 87.1 ±1.8 % antiplatelet activities whereas pure drug has shown 71.9 ±2.1% indicating enhanced activity. **Conclusion:** It was concluded that the pectin extracted from ripened mango peels can be a suitable carrier for the formulation of solid dispersion of clopidogrel which not only enhances the solubility but also resulted in the enhanced antiplatelet activity.

Key words: Pectin, Solid Dispersion, Clopidogrel, DDSolver, Mean Dissolution Time.

Submission Date: 22-04-2020;
Revision Date: 17-07-2020;
Accepted Date: 23-10-2020

DOI: 10.5530/ijper.54.4.194

Correspondence:
Dr. Vinay Pandit
Professor and Head,
Department of Pharmaceutics,
Laureate Institute of Pharmacy, Kathog,
Jawlamukhi,
Himachal Pradesh, INDIA.
Phone: +91 7018933755
E-mail: vinay2121@gmail.com

INTRODUCTION

Primarily, the oral route of drug administration has been used extensively for drug delivery. However, copious drugs remain poorly bioavailable when administered by this route that could be due to either low mucosal permeability of the drug or low solubility of the compound, resulting in low dissolution rate in the mucosal fluids and elimination of a fraction of the drug from the alimentary canal prior to absorption. Other reasons could be due to lack of stability in the gastrointestinal environment which leads to the degradation of the compound prior to its absorption.[1]

In spite of all, the oral route of drug delivery is still most preferred by the vast majority of patients since oral delivery is one of the simplest, safest route, does not pose the sterility problem and the risk of damage at the site of administration is also minimized.[2]

Drugs which are sited under Class II of Biopharmaceutical Classification System for drugs, having lower rate of dissolution thereby showing decreased bioavailability can be formulated into solid dispersions. Aqueous solubility of these drugs can also be improved by formulating them into

www.ijper.org

solid dispersions. Solid dispersions are water-soluble complexes of drug and a carrier which when comes in contact with aqueous medium get readily dissolve in the form of minute fine particles and thereby enhances the dissolution rate.[3]

Clopidogrel, a Class II antiplatelet drug, has a bioavailability of less than 50 % and is getting converted to its active metabolite in the liver after oral administration. After a single, oral dose of 75 mg, clopidogrel has half-life of approximately 6 hr. The bioavailability of clopidogrel is >50%. The active metabolite of clopidogrel inhibits platelet aggregation by activating the glycoprotein GP IIb /IIIa complex-mediated through binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor.[4,5] Clopidogrel is widely used in primary and secondary prevention of thrombotic cerebrovascular or cardiovascular disease.

Pectin, a natural polysaccharide found in citrus fruits as well as in most of the ripened fruits shows antithrombic activity.[6]

The pectin is widely used as a pharmaceutical excipient and its role as solid dispersion carrier was so far has been studied and was found to be suitable for the formulation of solid dispersions of aceclofenac and resulted in enhanced solubility of the selected drug.[7]

Thus, in this research work, it is hypothesized that solid dispersions containing pectin as the carrier of clopidogrel will result in better bioavailability, faster onset of action and possible dose reduction. The aim was to develop and evaluate the solid dispersions of clopidogrel in order to provide a faster onset of action as well as better patient compliance.

MATERIALS AND METHODS

Materials

Clopidogrel bisulphate (CLO) powder drug was given by the Aarti Drug Ltd.; All other chemicals and reagents were of analytical grade

Method of Estimation

The absorption maxima (λ_{max}) of CLO were determined in 0.1N HCl by scanning 16µg/ml of the drug in the range of 400-200 nm using UV spectrophotometer. Beers range was found to be 5-40 µg/ml.

Extraction of pectin from mango peels

The fresh fruit peels of ripened mango were collected in June-July, segregated consistent with their type, delve pieces for simple drying and washed with water thrice. Sample drying was done in the oven at 60°C to lower down moisture content to 5–6%. The dried peel was milled to sieve size of 80 meshes and packed in the airtight, moisture-proof bag at room temperature and prepared to the extraction process.[8,9]

Extraction Procedure

Ground and defatted mango peels were mixed well with water of various pH (1.5, 2.0, 2.5, 3.0, 3.5), keeping substrate to water ratio 1:40 (w/v). The specified pH of the mixture was adjusted with 0.1 N sulphuric acid on pH meter. Thereafter, the mixture was heated at 100°C temperature for an hour with frequent stirring. The contents were filtered through a muslin cloth and the filtrate was precipitated with 95% ethanol. Dried pectin was obtained by two methods i) drying the precipitates at 40°C in vacuum pump. ii) The sample was freeze-dried[10] in Lyovapor™ L-200 at –40°C and 4 Pa for 24 hr. The final product is a dry powder. Yield (%) of pectin is predicated on the gram of peel sample taken and is calculated by formula as given below;

$$Y\ pec\ (\%) = P / Pi \times 100$$

where, Ypec (%) is that the extracted pectin yield in percent (%).

P is that the amount of dry pectin in g and Pi is that the initial amount of mango peels in gram.

Preliminary solubility studies

The physical mixtures (PMs) of pure drug and different water-soluble polymers viz., mannitol, citric acid, urea, PEG 4000, PEG 6000, PEG 20 K, PVP K30 and extracted Insoluble pectin in the ratio 1: 1,1:3 and 1:5 were prepared and mixed for 5 min with the use of a pestle and mortar and sieved through a 400- µm mesh and stored in a desiccated environment. The prepared Physical Mixtures were subjected to solubility studies, as described by Higuchi and Connors, 1965. The prepared Physical mixtures were added to 25 ml of aqueous solution in screw-capped bottles, Samples were shaken for the 24 hr at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. The filtrate was diluted suitably with 0.1 N HCl and analyzed spectrophotometrically for the CLO at 218 nm against similarly treated blank. Based on the results of solubility of these physical mixtures, PVP K 30 and pectin was further formulated into solid dispersions.

Preparation of solid dispersions

Solid dispersions were prepared by three different methods viz., kneading method, fusion method and solvent wetting method.

Kneading method

The drug and carrier were gently mixed to get a uniform mixture.[11] Water: methanol in the ratio of 1: 1 was added in small quantity to make a paste. The paste was allowed to stand for 45 min and dried in a hot air oven at 40 ± 2°C. The product obtained was pulverized and passed through the mesh (#) 85. The solid dispersion containing lactose was prepared in the same manner.

Fusion method

The carrier was melted in a china dish and the drug was dispersed in it to get a molten mixture which was constantly stirred. The dispersion was cooled.[12] The product obtained was dried at room temperature and was passed through the mesh (#) 85. The solid dispersion containing lactose was prepared in the same manner.

Solvent wetting method

The solvent-wetting method was used for preparing solid dispersions.[7] A weighed amount of drug was dissolved in isopropyl alcohol. The required amount of pectin was placed in a mortar and then the drug solution was poured over the carrier. The solvent was removed by evaporation at room temperature. The solid mass obtained was sieved through sieve number 60 and stored in a desiccator for further use. The solid dispersion containing lactose was prepared in the same manner.

The prepared solid dispersions were evaluated[13] for percentage yield, Drug content, Solubility Studies, Fourier Transform Infrared Spectroscopy, *in vitro* Release Studies and *in vitro* Data analysis by using DDSolver ver.1.0.

Percentage yield

The percentage yield was relating to the dry product and was calculated by using the following formula:

$$\% \text{ Yield} = \frac{\text{P.Y.}}{\text{T.Y.}} \times 100$$

Where, P.Y refers to practical Yield, T.Y refers to the theoretical yield.

Drug content

Solid dispersion equivalent to 75 mg of CLO was dissolved in the 100 ml volumetric flask in 0.1N HCl and absorbance was measured at 218 nm in triplicate.

Solubility Studies of Solid Dispersions

Solubility studies were carried out by taking an excess of pure CLO and prepared solid dispersions into screw-capped bottles containing distilled water. Bottles were shaken mechanically at room temperature for 48 hr and aliquots were withdrawn, filtered (0.22 µm) and drug content was determined spectrophotometrically at 218 nm.

Fourier Transform Infrared Spectroscopy

FTIR spectra were recorded by potassium bromide (KBr) disc method using Shimadzu FTIR-8700 spectrophotometer (Tokyo, Japan). The scanning range was 400 to 4000/cm and the resolution was 4/cm.

Powder X-ray Diffractometry

Powder X-ray diffraction (PXRD) patterns for pure CLO, PM and selected formulations were recorded on a Rigaku Geigerflex diffractometer using Ni-filtered, CuKα radiation, a voltage of 40 kV and a 25-mA current.

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) analysis was performed using Perkin-Elmer series 7 DSC on 2 to 8 mg samples (Sartorius BP 210 S Germany) of pure CLO, PM and selected formulations. Samples were heated in an open aluminum pan at a rate of 10°C/min in a 0 to 250°C temperature range under a nitrogen flow of 40 ml/min as purging gas.

In-vitro Release Studies

The *in vitro dissolution for the selected solid dispersions i.e. SD6 (equivalent to 75 mg of CLO) was carried out by using USP type II apparatus (Paddle method). The dissolution medium used was distilled water (900 ml), maintai*ned at 37 ± 0.5°C with a rotational speed of 75 rpm. At an interval of 15 min, samples were withdrawn and filtered through filter paper (0.22 µm) and were analyzed spectrophotometrically at 218 nm after appropriate dilutions, against a similarly treated blank. Similarly, the pure drug (15 mg) and PM were subjected for *in vitro drug release studies and the release profile was compared with selected formulations.*

The data obtained from *in vitro release studies were analyzed by curve fitting method to various models viz., Zero, First-order kinetics, Higuchi and Korsmeyer-Peppas model, using DDSolver 1.0 ver. software. Dissolution efficiency (DE) is the area under the dissolution curve up to a certain time 't' expressed as a percentage of the area of the* rectangle described by 100% dissolution at the same time.

Mean dissolution time (MDT) and Dissolution efficiency was calculated by using the equation[14]

$$MDT = \frac{\sum_{i=1}^{n} \bar{\tau}_i \cdot \Delta M_i}{\sum_{i=1}^{n} \Delta M_i} \text{ and } DE = \frac{\int_0^t y \cdot dt}{y_{100} \cdot t} \times 100$$

Where, n is the number of sampling points, ti time at the midpoint between I and i=1, is an additional amount of drug dissolved between I and i=1 and y_{100} is the maximum percentage of drug dissolved over the period 0-t.

Determination of Antiplatelet activity

Preparation of platelets

Albino rats weighing 200–250 g was used for the study. The rats were divided into four groups as Group 1 (Control-Blank), Group 2 (administered with Pure drug) and Group 3 (administered with SD6) having 3 rats in each group. The rats were administered with a dose of CLO (5mg/kg) orally by gavage. *After 3 hr the rats were anaesthetized to with diethyl ether. From Abdominal aorta, blood (0.2ml) was collected using a syringe and transferred to a tube containing 3.8 % sodium citrate (1:9, v/v), which was then centrifu*ged at 1300 rpm for 10 min at room temperature. The supernatant plasma rich in platelets (PRP) was collected and stored in the freezer until further studies. The study was conducted with prior approval of IEC vide letter no. LIPH/2019/Estt-4467, Dated 14/12/2019.

Determination of platelet aggregation

The studies were conducted as per previously reported,[15] using a turbidimetric method. In brief, 10 µl of supernatant was diluted with 500 µl of Tyrode solution containing 35 mg/ml bovine serum albumin and the count was done using a haemocytometer. The platelet density was adjusted to 2×108 cells/mL with Tyrode solution. *Bovine serum albumin (35 mg/mL) was added to the Tyrode solution in order to reduce the platelet density low enough for easy counting. Platel*et aggregation was recorded by using the principle of Light transmission aggregometry based on changes in turbidity measured as a change in light transmission, which is proportional to the extent of platelet aggregation induced by addition of an agonist. *The aggregating agent collagen (2µg/mL) was added to the above solution and Platelet aggregations were recorded after 5 min using Lumi-aggregometer (Chrono-Log, Co.,). Results were expressed as a percentage of aggregation; the extent of aggregation was e*stimated by the change in light transmission.

RESULTS AND DISCUSSION

The calibration curve of CLO was prepared in the concentration range 5-40 µg/ml in methanol. The absorbance values are tabulated in Table 1. The CLO was found to obey Beer-Lambert's law in the concentration range of 5-40 µg/ml (Figure 1) the calibration curve obtained was linear and had regression coefficient (R^2) value 0.998 with less standard deviation, indicating good linearity and reproducibility.

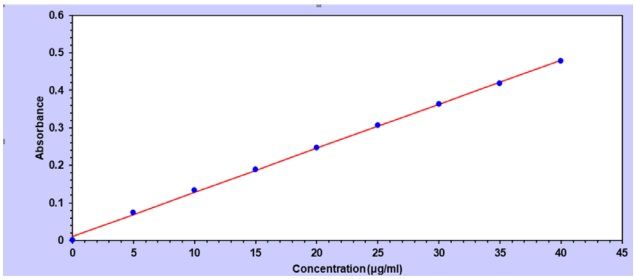


Figure 1: Calibration curve of CLO.

Table 1: Properties of extracted pectin from mango peel.

Solution of pH	pH = 1.5	pH = 2.0	pH = 2.5	pH = 3.0	pH = 3.5
Volume taken for extraction (ml)	100	100	100	100	100
Amount of peel sample added(g)	10	10	10	10	10
Extraction temperature (°C)	100	100	100	100	100
Extraction time (min)	90	90	90	90	90
Volume of Ethanol added (ml)	60	60	60	60	60
Centrifuge (rpm)	3000	3000	3000	3000	3000
Centrifuge time (min)	15	15	15	15	15
Weight of dried pectin obtained (g)	1.56	2.24	1.29	1.05	1.00
Yield of pectin obtained (%)	15.6	22.40	12.90	10.50	10.00
Colour of pectin yield	Light Brown	Light Brown	Light Brown	Light Brown	Light Brown
Solubility	Slightly soluble	Slightly Soluble	Soluble	Soluble	Soluble

Evaluation of Pectin Extract

Pectin was extracted from the mango peels grown in Himachal Pradesh. The result is shown in Table 1. The results indicate that pH affects the solubility as well as the yield of the extracted pectin. The pectin extracted at pH 2.5 and above is soluble in water. This can be attributed to one of the studies which describe solubility of pectin can be increased if extracted from ripened fruit due to enhanced pectin lytic activities of polygalacturonase.[16] Similarly, in another study also it has been reported that during fruit ripening, β–galactosidase enzyme increases the number of free pectin molecules and cuts.[17] Further, the sugar chains in the pectin structures result in enhanced water solubility of the pectin.[18] As ripening proceeds in fruits, the pectin becomes more soluble.

Preliminary solubility studies

In case of solid dispersions initially, preliminary solubility analysis (Table 2) were carried out to select the appropriate water-soluble and water-insoluble carriers for the preparation of solid dispersion in which pure drug solubility found to be 0.011 mg/ml. Solubility studies have shown that PVPK 30 and pectin in 1:1 and 1:2 has increased the solubility of the drug by 15 folds.
Preparation of solid dispersions

From physical mixtures of PVPK30 and pectin in the ratio of 1:1 and 1:2 was selected for the formulation of solid dispersion. Solid dispersions were prepared by three different methods viz., kneading method, fusion method and solvent wetting method. After the formulation of solid dispersion, formulations were subjected to evaluation. The formulation prepared by the kneading method shown the % yield of 91.56±0.002 to 94.71±0.004 whereas Solvent Wetting Method has shown better % yield that varies from 97.02±0.003 to 98.15±0.002 (Table 3). The % yield obtained by the hot-melt method was low and most of the formulation containing pectin turned brown/ black that could be due to the effect of heating.

Fourier Transform Infrared Spectroscopy

FTIR spectra of pure drug, PM and SD6 were recorded by potassium bromide (KBr) disc method using Shimadzu FTIR-8700 spectrophotometer (Tokyo, Japan) and results are shown in Figure 2. The major peaks of the CLO were also observed in the PM as well as in SD6 indicating the compatibility of the drug in the formulation.

Powder X-ray diffraction

Powder X-ray diffraction (PXRD) patterns for pure CLO, PM and selected formulation SD 6 were recorded and results are shown in Figure 3. The results indicated the conversion of crystalline drug to amorphous form as the peaks in the SD6 are decreased when compared to pure drug.

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) analysis of pure CLO, PM and selected formulations were carried out and shown in Figure 4. The DSC indicates the phase behavior of the materials. The sharp endothermic peak at 180.69°C corresponding to CLO melting point was observed which indicates its crystalline nature. The thermal behavior of the pectin is with a large endo-thermal effect due to polymer dehydration. DSC studies also exhibited that there no interaction among drug and carrier at a molecular level in solid dispersion of pectin.

In vitro Release Studies

The *in vitro* dissolution for the selected solid dispersion i.e. SD6, pure drug and PM were subjected for *in vitro*

Table 2: Preliminary solubility studies of physical mixtures.

S. No	Carrier (Drug: carrier)	Solubility mg/ml	S. No	Carrier (Drug: carrier)	Solubility mg/ml
1.	Pure drug	0.011±0.002	9.	PEG 6000 1:1	0.115±0.001
2.	Mannitol 1:0.5	0.021±0.004	10.	PEG 6000 1:2	0.138±0.003
3.	Mannitol 1:1	0.053±0.005	11.	PVP K30 1:0.5	0.081±0.004
4.	Mannitol 1:2	0.121±0.002	12.	PVP K30 1:1	0.167±0.002
5.	Citric acid 1:0.5	0.019±0.002	13.	PVP K30 1:2	0.205±0.004
6.	Citric acid 1:1	0.034±0.003	14.	Pectin 1:0.5	0.083±0.002
7.	Citric acid 1:2	0.099±0.001	15.	Pectin 1:1	0.168±0.002
8.	PEG 6000 1:0.5	0.068±0.005	16.	Pectin 1:2	0.215±0.001

Mean ± S.D, *n*=3

Table 3: Preliminary solubility studies of prepared solid dispersions.						
Formulation code	**Method of preparation**	**Drug: Pectin**	**Drug: PVP K30**	**% Yield**	**% Drug Content**	**Solubility mg/ml**
CLO	Pure Drug	-	-			0.011
SD1	Kneading	1:1	-	93.14±0.002	98.56±0.005	0.212±0.003
SD2		1:2	-	91.56±0.002	99.02±0.008	0.305±0.004
SD3		-	1:1	94.68±0.003	98.56±0.007	0.184±0.005
SD4		-	1:2	94.71±0.004	98.15±0.005	0.293±0.005
SD5	Solvent Wetting	1:1	-	98.15±0.002	99.10±0.007	0.325±0.003
SD6		1:2	-	97.83±0.003	98.79±0.005	0.331±0.003
SD7		-	1:1	98.11±0.004	97.05±0.004	0.285±0.003
SD8		-	1:2	97.02±0.003	97.88±0.008	0.312±0.002
SD9	Fusion	1:1	-	83.68±0.010	71.52±0.009	0.102±0.005
SD10		1:2	-	85.14±0.009	75.62±0.008	0.128±0.004
SD11		-	1:1	85.18±0.021	73.65±0.007	0.204±0.005
SD12		-	1:2	89.22±0.18	74.58±0.006	0.235±0.004

Mean ± S.D, n=3

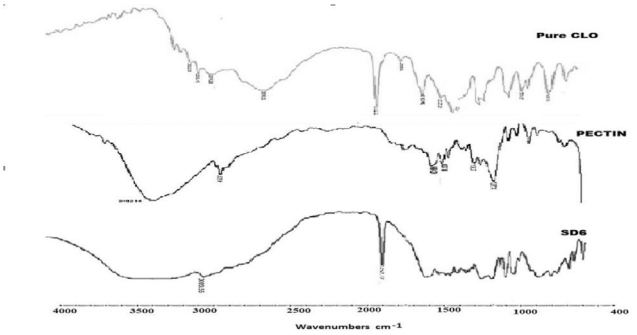


Figure 2: FTIR pattern of Pure drug, Pectin and Solid dispersion SD6.

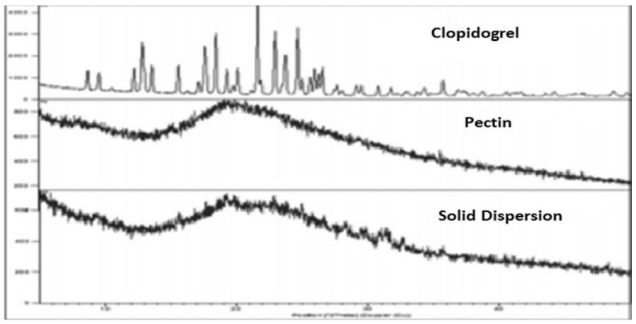


Figure 3: XPRD pattern of pure drug, Pectin and Solid dispersion SD6.

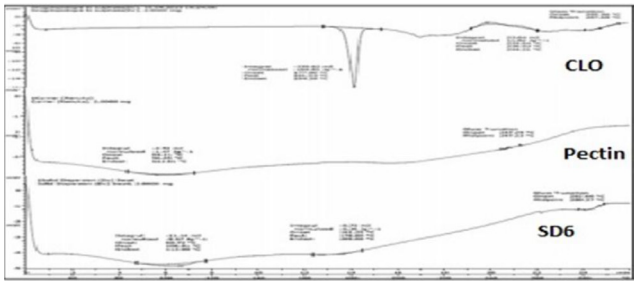


Figure 4: DSC of Pure drug, Pectin and Solid dispersion SD6.

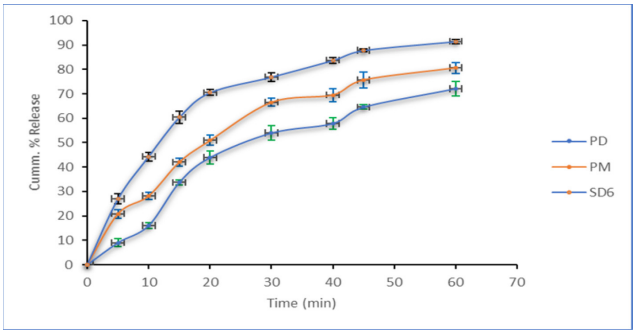


Figure 5: *In-vitro* release studies of Pure Drug (PD), Physical Mixture (PM) and Optimized formulation (SD6).

drug release studies and the release profile was compared with selected formulations. The *in-vitro* release shows 60.40 %, 42.03 % and 33.74 % for SD6, PM and PD respectively in 15 min (Figure 5). This indicates that solid dispersion showed an increased release rate when compared to pure drug.

The similarity f_2 when compared between pure drug and Optimized formulation SD6 was found to be 43.74, indicating the difference between two dissolution profiles. The Mean Dissolution Time and Dissolution efficiency for the solid dispersion SD6 were found to be 14.64 min and 0.691 % respectively indicating the enhanced dissolution profile of formulated solid dispersion (Table 4).

Table 4: Data analysis of *in vitro* release studies.				
Mathematical Modelling		**Pure Drug**	**Physical Mixture**	**SD6**
Hixson Crowell Model	R^2	0.9351	0.9369	0.9373
	kHC	0.007	0.009	0.015
Kosmeyer Peppas Model	R^2	0.9396	0.9758	0.9694
	kKP	5.341	10.38	19.22
	N	0.651	0.521	0.399
Higuchi Model	R^2	0.9011	0.9772	0.9456
	kH	9.118	10.289	13.175
First Order	R^2	0.9592	0.9739	0.9791
	K1	0.024	0.033	0.055
Zero Order	R^2	0.7977	0.7339	0.4762
	K0	1.438	1.651	1.971
MDT (min)		21.40677	18.01913	14.64281
DE (%)		0.463976	0.564372	0.691479

The data obtained from *in vitro* release studies were analyzed by curve fitting method to various models viz., Zero, First-order kinetics, Higuchi and Korsmeyer-Peppas model, using DDsolver v1.0 software. The goodness of fit model for the optimized formulation SD6 was found to be Higuchi model having r^2 value of 0.9791 and the n value of SD6 as shown in Table 4 indicates Fickian diffusion which follows Ficks First Law.

Determination of Antiplatelet activity

The mechanism of action of CLO is the irreversible binding of the adenosine diphosphate receptor on platelets. Adenosine diphosphate is a potent activator of platelets and stimulates aggregation. Platelet aggregation is considered to be primarily responsible for arterial thrombosis.[19] In one of the studies,[20] the electrical injury was caused to the rat carotid artery resulted in an increased reduction in rates of thrombosis up to a CLO bisulfate dose of 5 mg/kg, which was the dose used in the present study. To assure consistent, reliable dosing, the medication was administered by gavage.

In vitro platelet aggregation and inhibition study induced by the agonist collagen, with added samples of pure drug, SD6 and blank pectin solid dispersion was conducted. All the samples inhibited the platelet aggregation to a different extent. The inhibition of platelet aggregation was observed in the following order: SD6>Blank Formulation>PD. The three samples i.e. pure drug, SD6 and blank formulation blocked platelet aggregations by 71.9 ±2.1, 87.1 ±1.8 and 59.2 ±4.8 % respectively. The solid dispersion containing pectin has shown synergistic anti-platelet aggregation property indicating suitable for the formulation of solid dispersions of CLO.

CONCLUSION

CLO is one of the drugs of choice for anti-platelet activity. The pectin is one of the pharmaceutical and food additives used widely. The synergistic activity of the pectin has to be explored as anti-platelet activity. The solid dispersion of the pectin not only enhanced the solubility of the class II drugs but also has shown synergistic effect in antiplatelet activity. Thus, it was concluded that the pectin can be used as carrier for the formulation of solid dispersions. The pharmacological activities of pectin from different sources can also be evaluated in future studies.

ACKNOWLEDGEMENT

The authors would like to acknowledge Dr. Ran Singh, Managing Director, Laureate Institute of Pharmacy, Dr. S.B Sharma, Dean Research, Motherhood University to provide necessary facilities to conduct the research studies.

CONFLICT OF INTEREST

Authors have no conflicts of interest.

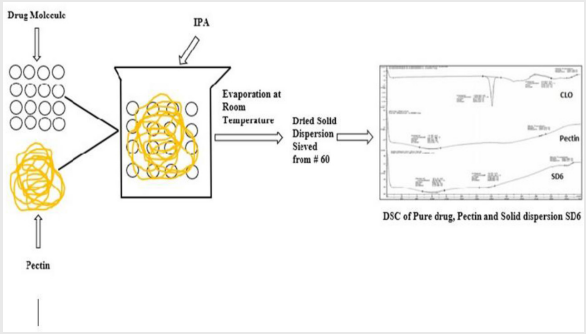
ABBREVIATIONS

CLO: Clopidogrel; **PM:** Physical Mixture; **PD:** Pure Drug; **SD:** Solid Dispersion; **PXRD:** Powder X-ray diffraction; **DSC:** Differential Scanning Calorimetry; **DE:** Dissolution Efficiency; **MDT:** Mean Dissolution Time; **mg:** Milligram.

REFERENCES

1. Moe's AJ. Gastric Retention Systems for Oral Drug Delivery. Business Briefing: Pharmatech. 2003;157-9.
2. Wen H, Jung H, Li X. Drug Delivery Approaches in Addressing Clinical Pharmacology-Related Issues: Opportunities and Challenges. The AAPS Journal. 2015;17(6):1327-40.
3. Kumari R, Chandel P, Kapoor A. Paramount Role of Solid Dispersion in Enhancement of Solubility. IGJPS. 2013;3(1):78-89.
4. Shah VP, Konecny JJ, Everett RL, McCullough B, Noorizadeh AC, Skelly JP. *In vitro* dissolution profile of water-insoluble drug dosage forms in the presence of surfactants. Pharmaceutical Research. 1989;6(7):612-8.
5. Brown CK, Chokshi HP, Nickerson B, Reed RA, Rohrs BR, Shah PA. Dissolution testing of poorly soluble compounds. Pharm Technol. 2004;28:56-43.
6. Román Y, Barddal HPO, Iacomini M, Sassaki GL, Cipriani TR. Anticoagulant and antithrombotic effects of chemically sulfated fucogalactan and citrus pectin. Carbohydrate Polymers. 2017;174:731-9.
7. Shobhit K, Satish KG. Mango Peel Pectin as a carrier for Solid Dispersions. Polim Med. 2013;43(4):141-6.
8. Krishnamurthi CR, Giri KV. Preparation, purification and composition of pectin from Indian fruits and vegetables. Brazil Arch Bio Technol. 2003;44:476-83.
9. Ermias G, Teshome GW. Extraction and characterization of pectin from selected fruit peel waste. Int J Sci Res Pub. 2016;6(2):447-54.
10. Kumar N, Nautiyal U. A Review Article on Lyophilization Techniques Used In Pharmaceutical Manufacturing. Int J Pharm Med Res. 2017;5(6):478-84.
11. Modi A, Tayade P. Enhancement of dissolution profile by solid dispersion (Kneading) technique. AAPS Pharm Sci Tech. 2006;7(3):68.
12. Natalija Z, Ales O, Marjan B, Stane S. Physical properties and dissolution behaviour of nifedipine/mannitol solid dispersions prepared by hot melt method. Int J Pharm. 2005;291(1-2):51-8.
13. Pandit V, Pai RS, Devi K, Suresh S. *In vitro-in vivo* evaluation of fast-dissolving tablets containing solid dispersion of pioglitazone hydrochloride. JAPTR. 2012;3(3):160-70.
14. Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C, *et al.* DDSolver: An add-in program for modeling and comparison of drug dissolution profiles. The AAPS Journal. 2010;12(3):263-71.
15. Gavin EJ. Platelet Aggregation: Turbidimetric Measurements. Methods in Molecular Biology. 2004;272:65-76.
16. Taylor JE. Exotics: Guava. In Biochemistry of Fruit Ripening. Springer: Dordrecht, The Netherlands. 1993;151-87.
17. Keller M. Developmental Physiology. In The Science of Grapevines: Anatomy and Physiology; Academic Press: Washington, DC, USA. 2015;196-268.
18. Hoa HD, Nguyen HA, Nguyen VH, Geoffrey PS. Properties of Pectin Extracted from Vietnamese Mango Peels. Foods. 2019;8(12):629.
19. Esclamado RM, Carroll WR. The pathogenesis of vascular thrombosis and its impact in microvascular surgery. Head Neck. 1999;21(4):355-62.
20. Bernat A, Mares M, Defreyn AM, Maffrand G, Herbert JP. Effect of various antiplatelet agents on acute arterial thrombosis in the rat. Thromb Haemost. 1993;70:812-6.

PICTORIAL ABSTRACT



SUMMARY

Clopidogrel is a BCS-II class drug with antiplatelet activity. Its bioavailability is less due to its low dissolution efficiency. Pectin from ripened mango peels was extracted and evaluated for solid dispersion carrier properties as well as for synergistic effect with clopidogrel. Dissolution efficiency and MDT indicated the faster dissolution of optimized formulation. The *in-vitro* antiplatelet activity of optimized formulation indicated the synergistic effect of pectin when used in combination with clopidogrel.

About Authors

Mr. Chander Pal Singh Verma, working as Professor & Head, Department of Pharmacognosy at Laureate Institute of Pharmacy, Kathog, Jawlamukhi. He is currently pursuing his doctoral studies at Motherhood University, Roorkee, UP. Prof. Verma has a keen interest in Herbal medicines and excipients obtained from natural resources. Professor has published and presented a number of research and review articles in a number of reputed national/ international journals.

Dr. Santosh Kumar Verma, working as Dean, School of Pharmacy, Motherhood University, Roorkee, Uttara Khand. Professor Verma has published and presented a number of research and review articles in a number of reputed national/ international journals. His area of research is novel drug delivery systems. He has guided more than 40 PG and 2 doctoral research works.

Dr. Mahender Singh Ashawat, working as Director cum Principal at Laureate Institute of Pharmacy, Kathog, Jawlamukhi. His current area of research is herbal formulation and their evaluation. Dr. Ashawat has guided more than 40 PG and 5 doctoral research works. Professor has published and presented a number of research and review articles in a number of reputed national/ international journals.

Dr. Vinay Pandit, working as Professor & Head, Department of Pharmaceutics at Laureate Institute of Pharmacy, Kathog, Jawlamukhi. His current area of research is to improve the solubility and dissolution rate of a poorly water-soluble drug and fast-dissolving drug delivery system. Dr. Pandit has published a number of research, review papers, and acted as a reviewer in various national and international reputed journals. He has been awarded with young scientist award by the Society of Pharmaceutical Education and Research, Bhopal.

Cite this article: Verma CPS, Verma S, Ashawat MS, Pandit V. Development of Solid Dispersions of Clopidogrel using Innate Excipient: Synergistic Antiplatelet Activity. Indian J of Pharmaceutical Education and Research. 2021;55(1):1007-15.