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INCREASING COMPLEX FORMATION OF WEAK ACID DRUG WITH ION EXCHANGE RESIN

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Keywords:

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ABSTRACT: Functionality of Ion Exchange Resin (IER) mainly depends on solubility and degree of ionization and molecular weight of drug. For this reason the application of IER is limited to only strong acidic and basic drugs or drug existing as salt; not for weak acidic and weak basic drugs due to their low ionization properties. If we increase the ionization of weak acid and bases, then application of IER will not only be limited to salts or strong acid or strong bases but also for weak acid and bases and hence almost all drugs will be complexed with IER and total exploitation of application of IER can be achieved. Solubility increasing approach such as cosolvent and 2 Hydroxypropyl betacyclodextrin and ionization increasing approach such as keeping the pH above drug ionization constant (pKa) were followed to evaluate their effect on loading of a weekly acidic drug, Repaglinide (taken as model drug) and found that keeping the pH of the complexation medium more than drug pKa had maximum percentage drug loading to resin, where percentage of drug resin complexation increased by four times. However the best approach of increasing drug loading was achieved by combination of solubility increasing approach and ionization increasing approach *i.e.* using cosolvent and making the pH more than pKa of drug that resulted in percentage of drug loading more than 90%.

INTRODUCTION: Ion exchange resins (IERs) are water insoluble, cross linked, porous polymer containing functional (Ionogenic) groups with mobile ions, which may replaced with ions of same charge dissolved in the surrounding liquid media [1]. IERs have excellent properties like high ion exchange and good absorption capacity, physicochemical stability and their insolubility in any solvents make them suitable candidates as taste masking and sustain release of drugs [2].

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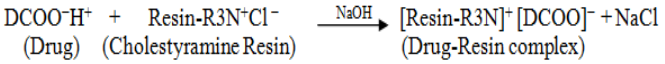
Since most drugs possess ionic sites in their molecules, drug can be loaded into resin by exchanging with counter ion of IER and hence, drug resin complex (DRC) is formed. The drug is released from DRC by exchanging with ions in gastro-intestinal fluid followed by drug diffusion [3]. Research over the last few years has revealed that IER are equally suitable for drug delivery technologies, including controlled release, transdermal, nasal, topical and taste masking [4].

However, the functionality of IER in the formulation and development of dosage form mainly depends on solubility and degree of ionization and Molecular weight of drug. Among these Factors, Ionization and solubility plays the most important role in drug loading on the IER since loading cannot be proceed without drug

dissolving and ionization, no matter how charge and molecular weight of drug is [5].

More is the solubility ionization of the drug more will be the percentage drug binding to resin; more is the functionality (*i.e.* for example taste masking). For this reason the application of IER is limited to only strong acidic and basic drugs or drug existing as salt; not for weak acidic and weak basic drugs which show low ionization properties. As maximum drugs are weak acid and weak bases, use of IER in these cases are not fruitful and hence application of IER in all drugs is not exploited. If we increase the ionization of weak acid and bases, then application of IER will not only be limited to salts or strong acid or strong bases but also for weak acid and bases and hence almost all drugs will be complexed with IER and total exploitation of application of IER such as taste masking will be made almost all drugs.

So this study was carried forward to increase the loading of a weekly acidic drug on to an IER by increasing the solubility and ionization of the drug. Repaglinide is chosen as the model drug which is weak acidic and poorly soluble drug. Cholestyramine resin is chosen as the IER since it is a cationic ion exchange resin that exchange with H^+ ion of Repaglinide and form complex as follows.



Repaglinide has a carboxylic (–COOH) group which has less ionizing in nature. Following three approaches were followed to increase the drug loading to IER.

1. **Approach I:** By increasing drug solubility (by co-solvent Method)
2. **Approach II:** By increasing drug solubility (by 2Hydroxypropyl betacyclodextrin method)
3. **Approach III:** By increasing drug ionization (by Henderson–Hasselbalch method, making dug solution pH > pKa of the drug).

MATERIALS AND METHODS: Repaglinide was obtained from M/s Torrent Pharmaceuticals Pvt. Ltd., Ahmedabad, India. Cholestyramine resin (Tulsion 412) was obtained as a gift sample from Thermax Ltd., Pune, India.

Purification of Cholestyramine Resins: Purification of cholestyramine resin was achieved by the method described by Torres *et al*., 1990 [6]. Slurry of 5 g of the resins was treated with 3 × 50 ml of deionized water, 2 × 50 ml of 95% ethanol, 1 × 50 ml of 50% ethanol, and 1 × 85 ml of deionized water. Each stage of treatment takes at least 1 h using a batch process with magnetic stirring. Purification is achieved by recycling the ion exchanger twice between its basic and acidic forms, respectively with 60 ml of 2 M sodium hydroxide (NaOH) and 60 ml of 2 M hydrochloric acid (HCl). This procedure was repeated once and finally the resins were recovered by vacuum filtration and washed thoroughly with deionized water. They were then dried to constant weight at 50 °C in a hot air oven for 12 h and placed in a desiccator.

Optimization of Complexation Time (Stirring Time) in the Preparation of DRC: Accurately weighed Repaglinide (1.0 gm) was dispersed 100 ml purified water and 1.0 gm cholestyramine resins dispersed in it followed by stirring on a magnetic stirrer for different stirring time 1, 2, 3, 4 and 5 hr. For each batch, drug resin suspension was filtered using Whatman filter paper (#41) after required stirring time. Drug loaded resin remaining on the filter paper are washed with methanol to remove unbound drug, if any and dried in hot air oven at 50°C till the LOD of Drug-resin complex reaches below 1.5% w/w. Simultaneously the filtrate containing unbound drug was assayed spectrophtometrically by UV Spectrophotometer (UV-1800, Shimadzu, Japan) to find out remaining amount of drug.

Preparation of Drug Resin Complex (DRC) without Using Any Approach (*i.e.* Blank): Complexes of drug and resin in the ratios 1:1, 1:2, 1:3, 1:4, 1:5 parts by weight were prepared by batch method 7. For each batch of drug-resin ratios required amount of Repaglinide (1.0 gm) is dispersed 100 ml deionized water. Then required amount of cholestyramine resins dispersed in it followed by stirring on a magnetic stirrer. After agitation, each batch was filtered using whatman filter paper (#41). Drug loaded resin remaining on the filter paper are washed with methanol to remove unbound drug, if any and dried in hot air oven at 50 °C till the LOD of Drug-resin complex reaches below 1.5% w/w. Simultaneously the

filtrate containing unbound drug was assayed spectrophtometrically by UV Spectrophotometer (UV-1800, Shimadzu, Japan) to find out remaining amount of drug .

Preparation of Drug Resin Complex (DRC) by Approach -I (By Co-solvent Method): Co-solvent is a technique for improving the solubility of poorly soluble drug. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs [8]. By this method the drug is dissolved in cosolvent such as ethanol before forming complex with IER. As per pre-formulation study of Repaglinide, it is freely soluble in ethanol.

So Complexes of drug and resin in the ratios 1:1, 1:2, 1:3, 1:4, 1:5 parts by weight were prepared. For each batch of drug-resin ratios required amount of Repaglinide (1.0 gm) is dissolved in 20 ml ethanol. Then 80 ml of water is added to it to make 1% w/v drug solution. Then required amount of cholestyramine resins dispersed in it followed by stirring on a magnetic stirrer for optimized stirring time. After agitation, each batch was filtered using whatman filter paper (#41) and proceeded as per procedure mentioned in step-3 to get the percentage drug loading.

Preparation of Drug Resin Complex (DRC) by Approach-II (by using 2-Hydroxypropyl Betacyclodextrin): W. Samprasit *et al*., 2013 [5] increased the drug loading of Piroxicam and Meloxicam by increasing solubility using Betacyclodextrin and 2-Hydroxypropyl betacyclo-dextrin and reported that 1:1 ratio of 2-Hydroxypropyl betacyclodextrin (2HP betacyclo-dextrin) and drug produce increased drug loading to anionic resin (Dwoex 1X 2-200, Quaternary ammonium salt of divenyl Benzene) as compared to that of without using 2-Hydroxypropyl beta-cyclodextrin.

So 2HP betacyclodextrin is preferred to be taken for increasing loading of Repaglinide. Five batches of drug resin complex in the ratios 1:1, 1:2, 1:3, 1:4, 1:5 parts by weight were planned to prepare. For each batch of drug-resin ratios required amount of Repaglinide (1.0 gm) is mixed with 100 ml of water to make 1% w/v drug solution. Then 1.0 gm of 2HP betacyclodextrin was added to it and stirred for 24 hour using magnetic stirrer [3]. Then required amount of cholestyramine resins dispersed in it followed by stirring on a magnetic stirrer for 2 hour (Optimized previously in step-2). After agitation, each batch was filtered using Whatman filter paper (#41) and proceeded as per procedure mentioned in step-3 to get the percentage drug loading.

Preparation of Drug Resin Complex (DRC) by Approach-III (Henderson–Hasselbalch Method, by Making Dug Solution pH > pKa of the Drug): Drug resin ratio of 1:1, 1:2, 1:3 were taken for this study, since it was found from the previous study in step-3, 4 and 5, that drug loading is changing significantly up to 1:2, but 1:3 ratio is also included to for getting exact picture of effect of resin quantity on drug loading.

For each drug resin ratio, accurately 1.0 gm of drug was dissolved in 100.0 ml of purified water. Its initial pH (Do) was checked by pH meter. Then prepared 10% w/v sodium hydroxide (NaOH) solution was added drop wise to it and pH was checked till getting desired pH. Similarly drug solution of different pH above than its pKa such as 7.0 ± 0.1, 8.0 ± 0.1, 9.0 ± 0.1, 10 ± 0.1, 11 ± 0.1 were obtained. Then required quantity of cholestyramine resin (*e.g.* 2.0 gm for drug-resin ratio 1:2) was added to drug solution of different pH and stirred for 2 hr (stirring time optimized earlier). After agitation, each batch was filtered using whatman filter paper (#41) and proceeded as per procedure mentioned in step-3 to get the percentage drug loading.

Preparation of DRC by Approach-IV (Combination of Approach-I and III): Accurately weighed 1.0 gm of drug was dissolved in 20 ml ethanol. Then 80.0 ml of purified water was added to it to make it 1% w/v solution. Its initial pH was checked by pH meter. Then prepared 10% NaOH solution was added drop wise to it and pH was checked till getting desired pH of 9.0 ± 0.1. Then 2.0 gm of cholestyramine resin (optimized drug-resin ratio 1:2) was added to drug solution and stirred for 2 hr (stirring time optimized earlier). After agitation, it was filtered using whatman filter paper (#41) and proceeded as per procedure mentioned in step-3 to get the percentage drug loading.

Characterization of DRC:

Drug loading in the DRC: To determine the actual loading capacity, filtrate was subjected for 10000 times dilution with distilled water and assayed spectrophtometrically and concentration of drug remaining in filtrate was calculated by using calibration curve in deionized water. The amount of drug bound to the resin was calculated as the difference between the initial and the remaining amount of drug in the filtrate. The loading capacity can be found out by using the following formula:

Drug Loading capacity = Amount of drug bound/Initial amount of drug × 100

Infrared Spectroscopy: IR Spectroscopy of DRC obtained from approach-IV was performed on Fourier transformed-infrared spectrophotometer (FTIR-8400S, Shimadzu, Japan) to confirm the presence of drug in DRC. The DRC and KBr (Potassium bromide) were mixed properly in the ratio 95:5 and were placed on the sample holder. The spectra were scanned over 3000 to 400 cm^{-1}.

Flow Properties of DRC:

Bulk Density: [9] Weighed accurately 10 gm of prepared drug-resin complex (DRC) was transferred into 100 ml measuring cylinder without tapping during transfer. The volume occupied by drug was measured. Bulk density (ρb) was measured by using formula:

$$\rho b = m / vb$$

Where: m = mass of the blend; vb = untapped volume

Tapped Density: [9] Weighed accurately 10 gm of DRC was taken into a graduated cylinder. Volume occupied by the drug was noted down. Then the cylinder was subjected to 1250 taps from a height of approx 3 cm manually and final volume (v t) was measured. Tapped density (ρt) is calculated by the below formula:

$$\rho t = m/vt$$

Where: vt = tapped volume; m = mass of the blend

Carr's Index (Compressibility): [9] The compressibility index measures of the property of powder to be compressed. The packing ability of drug was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping. It was indicated as Carr's compressibility index was calculated as follows and from its value flowability of powder can be found out as per below **Table 1**.

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

TABLE 1: FLOWABILITY OF POWDER FROM VALUE OF CARR'S INDEX

Carr's index	Flowability
5-15	Excellent
12-16	Good
18-21	Fair passable
23-35	Poor
33-38	Very Poor
>40	Very very Poor

RESULTS AND DISCUSSION:

Purification of Cholestyramine Resin: Since received cholestyramine resin was of industrial scale, it contains various impurities which might produce unwanted effect. Therefore its purification is needed. Washing the resin with various solvents such as deionized water, 95% ethanol, 50% ethanol solublize the impurities in these solvents and thereby remove them as the filtrate. Purification process causes activation of the resin for complex formation with bicarbonate ion as well as the drug.

Optimization of Complexation Time (Stirring time) in the Preparation of DRC: Drug loading to 1:1 drug-resin ratios at various stirring time is given **Table 2**.

TABLE 2: EFFECT OF STIRRING TIME IN DRUG LOADING

Time of Stirring (h)	Percentage drug loading for 1:1 drug-resin combination
1	8.3
2	16.1
3	16.6
4	18.5
5	17.9

From the **Table 1**, it was clear that after 2 h of stirring drug loading do not increase significantly with respect to time. Percent drug loading shows a plateau after 2 h and hence concluded that complexation between drug and resin was found to be optimum after 2 h of stirring.

Percentage Drug Loading with Different Approaches in Comparison to Blank: Drug

loading using co solvency method (Approach-I) and using 2-HP betacyclodextrin (approach II) for various drug-resin ratios are given in **Table 3** and is compared with percentage (%) drug loading without any approach (*i.e.* blank).

TABLE 3: EFFECT OF APPROACH-I AND II ON % DRUG LOADING AS COMPARED TO BLANK

Code	Drug : resin	Percentage Drug Loading		
		Blank	Approach-I	Approach-II
DRC1	1:1	15.1 ± 3.1%	39.8 ± 3.1%	47.6 ± 0.1%
DRC2	1:2	21.3 ± 2.0%	51.0 ± 2.2%	55.0 ± 2.7%
DRC3	1:3	22.1 ± 1.2%	52.4 ± 2.2%	57.4 ± 3.2%
DRC4	1:4	21.4 ± 4.5%	52.8 ± 2.1%	56.4 ± 2.1%
DRC5	1:5	24.0 ± 0.4%	54.7 ± 1.9%	59.7 ± 3.5%

Data are the average of values (mean) ± standard deviation (S.D.) (n = 3**)**

By using cosolvent and 2HP betacyclodextrin, increase the solubility of the drug and hence increased the drug binding to the resin by 2 - 3 times as compared to the blank. Increase in the amount of resin increases the amount of drug absorbed from the solution but decreases the amount of drug per 100 mg of DRC. There is no significant increase in drug loading in 1:3, 1:4 and 1:5 drug-resin combinations as compared to that of 1:2; only an increase of 3 - 5% was observed, but at the same time they consumed unnecessarily more resins as compared to 1:2 drug-resin combinations. Thus drug resin in the ratio 1:2 (*i.e.* DRC2) gives optimum loading and considered as optimized DRC by both the approaches. However there is no significant difference observed between drugs loading with both approaches in 1:2 drug resin complex, though difference in same observed in 1:1 ratio.

Percentage Drug Loading with by Approach-III (by Henderson–Hasselbalch Method, Making Dug Solution PH > Pka of the Drug): The pKa of a weak acid is the pH at which the acid is equally distributed between its protonated (unionized) and unprotonated (ionized) forms. This is illustrated by the Henderson–Hasselbalch equation:

$$pH = pKa + \log ([DCOO^{-}]/[DCOOH]$$

$$DCOOH \rightleftharpoons DCOO- + H+$$

Where [DCOO−] is the concentration of the drug Repaglinide (weak acid) in its ionized form and [D-COOH] is the concentration of the drug Repaglinide (weak acid) in its unionized form.

If the weak acid is equally distributed between its two forms, ([DCOO−] / [DCOOH]) = 1, log ([DCOO−] / [DCOOH]) = 0, and pH = pKa. If the weak acid is not equally distributed between its two forms, then the pH will be either less or greater than the pKa of the weak acid. Thus, a weak acid exists primarily in its ionized form at a pH above the pKa. As Repaglinide is an acid-base ampholyte with two protonation sites, whose pKa1and pKa2 were 4.16 and 6.01 separately, at the isoelectric pH (5.50) condition, two neutral forms of Repaglinide (zwitter ionic and uncharged) exist which result in the ampholytic nature of the drug molecule and its U-shape solubility profile with the low [10]. So to make the drug in its ionized form, pH of drug solution is to be increased above 6.01.

Percentage drug loading at different pH of drug solution is presented in **Table 4**.

TABLE 4: % DRUG LOADING BY APPROACH-III (AT DIFFERENT PH OF DRUG SOLUTION)

Drug solution (1% gm/ml)	pH of obtained drug solution	Drug resin proportion for complexation	Drug-Resin Complex (DRC)	% drug loading
D_1	7.0 ± 0.1		$DRC_{1/7.0}$	47.6 ± 0.7%
D_2	8.0 ± 0.1		$DRC_{1/8.0}$	70.1 ± 1.5%
D_3	9.0 ± 0.1	1:1	$DRC_{1/9.0}$	74.4 ± 5.4%
D_4	10.0 ± 0.1		$DRC_{1/10.0}$	76.2 ± 3.6%
D_5	11.0 ± 0.1		$DRC_{1/11.0}$	75.8 ± 1.4%
D_1	7.0 ± 0.1		$DRC_{2/7.0}$	52.1 ± 2.2%
D_2	8.0 ± 0.1		$DRC_{2/8.0}$	76.1 ± 0.9%
D_3	9.0 ± 0.1	1:2	$DRC_{2/9.0}$	81.9 ± 1.4%
D_4	10.0 ± 0.1		$DRC_{2/10.0}$	81.7 ± 2.3%
D_5	11.0 ± 0.1		$DRC_{2/11.0}$	84.8 ± 0.6%

D_1	7.0 ± 0.1		$DRC_{3/7.0}$	61.1 ± 1.1%
D_2	8.0 ± 0.1		$DRC_{3/8.0}$	79.6 ± 3.2%
D_3	9.0 ± 0.1	1:3	$DRC_{3/9.0}$	83.1 ± 2.1%
D_4	10.0 ± 0.1		$DRC_{3/10.0}$	84.7 ± 1.0%
D_5	11.0 ± 0.1		$DRC_{3/11.0}$	85.2 ± 0.3%

Data are the average of values (mean) ± standard deviation (S.D.) (n = 3)

With increase in pH more than pKa, increased the ionization and hence increased the drug-resin complexation up to 80 - 85%. Increasing pH of the solution shift the drug dissociation towards right due to consumption of H^+ by OH^- of NaOH to form water. Due to enhance forward reaction, ionization of dug increased and drug loading to resin increased as follows.

$$DCOOH \rightleftharpoons DCOO^- + H^+$$

$$NaOH \longrightarrow Na^+ + OH^-$$

$$DCOO^- + Resin\text{-}R3N^+Cl^- \xrightarrow{Na+} [Resin\text{-}R3N]^+[DCOO]^- + NaCl$$

(Drug) (Cholestyramine Resin) (Drug-Resin complex)

Since there is no significant increase in drug binding at pH 10 and 11 as compared to that in pH 9.0.This is due to maximum conversion of anionic drug form at pH 9.0. It is due to the fact that, degree of ionization doesn't significantly changed after pH 9.0.

More over Drug loading is not significantly increasing at Drug-Resin ratio of 1:3 as compared to that of 1:2 ($DRC_{2/9.0}$ *vs*. $DRC_{3/9.0}$).

Combination of Approach-I and Approach-III: By Henderson–Hasselbalch method, the drug loading was increased up to 80 - 85%, not more than this. It might be due to the reason that, some quantity of drug might be existing in insoluble form. So to increase the drug loading more than 90%, approach-I and approach-III both are followed combinely as approach-IV, where drug was first dissolved in a cosolvent (ethanol). The drug loading was found to be 91.3± 2.4%.

Characterization of DRC:

Infrared Spectroscopy: IR spectra of DRC2 obtained by using approach-IV were shown in **Fig. 1**. Presence of characteristic peaks of Repaglinide such as 1586 cm^{-1} (due to N-H bending of 1°, 2° amine), 1149 cm^{-1} (due to aliphatic C-N stretching) in the FTIR spectra of DRC confirmed the presence of drug in the DRC. It also reveal that drug binding to resin is not attributed to $-NH_2$ group of Repaglinide as there is no change in peak due to N-H bending as well as C-N stretching. Peak of Repaglinide due to aryl carboxylic acid (1688 cm^{-1}) vanished which indicate the potential binding of resin at carboxylic group of drug.

Characteristic peak of cholestyramine resin at 1030 cm^{-1} due to C-N stretching of quaternary amine was shifted to 1020 cm^{-1}. This might be due to replacement of Cl^- ion with drug-COO^- ion (ionic form of drug), which has comparatively less electro-negativity, causing a small decline in C-N stretching energy and thus decreasing the absorption wavelength. This confirmed the complex formation between drug and resin.

Flow Properties of DRC: From the result of Compressibility index shown in **Table 5**, it was found that the drug has poor flow property and compressibility property.

TABLE 5: FLOW PROPERTIES OF DRC

Mass of DRC (g)	Initial volume (ml)	Bulk density (g/ml)	Tapped volume (ml)	Tapped density (g/ml)	Carr's index (%)	Flow property
10	42	0.24	31	0.32	26.19	Poor

TABLE 6: EFFECT OF ALL APPROCHES ON % DRUG LOADING AS COMPARED TO BLANK

Code	Drug : resin	Percentage drug loading				
		Blank	Approach-I	Approach-II	Approach-III	Approach-IV
DRC1	1:1	15.1 ± 3.1%	39.8 ± 3.1%	47.6 ± 0.1%	74.4 ± 5.4%	--
DRC2	1:2	21.3 ± 2.0%	51.0 ± 2.2%	55.0 ± 2.7%	81.9 ± 1.4%	91.3 ± 2.4%
DRC3	1:3	22.1 ± 1.2%	52.4 ± 2.2%	57.4 ± 3.2%	83.1 ± 2.1%	--
DRC4	1:4	21.4 ± 4.5%	52.8 ± 2.1%	56.4 ± 2.1%	--	--
DRC5	1:5	24.0 ± 0.4%	54.7 ± 1.9%	59.7 ± 3.5%	--	--

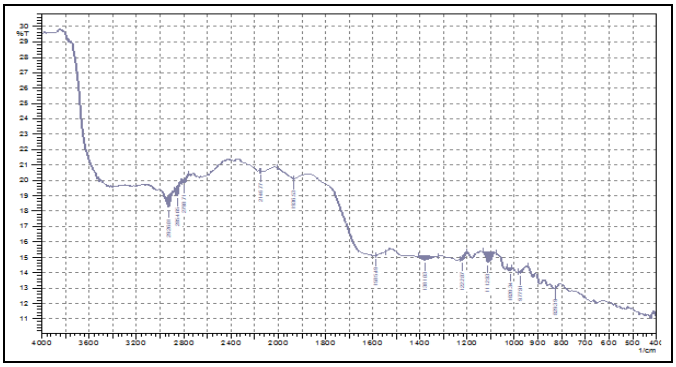


FIG. 1: IR SPECTRA OF OPTIMIZED DRC2

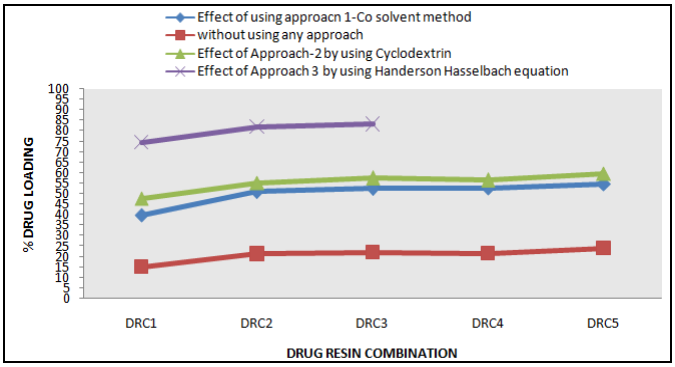


FIG. 2: EFFECT OF ALL APPROACH ON % DRUG LOADING AS COMPARED TO BLANK

CONCLUSION: Three approaches were made to increase the complexation of a poorly soluble week acidic drug with Cholestyramine resin (compared in **Table 6** and represented in **Fig. 2**) and found maximum drug loading up to 80 - 85% by using approach -3 *i.e.* increasing the dug solution pH > pKa of the drug. Also Drug Resin in the ratio 1:2 is found to be the optimized combination for effective drug loading.

However the best approach of increasing drug loading was achieved by combination of solubility increasing approach and ionization increasing approach *i.e.* using cosolvent and making the pH more than pKa of drug that resulted in percentage of drug loading more than 90%. This approach can be exploited for other weakly acidic drugs.

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